Functional group-selective poisoning of molecular catalysts: a ruthenium cluster-catalysed highly amide-selective silane reduction that does not affect ketones or esters†

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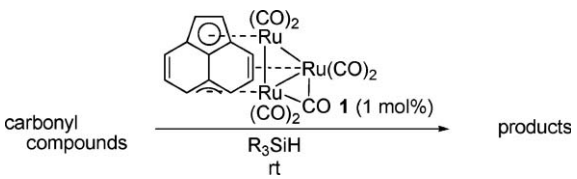
The addition of amines eliminates the catalytic activity of a triruthenium cluster in the hydrosilane reduction of ketones and esters without affecting the rate of reduction of amides; selective reduction of the amide group in amido ketones and amido esters is accomplished.

The chemoselective transformation of multi-functionalized substrates by virtue of catalysis is a challenge to be developed in organic synthesis.[1] The use of "catalyst poisoning" is one of the solutions, in which the addition of a catalyst inhibitor eliminates some of the properties of the original catalyst, leading to the accomplishment of "highly selective reactions". As seen in the famous Lindlar catalyst, which makes possible the selective hydrogenation of triple bonds to double bonds by the addition of quinoline or lead tetraacetate to $Pd/CaCO_3$,[2a] catalyst poisoning generally decreases the reaction rate, imposing other drawbacks, such as the difficulty of applying catalysts to the reaction of less-reactive functional groups.[2] The hydride reduction of carbonyl compounds is commonly performed using metal–hydride systems,[3] and the selective reduction of one carbonyl group in a molecule without affecting the others has long been desired. In reactions using typical reducing reagents, such as $LiAlH_4$ or $NaBH_4$, the reactivity of carbonyl compounds is known to decrease in the order ketone > ester > amide. Therefore, very little selective reduction of amides containing esters and ketones has been achieved. Notable exceptions are reductions with B_2H_6[4] and that with the $Ph_2SiH_2/RhH(CO)(PPh_3)_3$ system,[5] in which the reactivity of the amide group is sometimes higher than that of the ester moiety; the amidic group in amides containing ester groups is reduced preferentially to the aminoester. In contrast, to the best of our knowledge, there are few examples of reductions, in which the reactivity of amides are higher than ketones, such that the amides of keto acids are normally reduced to the amides of hydroxyacids.

We have recently found that a triruthenium carbonyl cluster, $(\mu_3,\eta^2;\eta^3;\eta^5$-acenaphthylene$)Ru_3(CO)_7$ (**1**), efficiently catalyses the reduction of carbonyl compounds with trialkylsilanes at room temperature within a few hours (Scheme 1).[6] In the course of our study, we were aware that the addition of amines (0.01–1 equiv.), such as triethylamine, diisopropylethylamine or diethylaniline, to the catalyst solution inhibited the reduction of some substrates.‡ To our astonishment, detailed investigations of this amine effect showed that inhibition of the catalytic activity was highly selective of functional group and occurred in the reaction of ketones and esters, but not in the reduction of amides. This discovery provides a clear answer to the unsolved question of how the less-reactive amide group is selectively reduced while the ketone or ester group remains intact.

As representative examples, reaction profiles for the individual reduction of 2-decanone, methyl decanoate and *N*,*N*-dimethyldecanamide with $PhMe_2SiH$, catalyzed by **1** (1 mol%), are shown in Fig. 1 **A**, whereas those of acetophenone, methyl benzoate and *N*,*N*-dimethylbenzamide are depicted in Fig. 1 **C**. In the absence of Et_3N, the reduction of all the substrates took place smoothly. At room temperature, the $t_{1/5}$ values of 2-decanone, methyl decanoate and *N*,*N*-dimethyldecanamide were 1.4, 0.35 and 0.20 h, whereas those of acetophenone and *N*,*N*-dimethylbenzamide were 6.7×10^{-2} and 2.0×10^{-2} h, respectively. The reaction of methyl benzoate was somewhat slower than the other substrates; the $t_{1/5}$ value was 0.1 h at 50 °C. In sharp contrast, addition of Et_3N (1 equiv. with respect to the substrate) eliminated the catalytic activity of **1** in the reduction of ketones and esters, as shown in Fig. 1 **B** and **D**; under the same conditions as above, no reduction product was detected in the reactions of methyl decanoate, methyl benzoate and acetophenone, whereas less than 2% 2-decanone was converted to the corresponding silyl ether after 5 h. Interestingly, no retardation was observed in the reduction of amides in the presence of Et_3N ($t_{1/5}$ = 0.17 h for *N*,*N*-dimethyl decanamide and 1.9×10^{-2} h for *N*,*N*-dimethyl benzamide). Thus, the catalytic activity towards ketones and esters was eliminated *completely*, whilst the reaction rates of the amides were unchanged.† In other words, functional group-selective poisoning of **1** can be achieved by the addition of *appropriate* amines.

