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Direct Zn–diamine promoted reduction of C=O and C=N bonds by polymethylhydrosiloxane in methanol

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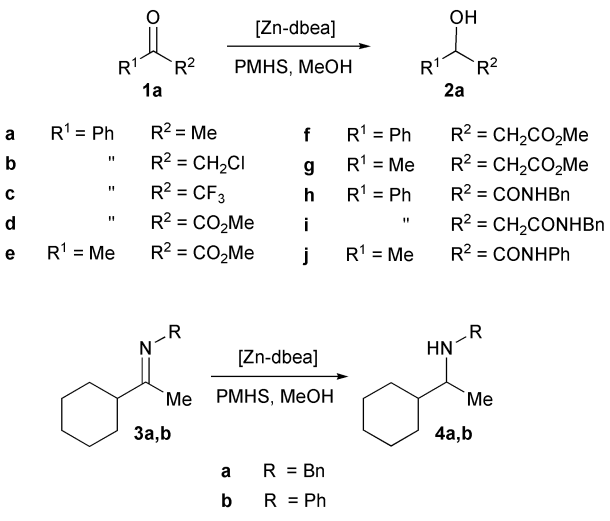
Ketones and imines are chemoselectively reduced at room temperature in methanol to the corresponding alcohols and amines in high yields in a one-step procedure using polymethylhydrosiloxane (PMHS) and a simple zinc–diamine catalyst.

Polymethylhydrosiloxane (PMHS), a safe and inexpensive polymer co-product of the silicon industry, has proved to be an efficient alternative reducing agent of C=O and C=N bonds when associated to different types of catalysts.[1] In this context, Mimoun recently reported a new system based on zinc–hydride catalysts that enables to reduce chemoselectively non-functionalised (or α,β-unsaturated) aldehydes, ketones and even esters.[2] However, those systems can not operate in protic solvents due to dehydrogenative silylation of the latter by PMHS; therefore, the recovered product is a silyl ether which must be subjected to a separate and somewhat delicate hydrolysis step. Mimoun *et al.* also developed a chiral version employing catalyst combinations of $ZnEt_2$ with optically active diamines to reduce aryl alkyl ketones in valuable enantioselectivities *via* the same two-step procedure ((i) hydrosilylation; (ii) hydrolysis).[3] We report here a simple diamine–zinc catalyst system that operates in an alcoholic solvent, and that overcomes these limitations and broadens the scope of this process.

The typical catalyst system is formed from a 1 : 1 combination of diethylzinc and commercially available *N*,*N*'-dibenzylethylenediamine (dbea). With this system, most conveniently generated *in situ* (*vide infra*), a large range of ketones and imines are chemoselectively reduced at room temperature in methanol to the corresponding alcohols and amines in high yields in a one-step procedure (Scheme 1, Table 1). For all the ketones investigated, the reduction in methanol proceeds significantly faster than using the two-step procedure in toluene. For instance, the reduction of acetophenone (**1a**) is completed within 1 h in methanol while only *ca.* 8% conversion is observed in toluene over the same reaction time. Also, the conversion of α-chloroacetophenone (**1b**) in toluene reaches a maximum of 43% after 24 h, but is quantitative within 1 h in methanol. The reaction tolerates a variety of functional groups. In particular, the [Zn–diamine]–PMHS–MeOH system is not active under mild conditions (RT) in the reduction of esters and is thus totally chemoselective for the reduction of C=O towards COOR functions, enabling the valuable conversion of α- and β-keto esters (**1d**–**g**) into α- and β-hydroxy esters (**2d**–**g**). When carried out in toluene, the reduction using the Zn–diamine catalyst is not selective in the case of methyl pyruvate (**1e**) and does not proceed at all in the case of methyl benzoylacetate (**1f**); those substrates are yet fast and chemoselectively reduced with the present catalyst system. Similarly, α- and β-ketoamides (**1h-j**) are reduced into α- and β-hydroxyamides (**2h-j**), which are readily recovered in > 96% yield and high purity from the final reaction mixture, due to their very low solubility in hydrocarbons contrary to the silicon residues.†

Only 1.0 equivalent of PMHS can be used to complete the reduction of some ketones, *e.g.* α,α,α-trifluoroacetophenone (**1c**) and methyl phenylglyoxylate (**1d**). On the other hand, excess PMHS (2–5 equiv.) proved necessary in most cases, in particular for readily enolisable ketones such as **1f**, **1g** and **1i**. In



Scheme 1 One-step reduction of ketones and imines with the [Zn–dbea]–PMHS–MeOH system.

