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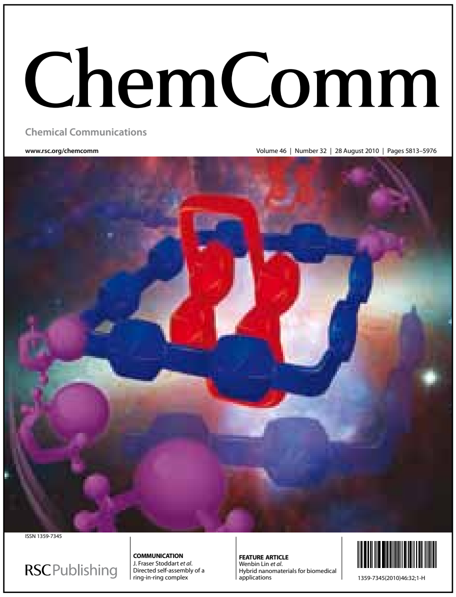

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ARTICLE TYPE

Facile and Efficient KOH-Catalysed Reduction of Esters and Tertiary Amides

José A. Fernández-Salas, Simone Manzini and Steven P. Nolan*

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Esters and tertiary amides were efficiently reduced to their corresponding alcohols and amines in high yields under mild and environmentally friendly conditions. The presented KOH-catalysed system involves a simple hydrosilylation procedure that is carried out under solvent-free conditions and does not require the use of inert conditions.

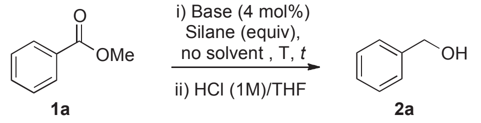
The reduction of carboxylic acid derivatives such as esters or amides into the corresponding alcohols or amines, is a most important transformations in organic synthesis.[1] The use of stoichiometric hydride reducing agents (e.g DIBAL-H, $LiAlH_4$ or $LiBH_4$) remains to date the most commonly practiced method for these reductions; this despite the protocol being afflicted with several disadvantages such as moisture and air-sensitivity and difficult purification.[2] Alternatively, catalytic hydrogenation[2c,3] represents an excellent method to reduce esters,[2c,3a] while the amide version is less well-developed, especially for the reduction of tertiary amides.[3b,c] Moreover, the required harsh conditions (high pressure and elevated temperatures) represent serious drawbacks in the hydrogenation procedures. Due to these difficulties and limitations, the catalytic hydrosilylation of carbonyl moieties has become an important synthetic transformation in organic chemistry, widely used in academic laboratories and in industry,[4] as an alternative reduction strategy. As an illustration of the importance of the transformation, numerous catalytic systems have been developed for the hydrosilylation of both esters (Rh,[5] Ru,[6] Mo,[7] Pd,[8] Mn,[9] In,[10] Ti,[11] Fe[12] and organo-zinc[13]) and amides (Rh,[14] Ru,[15] Pt,[16] Ir,[17] Ti,[18] Cu,[19] Fe[20] and organo-zinc[21]). The hydrosilylation of carbonyl compounds in the presence of base has also been studied,[22] although the scope is limited to ketones[22a] and hydroxyl esters.[22b] In addition to required harsh conditions and long reaction times,[22b] some metal-catalysed operational difficulties,[22] such as the requirement of inert conditions, have plagued the use of this methodology.

Many of the above-mentioned protocols require the use of large amounts of the silane, expensive catalysts, high temperatures, dry solvents and inert conditions. Taking into account the interest in developing new catalytic hydrosilylation procedures, we report a general base-catalysed methodology for the reduction of both esters and tertiary amides. The first base-catalysed methodology for the hydrosilylation of amides is reported.