These results clearly suggest the possibility that selective reduction of the amide group can be achieved with unchanged ester and ketone moieties present in the same molecule. This was



Scheme 1 Silane reduction of carbonyl compounds with ruthenium cluster complex **1**.

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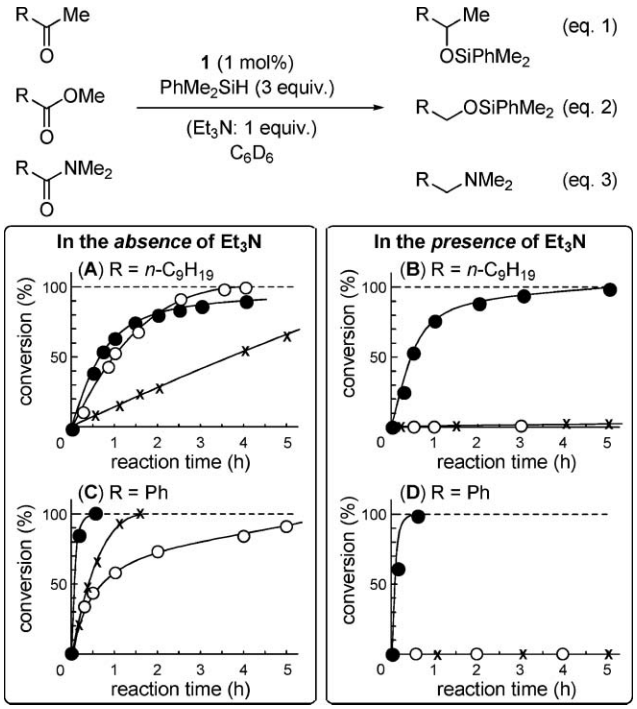
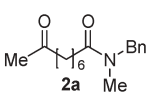
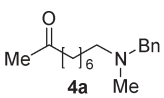
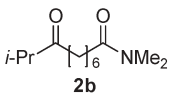
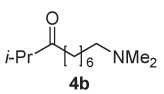
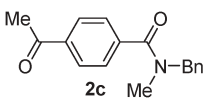
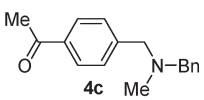
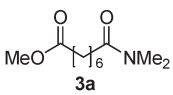
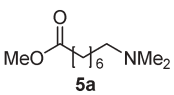
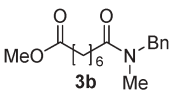
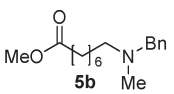
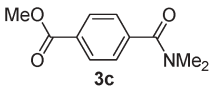
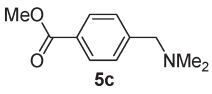


Fig. 1 The reaction profiles of eqns 1–3. Reactions were carried out using carbonyl compounds (0.2 mmol), $PhMe_2SiH$ (0.6 mmol) and **1** (0.002 mmol) in the absence (**A** and **C**) or presence (**B** and **D**) of Et_3N (0.2 mmol; 1 equiv. with respect to the carbonyl compound) at room temperature. The reaction of methyl benzoate was performed at 50 °C; eqn 1 (×), eqn 2 (○), eqn 3 (●).