Table 1 One-step reduction of ketones **1a–j** and imines **3a,b** with the [Zn–dbea]–PMHS–MeOH system.[a]

Entry	Substrate	Equivalents of PMHS	Time[b]/h	Yield **2**/**4**[c] (mol %)
1	**1a**	1	1	55
2	**1a**	2	1	99 (86)
3	**1b**	2	1	99
4	**1c**	1	1	99
5	**1d**	1	1	99 (67)
6	**1e**	2	1	99
7	**1f**	2	24	50
8	**1f**	5	24	76
9	**1g**	2	6	68
10	**1g**	5	1	99
11	**1h**	2	1	99 (98)
12	**1i**	2	1	70
13	**1i**	5	1	99
14	**1j**	1	1	75
15	**1j**	2	1	99 (96)
16	**3a**	2	18	99
17	**3b**	2	24	65
18	**3b**	4	24	99 (91)

[a] *General conditions*: **1** or **3**–$ZnEt_2$–dbea = 2.75 : 0.055 : 0.055 mmol in methanol–toluene (80:20 v/v, 2.5 mL), T = 20 °C. [b] Reaction time was not necessarily optimised. [c] Yield of **2** and **4** as determined by quantitative GLC (BPX 5 column) and ^{1}H NMR; no side product was formed; data into parentheses refer to isolated yields of spectroscopically pure products.

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the same vein, some imines, such as **3a**, are readily reducible using a slight excess of PMHS while others, *e.g.* **3b**, require a larger amount to go to completion. Two explanations account for the consumption of extra equivalents of PMHS: (i) the [Zn–dbea]–PMHS system is still moderately active for the dehydrogenative silylation of MeOH and the overall efficiency of the process depends on the relative kinetics for C=O (C=N) reduction *vs.* MeOH silylation; (ii) possibly, the catalyst system is also operative for the dehydrogenative silylation of the enol tautomer of ketones to give an enol-silyl ether (not observed by NMR) that would hydrolyse back in methanol to the free enol/ketone. Molecular hydrosilanes such as $PhSiH_3$, Ph_2SiH_2, Et_2SiH_2, can be equally used but are not as convenient as PMHS due to their higher sensitivity and price.

So far, methanol has been found the most suitable protic solvent for this system. Generally, reduction of the ethyl analogues of **1d**–**g** performed in ethanol was found to be somewhat less selective and more sluggish compared to experiments conducted in MeOH. An exception to this trend concerns aromatic α-ketoesters; *i.e.*, reduction of ethyl phenylglyoxylate in ethanol to ethyl mandelate proceeds quantitatively within 1 h under typical conditions (Table 1).[6] Though experiments were routinely carried out using 2.0 mol% of catalyst precursors, reduction of ketoester **1d** using as low as 0.5 mol% of [Zn–dbea] is completed within 75 min. $ZnEt_2$, which alone has no catalytic activity, may also act as a scavenger;[3] then, a substoichiometric amount of dbea, as low as 0.2 mol%, suffices to activate the 1 mol% of $ZnEt_2$ used (total conversion of **1d** within 2 h).

Preliminary mechanistic investigations have shown that $ZnEt_2$ and dbea react rapidly (< 15 min) at 20 °C in toluene solution to give a single complex, $[EtZnNBn(C_2H_4)NHBn]_2$ (**I**), which has been formally characterized by elemental analysis, NMR[4] and a single crystal X-ray diffraction study‡ (Fig. 1). Such ready formation of a dimeric alkyl(amino-μ-amido) Zn complex, with concomitant release of ethane, was unexpected considering the relatively harsh conditions (60–70 °C, 3–5 h) required for preparing analogous complexes, *e.g.* $[RZnNMe(CH_2)_nNMe_2]_2$ (R = H, Me, Et; n = 2, 3),[5] and that *N*,*N*′-ethylenebis(1-phenylethylamine) (ebpe) reacts with ZnR_2 (R = Me, Et) to form stable adducts ZnR_2(ebpe).[3] Dimer **I** is only a catalyst precursor, which transforms rapidly in the presence of MeOH, ketone substrate and hydrosilane into mixtures of complexes that have not been formally identified so far.