At first, the reduction of methyl benzoate (**1a**) was investigated and the reactivity of several silanes was examined under neat reaction conditions (Table 1). Neither $PhMe_2SiH$ (3 equiv.) nor Et_3SiH (3 equiv.) led to formation of reduced products, even when the reaction was carried out at 60°C (Table 1, entries 3 and 4). However, Ph_2MeSiH (3 equiv.) gave full conversion to benzyl alcohol (**2a**) at 60°C after 4 h (Table 1, entries 2). Noteworthy is that in the presence of 1 equiv. of $PhSiH_3$ the desired alcohol was obtained at r.t. under neat conditions in only 1h (Table 1, entry 6).

The effect of the nature of the base was also evaluated. It is possible to perform the reaction in the presence of a strong base (KHMDS) or in the presence of weaker bases such as hydroxide bases (KOH and CsOH). In contrast, when the reaction was performed using NaOH or K_2CO_3, the hydrosilylation reaction did not take place. Besides the very low price of potassium hydroxide, its use allows us to carry out the reaction under aerobic conditions (unlike with KHMDS).

Table 1. Optimization of the conditions for the reduction of esters with silanes.[a]



Entry	Base	Silane (equiv.)	T[a] (°C)	*t* (h)	Conv. **2a** (%)[a]
1	KOH	Ph_2MeSiH (3.1)	r.t.	4	0
2	KOH	Ph_2MeSiH (3.1)	60	4	>98
3	KOH	$PhMe_2SiH$ (3.1)	60	4	0
4	KOH	Et_3SiH (3.1)	60	4	0
5	KOH	$PhSiH_3$ (3.1)	r.t.	1	>98
6	**KOH**	**$PhSiH_3$ (1.1)**	**r.t.**	**1**	**>98**
7	KHMDS	$PhSiH_3$ (1.1)	r.t.	1	>98
8	NaOH	$PhSiH_3$ (1.1)	r.t.	1	0
9	CsOH	$PhSiH_3$ (1.1)	r.t.	1	>98
10	K_2CO_3	$PhSiH_3$ (1.1)	r.t.	1	0

[a] Reaction conditions: Base (4 mol%), ester (**1a**) (1 mmol) and silane (1.1-3.1 mmol). Hydrolysis was performed using HCl (1 mL, 1M) in THF (0.5 mL). [b] Conversion determined by ^{1}H-NMR spectroscopy.

After having optimized the reaction conditions, the scope of the hydrosilylation of esters with $PhSiH_3$ was examined using KOH (4 mol%) (Table 2). Several aromatic, aliphatic and heteroaromatic esters were tested. Substitution with bulkier alkyl groups on the ester did not lead to a decrease in yield (Table 2, entry 2) and even with the highly hindered *tert*-butyl group the reaction took place with a moderate yield (Table 2, entry 3).

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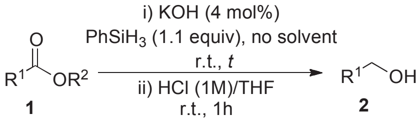
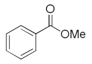
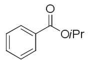
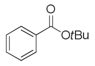
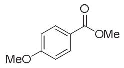
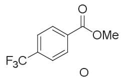
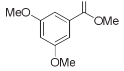
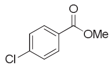
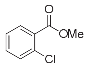
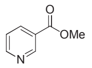
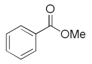
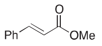
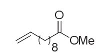
Arenes substituted with an electron-donating or electron-withdrawing group in either the *ortho*, *meta* or *para* position were successfully reduced to the corresponding alcohols in high yields (80-96%) (Table 2, entries 4-8) with only minor influence on the reactivity. More electron-rich aryl esters (**1d** and **1f**) require longer reaction times to achieve full conversion to the desired alcohols (see entries 4 and 6 with 5 and 7). Unfortunately, the reduction of conjugated systems, such as the methyl cinnamate **1k**, gave a complex mixture of products (Table 2, entry 11). Gratifyingly, the system permitted pyridyl (**1i**), benzyl (**1j**) and alkyl (**1k**) esters to be converted to the desired alcohols in very good isolated yields (80-86%) (Table 2, entries 9, 10 and 12). The catalytic system displays very good efficiency for most of the examined esters, providing good to excellent yields of alcohols (80-96%) under neat conditions at r.t. in rather short reaction times (0.5-3 h).