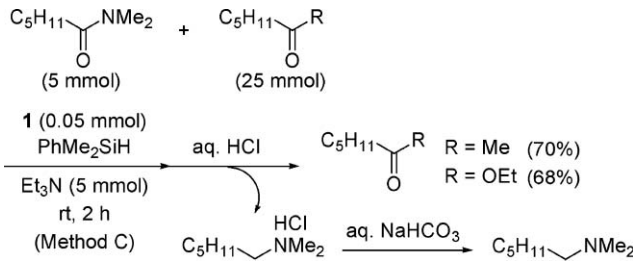
nicely realized: The amide-selective reduction of the molecules listed in Table 1 was successfully accomplished by three methods.§ As reported previously,[6b] **Method A** is reduction in a benzene or toluene solution. **Method B** improves the reaction rate by prior activation of the catalyst. **Method C** is a further improvement of **Method B** using the minimum amount of solvent, leading to great enhancement of the rate. All reactions proceeded at room temperature, and the starting materials were consumed in 0.5–20 h. The products were the corresponding amino ketones (**4**) or amino esters (**5**). The only detectable by-products were the amino alcohols resulting from further reduction of the primary products (amino ketones **4** and amino esters **5**) with excess amounts of hydrosilane.

As shown in Table 1, judicious choice of **Method A**, **B** or **C** and the amount of silane led to reduction of the amide group in the molecules to give the desired amines in good yields. The ratio of the desired amine to the amino alcohol by-product became 100 : 0 when the reaction conditions were controlled. The addition of Et_3N was not always necessary because reduction of the amide group produced an amino moiety, which generated catalytic poisoning similar to Et_3N. In the case of the reduction of both the aromatic and aliphatic amido esters (**3a–c**), amide-selective reduction was achieved by all three methods in the absence of Et_3N, and the corresponding amino esters **5a–c** were isolated by alumina column chromatography in 81–96% yields (Table 1, entries 7–11). In contrast, the concomitant reduction of ketones is relatively rapid in the reduction of amido ketones (**2a–c**), which caused a decrease in selectivity. However, this was improved by the addition of Et_3N (1 equiv.). The use of appropriate amounts of

Table 1 Amide-selective reduction with $PhMe_2SiH$ catalysed by **1**[a]

Entry	Substrate	Method[b] (equiv. Si–H)	Time/h	Product	Yield (%)[c]	Selectivity (%)[d]
1	 **2a**	A (3.0)	20	 **4a**	81 (92)	92
2		B (3.0)	8		81 (93)	93
3		C (3.0)	1		72 (83)	83
4		C (2.5)	1		91 (>99)	>99
5[e]	 **2b**	C (2.5)	1.5	 **4b**	94 (>99)	>99
6[f]	 **2c**	B (3.5)	18	 **4c**	88 (>99)	>99
7[f]	 **3a**	A (3.0)	6	 **5a**	88 (>99)	>99
8[f]		B (3.0)	1.5		91 (>99)	>99
9[f]		C (3.0)	0.5		87 (>99)	>99
10[f]	 **3b**	C (3.0)	0.5	 **5b**	96 (>99)	>99
11[f]	 **3c**	B (3.0)	3.5	 **5c**	81 (>99)	>99

[a] All reactions were carried out using 1 mmol of substrate, 2.5–3.5 mmol of $PhMe_2SiH$, 1.0 mmol of Et_3N and 0.01 mmol of **1** at room temperature. [b] See footnote and ESI. [c] Isolated yield. The yield in parentheses is that determined by ^1H NMR. [d] The ratio (%) of the desired amino ketones or amino esters in the crude product (determined by ^1H NMR in the presence of an internal standard). In entries 1–3, the by-product was the corresponding amino alcohol. [e] 0.5 mmol of substrate and 0.005 mmol of **1** were used. [f] In the absence of Et_3N.



Scheme 2 Separation of amides contaminated with ketones and esters by a **1**-catalyzed, amide-selective reduction with $PhMe_2SiH$.