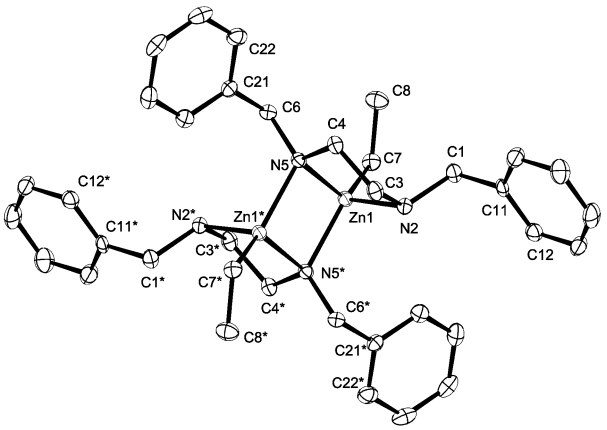

Fig. 1 Structure of catalyst precursor **I**. All hydrogen atoms have been omitted for clarity.

In conclusion, we have developed an alternative, simple and cost-effective procedure that allows the chemoselective reduction of a variety of carbonyl and imine compounds. Current efforts are directed towards mechanistic issues to rationalize the effectiveness of the diamine-modified system in protic solvents and the development of an efficient enantioselective version of this system with chiral diamines for the reduction of functionalised ketones and imines.

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Notes and references

† In a typical experiment (entry 11), to a solution of dbea (13.2 mg, 0.055 mmol) in freshly distilled toluene (0.5 mL) under nitrogen, were successively added $ZnEt_2$ (50 μL of a 1.1 M solution in toluene, 0.055 mmol), a solution of **1h** (657 mg, 2.75 mmol) in MeOH (2.0 mL), and finally PMHS (0.32 mL, 5.0 mmol). The resulting solution was stirred with a magnetic stir bar and the reaction was monitored by GLC. After completion of the reaction, volatiles were removed under vacuum to give a white oil which was triturated with pentane (2.0 mL). The resulting precipitate was separated off from the liquid phase, washed with a minimal amount of pentane, and dried under vacuum to give expected hydroxyamide **2h** as a spectroscopically pure white powder (650 mg, 98%).

‡ *Crystal data* for zinc complex **I**: $C_{36}H_{48}N_4Zn_2$, M = 667.52, orthorhombic, *Pbca* (no. 61), a = 8.6479(4), b = 19.4712(9), c = 19.5345(9) Å, V = 3289.3(3) Å^3, T = 100 K, Z = 4, μ(Mo-Kα) = 1.489 mm^{-1}, D_c = 1.348 g cm^{-3}, 34336 reflections measured, 6259 independent (R_{int} = 0.0901), F^2 refinement, R_1 = 0.0535, wR_2 = 0.0889, 3713 independent observed reflections [$I > 2\sigma(I)$], 195 parameters. CCDC reference number 195656. See http://www.rsc.org/suppdata/cc/b2/b210144k/ for crystallographic data in CIF or other electronic format.

1 For a review on PMHS, see: (*a*) N. J. Lawrence, M. D. Drew and S. M. Bushell, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3381–3391; for a recent review on metal-catalyzed hydrosilylation of ketones and imines, see (*b*) J.-F. Carpentier and V. Bette, *Curr. Org. Chem.*, 2002, **6**, 913–936; (*c*) M. T. Reding and S. L. Buchwald, *J. Org. Chem.*, 1995, **60**, 7884–7890; (*d*) Y. Kobayshi, E. Takahisa, M. Nakano and K. Watatani, *Tetrahedron*, 1997, **53**, 1627–1634; (*e*) M. D. Drew, N. J. Lawrence, D. Fontaine and L. Sehkri, *Synlett*, 1997, 989–991; (*f*) M. D. Drew, N. J. Lawrence, W. Watson and S. A. Bowles, *Tetrahedron Lett.*, 1997, **38**, 5857–5860; (*g*) X. Verdaguer, M. C. Hansen, S. C. Berk and S. L. Buchwald, *J. Org. Chem.*, 1997, **62**, 8522–8528; (*h*) J. Yun and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 5640–5644; (*i*) N. J. Lawrence and S. M. Bushell, *Tetrahedron Lett.*, 2000, **41**, 4507–4512; M. C. Hansen and S. L. Buchwald, *Org. Lett.*, 2000, **2**, 713–715.

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4 Variable temperature ^{1}H NMR spectroscopy of **I** in toluene-d_8 showed dynamic phenomena with a single species observed on the NMR time scale at 40 °C and two species (6:1 ratio) observed at −40 °C. The relative intensity of these two sets of signals is not affected by a 50% dilution, indicating that this is not a mixture of dimer and monomer but rather of conformers[5c].

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6 Reduction of methyl ketoesters in ethanol and *vice versa* afforded mixtures of methyl and ethyl hydroxyesters due to relatively slow transesterification. No transesterification was observed for the reduction of *tert*-butyl ketoesters conducted in methanol.