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Chemoselective Ruthenium-Catalysed Reduction of Carboxylic Acids

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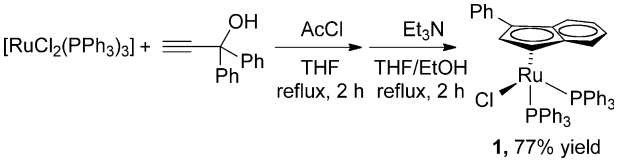
Abstract: A very general and efficient catalytic protocol for the selective reduction of carboxylic acids to their corresponding alcohols under mild conditions is described. Various carboxylic acids, including benzoic acids, were reduced in good yields using the presented methodology. The ruthenium-catalysed method yields a highly chemoselective reduction permitting the reduction of a carboxylic acid functionality in the presence of numerous other potentially reducible moieties.

Keywords: carboxylic acids; homogenous catalysis; hydrosilylation; reduction; ruthenium

The reduction of carboxylic acid derivatives to produce the corresponding alcohols has drawn much interest in organic synthesis and represents a straightforward manner to produce these useful compounds.[1] Stoichiometric hydride reducing agents (e.g., DIBAL-H, $LiAlH_4$ or $LiBH_4$) are most commonly employed in such reductions. This is despite the protocol being afflicted with several disadvantages such as poor functional group tolerance, moisture- and air-sensitivity and often difficulties encountered with product isolation and purification.[2] On the other hand, catalytic hydrogenation[3] represents an excellent method to reduce carboxylic acids. In spite of its utility, the required harsh conditions (high pressure and elevated temperatures) represent serious drawbacks in the hydrogenation procedure. Due to its safety and operational simplicity, the catalytic hydrosilylation of carbonyl moieties has recently become an important alternative as a reduction strategy.[4] Metal-catalysed hydrosilylations of carboxylic acid derivatives such as esters[5] or amides[6] to the corresponding alcohols and amines have been widely developed. In contrast, only a limited number of systems has been described for the hydrosilylation of carboxylic acids.[7–12] Most of these methodologies involve elegant catalytic methods [Fe,[7] Ru,[8] and $B(C_6F_5)_3$[9]] for the hydrosilylation of carboxylic acids to aldehydes. Regarding the reduction to the corresponding alcohols, only few catalytic procedures have been described.[7,10,11,12] The limited reaction scope[10,11] and the use of light-mediated protocols[7] can be considered as principal drawbacks in the above-mentioned reducing procedures. In addition, an investigation into the chemoselective reduction of carboxylic acids in the presence of a variety of functional groups has not yet been undertaken. This is warranted as it would unequivocally establish the true potential of the approach. Recently, we reported on the synthesis of $[RuCl(PPh_3)_2(3\text{-phenylindenyl})]$[13] (**1**), a complex that has proven to be highly efficient in a number of catalytic transformations, such as alcohol racemisation,[13] ketone reduction,[14] alcohol oxidation[15] and S–S, S–Si and S–B dehydrogenative coupling.[16] Moreover, complex **1** can be easily and inexpensively synthesised starting from a propargylic alcohol and $[RuCl_2(PPh_3)_3]$ (Scheme 1).[17]

Taking into account the interest in developing new catalytic procedures for the reduction of carboxylic acids and to further extend the utility of **1**, we describe here a very general and efficient ruthenium-catalysed hydrosilylation of carboxylic acids under mild conditions, and for the first time, report on a highly chemoselective version of this transformation in the presence of other functional groups.

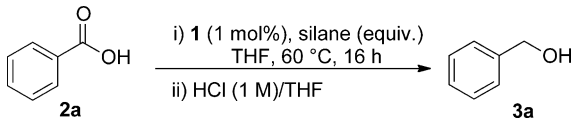
At first, we studied the hydrosilylation of benzoic acid (**2a**) as a model reaction in the presence of **1** (1 mol%) (Table 1). The reaction was initially conducted in the presence of $PhSiH_3$ (3 equiv.) while test-



Scheme 1. Synthesis of **1**.