Table 2. KOH-catalysed reductions of esters.[a]

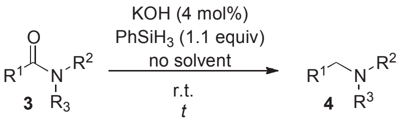


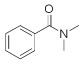
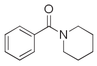
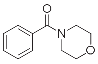
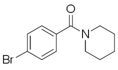
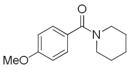
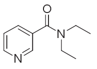
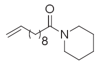
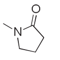
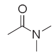
Entry	Ester	*t* (h)	Yield (%)[b]
1	 (**1a**)	1	86 (**2a**)
2	 (**1b**)	1.5	84 (**2a**)
3	 (**1c**)	3[c]	68 (**2a**)
4	 (**1d**)	1.5	81 (**2b**)
5	 (**1e**)	0.5	96 (**2c**)
6	 (**1f**)	3	80 (**2d**)
7	 (**1g**)	0.75	96 (**2e**)
8	 (**1h**)	1.5	86 (**2f**)
9	 (**1i**)	1.5	85 (**2g**)
10	 (**1j**)	0.5	83 (**2h**)
11	 (**1k**)	1	-[d]
12	 (**1l**)	1	80 (**2i**)

[a] Reaction conditions: KOH (4 mol%), ester (**1**) (1 mmol) and $PhSiH_3$ (1.1 mmol). Hydrolysis was performed using HCl (1 mL, 1M) in THF (0.5 mL). [b] Isolated yields. [c] At 60°. [d] Complex mixture.

After demonstrating the general applicability of our procedure to the hydrosilylation of esters, we further extended the method by studying the reduction of tertiary amides (Table 3). Aromatic, heterocyclic and aliphatic amides are reduced successfully under optimized reduction conditions for the esters. Comparing different *para*-substituted aryl amides, we found that the presence of an electron-withdrawing group (**3d**) raised the reactivity in comparison with electron-donating substituted amides, which required a slightly higher temperature (60°C) to efficiently yield the desired amine (**4e**) (Table 3, entries 4-5). Notably, heterocyclic amide **3f** is well tolerated and led efficiently to the desired amine at r.t. (Table 3, entry 6). Linear alkyl (**3g** and **3i**) and cyclic amides (**3h**) can also be reduced with good yields (79-86%) using this methodology, although longer reaction times are required. A benzamide derived of morpholine (**3c**) was reduced with good isolated yield (Table 3, entry 3). Overall, the reduction system performed very well for all studied amides, leading smoothly to the corresponding amines in high yields (79-91%). It should be noted that the final amines were obtained without any work up prior to isolation (see ESI for details). Primary and secondary amides were also subjected to the optimized conditions, but in both cases no reaction was observed and the starting material was recovered.

Table 3. KOH-catalysed reduction of tertiary amides.[a]



Entry	Amide	*t* (h)	Yield (%)[b]
1	 (**3a**)	3	90 (**4a**)
2	 (**3b**)	4	91 (**4b**)
3	 (**3c**)	4	75 (**4c**)
4	 (**3d**)	3[c]	81 (**4d**)
5	 (**3e**)	3[d]	88 (**4e**)
6	 (**3f**)	16	80 (**4f**)
7	 (**3g**)	16[d,e]	86 (**4g**)
8	 (**3h**)	16[e]	82[f] (**4h**)
9	 (**3i**)	16[e]	79[f] (**4i**)

[a] Reaction conditions: KOH (4 mol%), amide (**3**) (1 mmol) and $PhSiH_3$ (1.1 mmol). [b] Isolated yields. [c] THF was added as solvent (1.25 M). [d] At 60°C. [e] Reaction with 1.5 equiv. of $PhSiH_3$. [f] Determined by GC methods using dodecane as internal standard.