$PhMe_2SiH$ is sometimes important to raise the selectivity; for example, the reduction of *N*-benzyl-*N*-methyl-6-oxo-heptanamide (**2a**) with $PhMe_2SiH$ (3 equiv. with respect to **2a**), in the presence of Et_3N, showed 83–93% selectivity by all three methods. However, the use of 2.5 equiv. of silane by **Method C** suppressed the reduction of **4a** to amino alcohol, giving the desired amino ketone **4a** as a single product (Table 1, entries 1–3 *vs.* 4). The reactivity of the aromatic substrate was relatively low compared to aliphatic examples, and the use of a larger amount of $PhMe_2SiH$ (3.5 equiv.) and the application of a longer reaction time (18 h) afforded product **4c** in a satisfactory yield with 100% selectivity (Table 1, entry 6).

The present amide-selective reaction is also applicable to the facile separation of amides from a mixture of amides and ketones, or of amides and esters. When the catalytic reduction of these mixtures were carried out in the presence of appropriate amounts of Et_3N and $PhMe_2SiH$, only the amides were converted to the corresponding amines, with the ketones and esters remaining intact. A subsequent acidic work-up gave aqueous phases containing an ammonium salt of the formed amine, while unreacted ketones and esters were recovered from the organic phase (Scheme 2). In a typical example, a 5 : 1 molar ratio mixture of 2-heptanone and *N*,*N*-dimethyldecanamide (total 30 mmol) was subjected to a reduction with $PhMe_2SiH$ (15 mmol) in the presence of **1** (0.05 mmol) and Et_3N (5 mmol) to afford *N*,*N*-dimethyldecanamine (0.8 g; 79%) and unreacted 2-heptanone (2.0 g; 70%), respectively. Similarly, reduction of a 5 : 1 mixture of ethyl hexanoate and *N*,*N*-dimethyldecanamide (total 30 mmol) resulted in the separation of the unreacted ester (2.46 g; 68%) and the amine (0.82 g; 71%).†

The catalytic transformation of multi-functionalized organic molecules with high chemoselectivity has long been desired by organic chemists. The silane reduction presented in this Communication is a clear solution to this issue, containing the first examples of the selective reduction of amides that leaves the ketone functionality unchanged. This reduction also offers a general solution to the selective reduction of amides without ester groups being affected. The key components that allow this are appropriate amines, which, as additives, eliminate catalytic reactivity towards ketones and esters without retarding the reduction rate of amides. This is noteworthy when you consider that catalyst poisoning often kills catalytic activity towards all functional groups. We conclude that the observed effect of amines is new and important as a rare example of the functional group-selective poisoning of homogeneous catalysts. Further studies on this new poisoning system, in particular, the mechanisms involved¶ and their application to the selective reduction of other functional groups, are now being conducted.

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Notes and references

‡ Pyridine and triphenylamine (1 equiv. with respect to carbonyl) completely inhibit the reduction of esters; however, they are not very effective for the inhibition of ketone reductions, which are slowly reduced (10–40% conversion of ketones in 5 h).

§ **Method A**: A solution of the substrate (1 mmol) and $PhMe_2SiH$ (3.0 mmol) in 2 mL of toluene (or benzene) was added to a flask charged with **1** (0.01 mmol), and the mixture was stirred at room temperature.

Method B: To a solution of **1** (0.01 mmol) in THP or 1,4-dioxane (180 μL) was added $PhMe_2SiH$ (3.0 mmol), and the mixture stirred for 30 min at room temperature. A solution of the substrate (1 mmol) in 2 mL of toluene (or benzene) was added to the catalyst solution, and the mixture was stirred at room temperature.

Method C: To a solution of **1** (0.01 mmol) in THP or 1,4-dioxane (180 μL) was added $PhMe_2SiH$ (2.5 or 3.0 mmol), and the mixture was stirred for 30 min at room temperature. The substrate (1 mmol: neat) was added to the catalyst solution, and the mixture was stirred at room temperature.

¶ The poisoning was observed in the presence of small amounts of amines (*ca.* 10 equiv. with respect to the catalyst). At the present stage, we consider that the chemical properties of the catalyst species may be being changed by the coordination of amines to the silyl-ruthenium intermediates formed by the reaction of **1** with $PhMe_2SiH$.

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