Advanced Synthesis & Catalysis

Table 1. Optimization of the conditions for the reduction of benzoic acid **2a**.[a]



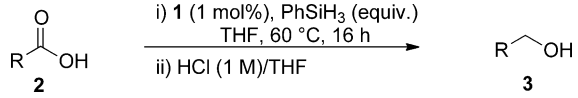
Entry	Silane [equiv.]	Solvent	Conv. **3a** [%][b]
1	$PhSiH_3$ (3)	MeOH	50
2	$PhSiH_3$ (3)	*i*-PrOH	60
3	$PhSiH_3$ (3)	CH_3CN	64
4	$PhSiH_3$ (3)	toluene	45
5	$PhSiH_3$ (3)	toluene[c]	55
6	$PhSiH_3$ (3)	THF	>98
7	$PhSiH_3$ (3)	THF	0[d]
8	Ph_2SiH_2 (3)	THF	0
9	Ph_2MeSiH (3)	THF	0
10	$PhMe_2SiH$ (3)	THF	0
11	Et_3SiH (3)	THF	0
12	PMHS (3)	THF	0
13	$(EtO)_2MeSiH$ (3)	THF	0
14	**$PhSiH_3$ (2)**	**THF**	**>98**
15	$PhSiH_3$ (1)	THF	70

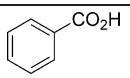
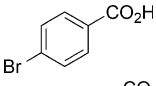
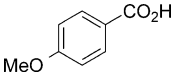
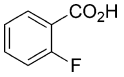
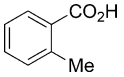
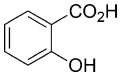
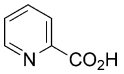
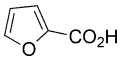
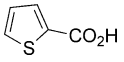
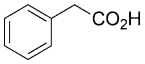
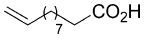
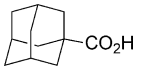
[a] *Reaction conditions:* **1** (1 mol%), **2a** (0.25 mmol) and silane (1–3 equiv.). Hydrolysis was performed using HCl (1 mL, 1 M) in THF (0.5 mL).
[b] Conversion determined by ^1H NMR spectroscopy.
[c] At 80 °C.
[d] In the absence of catalyst (**1**).

ing different solvents. Moderate conversions were obtained with polar (Table 1, entries 1–3) or non-polar (Table 1, entries 4 and 5) solvents. Interestingly, THF shows an enormous beneficial effect on the reaction, leading to complete conversion of benzoic acid to the corresponding benzyl alcohol (**3a**) (Table 1, entry 6). In absence of complex **1**, the reaction does not take place (Table 1, entry 7). In addition to $PhSiH_3$, several other silanes were also evaluated for this reaction (Table 1, entries 8–13). However, the unchanged starting material was recovered in all the cases. It is noteworthy that the amount of $PhSiH_3$ can be decreased to 2 equiv. without any loss in the conversion to the desired benzyl alcohol (Table 1, entry 14).

After optimizing the reaction conditions, the scope of the reduction of carboxylic acids with $PhSiH_3$ was examined using **1** (1 mol%) and THF as a solvent (Table 2). Several aromatic carboxylic acids were tested (Table 2, entries 1–6). Substituted benzoic acids with an electron-donating or electron-withdrawing group in either the *ortho* or *para* position were successfully reduced to the corresponding alcohols in good yields (73–84%) (Table 2, entries 1–6). However, *ortho*- or electron-donating substituted benzoic acids showed a slightly lower reactivity and 3 equiv. of $PhSiH_3$ were required to efficiently yield the desired products (Table 2, entries 3–5). Notably, the reduction

Table 2. Reduction of carboxylic acids (**2a–l**) catalysed by **1**.[a]

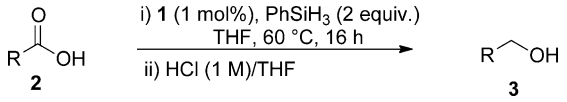


Entry	Acid		$PhSiH_3$ [equiv.]	Conv. [%][b]	Yield [%][c]
1		**2a**	2	>98	84 (**3a**)
2		**2b**	2	>98	80 (**3b**)
3		**2c**	3	92	77 (**3c**)
4		**2d**	3	>98	79 (**3d**)
5		**2e**	3	93	73 (**3e**)
6		**2f**	3	>98	78 (**3f**)
7		**2g**	2	–[d]	–
8		**2h**	2	>98	65 (**3h**)
9		**2i**	2	>98	60 (**3i**)
10		**2j**	3[e]	>98	80 (**3j**)
11		**2k**	3[e]	>98	79 (**3k**)
12		**2l**	3[e]	>98	78 (**3l**)