In conclusion, we have described a very straightforward, efficient and environmentally friendly methodology for the reduction of both esters and tertiary amides under very mild conditions. From a practical point of view, this KOH-catalysed system is the easiest procedure described for the reduction of esters and tertiary amides, avoiding the use of solvents, large excesses of silane and inert conditions. Further studies dealing

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with applications of the methodology to primary and secondary amides are ongoing in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

1 (a) *Comprehensive Organic Synhtesis*, Vol. 8 (Eds: B. M., Trost, I., Fleming), Pergamon, Oxford, **1991**. (b) *Modern Reduction Methods*, (Eds: P. G., Andersson, I. J., Munslow), WILEY-VCH, Weinheim, **2008**.

2 (a) *Reductions by Alumino and Borohydrides in Organic Synthesis*, (Eds: J. Seyden-Penne) 2nd ed., Wiley, New York, **1997**. (b) *Comprehensive Organic Transformations: a Guide to Functional Group Preparation* (Eds: R. C., Larock), WILEY-VCH, New York, **1989**. (c) *Handbook of Homogeneous Hydrogenation*, Eds: J. G., De Vries, C. J., Elservier), WILEY-VCH, Weinheim, Germany, **2007**. (d) G. W., Gribble, *Chem. Soc. Rev.* **1998**, *27*, 395-404.

3 (a) Y., Pouilloux, F., Austin and J. Barrault, *Catal. Today* **2000**, *63*, 87-100, and references cited therein; (b) A. A., Nuñez Magro, G. R., Eastham and D. J., Cole-Hamilton, *Chem. Commun*. **2007**, 3154-3156; (c) J., Coetzee, D. L., Dodds, J., Klankermayer, S. Brosinski, W., Leitner, A. M. Z., Slawin and D. J., Cole-Hamilton, *Chem. Eur. J.* **2013**, DOI: 10.1002/chem.201204270.

4 (a) *Hydrosilylation: A Comprehensive Review on Recent Advances*; (Eds: B., Marciniec), Springer, Netherlands, **2009**, chap. 9; (b) J. –F., Carpentier and V. Bette, *Curr. Org. Chem.* **2002**, *6*, 913-936; (c) O., Riant, N., Mostefaï and J., Courmarcel, *Synthesis* **2004**, 2943-2958; (d) D., Addis, S., Das, K., Junge and M., Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 6004-6011.

5 T. Ohta, M., Kamiya, K., Kusui, T., Michibata, M., Nobutomo and I., Furukawa, *Tetrahedron Lett.* **1999**, *40*, 6963-6963.

6 (a) M., Igarashi, R., Mizuno and T., Fuchikami, *Tetrahedron Lett.* **2001**, *42*, 2149-2151; (b) K., Matsubara, T., Iura, T., Maki and H., Nagashima, *J. Org. Chem*. **2002**, *67*, 4985-4988.

7 A. C., Fernandes and C. C., Romao, *J. Mol. Catal. A* **2006**, *253*, 96–98.

8 J., Nakanishi, H., Tatamidani, Y., Fukumoto and N., Chatani, *Synlett*, **2006**, 869-872.

9 Z., Mao, B. T., Gregg and A. R., Cutler, *J. Am. Chem. Soc*. **1995**, *117*, 10139-10140.

10 N., Sakai, T., Moriya and T. Konakahara, *J. Org. Chem*. **2007**, *72*, 5920-5922.

11 (a) S. C., Berk, K. A., Kreutzer and S. L., Buchwald, *J. Am. Chem. Soc.* **1991**, *113*, 5093-5095; (b) S. C., Berk and S. L., Buchwald, *J. Org. Chem.* **1992**, *57*, 3751-3753; (c) K. J., Barr, S. C., Berk and S. L., Buchwald, *J. Org. Chem.* **1994**, *59*, 4323-4326; d) M. T., Reding and S. L., Buchwald, *J. Org. Chem*. **1995**, *60*, 7884-7890; (e) X., Verdaguer, M. C., Hansen, S. C., Berk and S. L., Buchwald, *J. Org. Chem*. **1997**, *62*, 8522-8528.