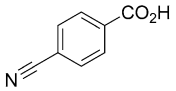
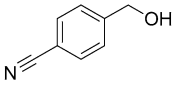
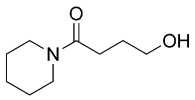
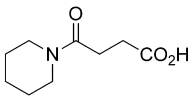
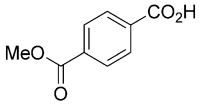
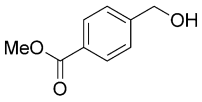
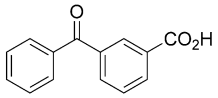
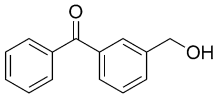
[a] *Reaction conditions:* **1** (1 mol%), carboxylic acid (**2**) (0.25 mmol) and silane (2–3 equiv.). Hydrolysis was performed using HCl (1 mL, 1 M) in THF (0.5 mL).
[b] Conversion determined by ^1H NMR spectroscopy.
[c] Isolated yields.
[d] Complex mixture.
[e] 2 mol% of **1**.

process can be achieved even in the presence of a free hydroxy group in the *ortho* position with a good isolated yield (Table 2, entry 6). It should be highlighted that the catalytic system displays a good efficiency for the reduction of substituted benzoic acid derivatives, which are not easily obtained using the previously reported hydrosilylation methodologies.[7,10,11] Heteroaromatic carboxylic acids were also studied. Furoic (**2h**) and thiophene (**2i**) acids can be reduced to the corresponding alcohols in moderate isolated yields (60–65%) (Table 2, entries 8 and 9). With respect to the 2-picolinic acid (**2g**), the desired product cannot be isolated and a complex mixture of products was obtained (Table 2, entry 7). The system

Table 3. Chemoselective reduction of carboxylic acids.[a]



2 **3**

Entry	Acid		Alcohol		Conv. [%][b]	Yield [%][c]
1		**2m**		**3m**	>98	80
2		**2n**		**3n**	>98	73
3		**2o**		**3o**	>98	81
4		**2p**		**3p**	90	77

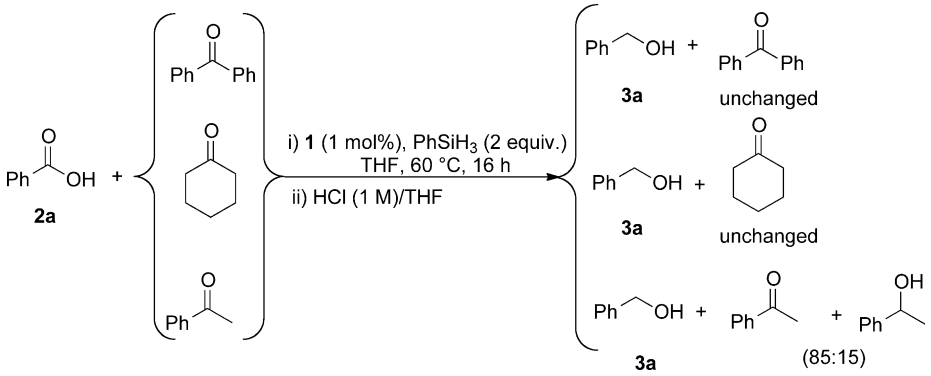
[a] *Reaction conditions:* **1** (1 mol%), carboxylic acid (**2**) (0.25 mmol) and silane (0.5 mmol). Hydrolysis was performed using HCl (1 mL, 1 M) in THF (0.5 mL).
[b] Conversion determined by ^{1}H NMR spectroscopy.
[c] Isolated yields.

permitted benzyl carboxylic acid (**2j**) to be converted to the desired alcohol in a good yield (80%) (Table 2, entry 10). Linear (**2k**) or even highly hindered (**2l**) alkyl carboxylic acids can be efficiently reduced to the corresponding alcohols (Table 2, entries 11 and 12). It must be noted that under these hydrosilylation reaction conditions terminal double bonds are also tolerated (Table 2, entry 11).