12 (a) S., Das, Y., Li, K., Junge and M., Beller, *Chem. Commun*. **2012**, *48*, 10742-10744; (b) D., Bezier, G. T., Venkana, L. C., Misal Castro, J., Zheng, T., Roisnel, J.-B., Sortais and C., Darcel, *Adv. Synth. Catal.* **2012**, *354*, 1879-1884; (c) K., Junge, B., Wendt, S., Zhou and M., Beller, *Eur. J. Org. Chem*. **2013**, 2061-2066.

13 (a) H., Mimoun, *J. Org. Chem.* **1999**, *64*, 2582-2589; (b) S. Das, K. Möller, K., Junge and M., Beller, *Chem. Eur. J.* **2011**, *17*, 7414-7417.

14 R., Kuwano, M., Takahashi and Y., Ito, *Tetrahedron Lett.* **1998**, *39*, 1017-1020.

15 (a) Y., Motoyama, K., Mitsui, T., Ishida and H., Nagashima, *J. Am. Chem. Soc.* **2005**, *127*, 13150-13151; (b) M., Igarashi and T., Fuchikami, *Tetrahedron Lett*. **2001**, *42*, 1945-1947; (c) S., Hanada, T., Ishida, Y., Motoyama and H., Nagashima, *J. Org. Chem*. **2007**, *72*, 7551-7559; (d) K., Matsubara, T., Iura, T., Maki and H., Nagashima, *J. Org. Chem.* **2002**, *67*, 4985-4988; (e) J. T., Reeves, Z., Tan, M. A., Marsini, Z. S., Han, Y., Xu, D. C., Reeves, H., Lee, B. Z., Lu and C. H., Senanayake, *Adv. Synth. Catal.* **2013**, *355*, 47-52.

16 S., Hanada, E., Tsutsumi, Y., Motoyama and H., Nagashima, *J. Am. Chem. Soc*. **2009**, *131*, 15032-15040.

17 S., Park and M., Brookhart, *J. Am. Chem Soc*. **2012**, *134*, 640-653.

18 K., Selvakumar and J. F., Harrod, *Angew. Chem. Int. Ed.* **2001**, *40*, 2129-2131.

19 S. Das, B., Join, K., Junge and M., Beller, *Chem. Commun*. **2012**, *48*, 2683-2685.

20 (a) S., Zhou, K., Junge, D., Addis, S., Das and M., Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 9507-9510; (b) D., Bézier, G. T., Venkanna, J.-B., Sortais and C., Darcel, *ChemCatChem* **2011**, *3*, 1747-1750; (c) Y., Sunada, H., Kawakami, T., Imaoka, Y., Motoyama and H., Nagashima, *Angew. Chem. Int. Ed.* **2009**, *48*, 9511-9514; (d) S., Das, B., Wendt, K., Möller, K., Junge and M., Beller, *Angew. Chem. Int. Ed.* **2012**, *51*, 1662-1666; (e) A., Volkov, E., Buitrago and H., Adolfsson, *Eur. J. Org. Chem*. **2013**, 2066-2070.

21 (a) S., Das, D., Addis, K., Junge and M., Beller, *Chem. Eur. J.* **2011**, *17*, 12186-12192; (b) S., Das, D., Addis, S., Zhou, K., Junge and M., Beller, *J. Am. Chem. Soc*. **2010**, *132*, 1770-1771.

22 (a) D., Addis, S., Zhou, S., Das, K., Junge, H., Kosslick, J., Harloff, H., Lund, A., Schulz and M., Beller, *Chem. Asian. J.* **2010**, 2341-2345; (b) M., Hojo, C., Murakami, A., Fujii and A., Hosomi, *Tetrahedron Lett.* **1999**, *40*, 911-914.