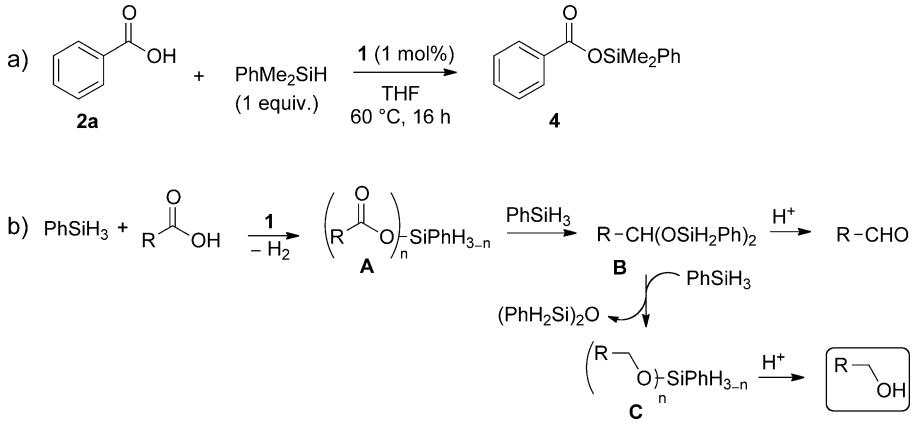
After demonstrating the general applicability of this hydrosilylation system, and with the aim to further extend the generality and the activity of **1**, we studied more challenging carboxylic acids with potentially reactive groups such as nitrile or carbonyl moieties (Table 3). Surprisingly, and to our delight, we found that carboxylic acids can be chemoselectively reduced to the desired alcohols in the presence of a nitrile (**2m**), a tertiary amide (**2n**), an ester (**2o**) or even a ketone (**2p**), which are well known to be much more reactive under any other hydrosilylation or reduction reaction conditions. It should be noted that the reduction products of these extra functional groups were never observed.

To further study the chemoselectivity of the reduction, a few competitive reactions were carried out. The reduction under the optimised reaction conditions of the benzoic acid (**2a**) in presence of various ketones takes place with full conversion. Surprisingly, the benzophenone and the cyclohexanone were recovered unchanged, and only the acetophenone was slightly reduced (15% conversion) (Scheme 2).

Several experiments were conducted to gain insight into the reaction mechanism. Using dimethylphenylsi-



Scheme 2. Competitive reactions.



Scheme 3. a) Formation of silyl ester **4**. b) Proposed mechanism of the ruthenium-catalysed reduction of carboxylic acids.

lane in the presence of **1**, the silyl ester **4** can be easily obtained (Scheme 3, reaction a).[18] Unfortunately, due to its high moisture-sensitivity, the possible formation of poly-dehydrogenative coupled products and the observed redistribution associated with the phenylsilane,[19] the analogous silyl ester intermediate **A** cannot be easily detected. At short reaction times (15 min), and after the hydrolysis of the disilylacetals (**B**), the corresponding aldehyde was detected by ^{1}H NMR spectroscopy. On the basis of these results, we propose that the reduction of the carboxylic acids with phenylsilane in the presence of **1**, takes place in three steps (Scheme 3, reaction b).[8] The desired primary alcohols are proposed to be produced by (i) a dehydrogenative coupling between the carboxylic acid and the silane, (ii) a reduction of the silyl ester derivative (**A**) by an Si–H addition in the C=O bond, followed by (iii) reductive cleavage of a C–O bond of the disilylacetal intermediate (**B**), and the final hydrolysis of the corresponding silyl ether (**C**). It is generally assumed that the silane is activated by the metal complex *via* oxidative addition to produce a metal silyl complex able to transfer the silyl group to a carbonyl moiety.[6c,20] However, we were unable to observe the desired ruthenium species in the corresponding stoichiometric reactions. Further investigations are currently ongoing in our laboratory, in order to better understand the mechanism of the hydrosilylation reaction.

In conclusion, we have described an efficient methodology for the reduction of carboxylic acids to the corresponding alcohols, under mild conditions, catalysed by [RuCl(PPh$_3$)$_2$(3-phenylindenyl)] (**1**). The described catalysed hydrosilylation procedure involves a very general and, for the first time, a highly chemoselective reduction of carboxylic acids to the corresponding alcohols even in the presence of potentially reducible functionalities such as nitriles and other carbonyl containing moieties. We expect that the present protocol will prove useful when selective carboxylic acid group reduction is targeted. The method is straightforward, is more atom- and step-economical than existing protocols where protection/deprotection steps are oftentimes required. The exploration of the activity of **1** and its congeners in the catalytic landscape is ongoing in our laboratories.

Experimental Section

General Procedure for Hydrosilylation of Carboxylic Acids

In a vial fitted with a screw cap, in the glove box, **1** (1 mol% or 2 mol%) and the corresponding carboxylic acid (0.25 mmol) were dissolved in THF (0.5 mL). Then, outside of the glove box, the PhSiH$_3$ was added (2–4 equiv.) and then, an empty balloon was placed in the vial cap. The resulting mixture was stirred 16 h at 60 °C. The reaction was hydrolyzed with aqueous HCl (1 mL, 1 M) in THF (0.5 mL) at room temperature for 1 h. Then, the aqueous phase was extracted with Et$_2$O (3×5 mL). The organic layer was washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel.

Acknowledgements

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