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Hydrosilylation

Highly Efficient and Chemoselective Zinc-Catalyzed Hydrosilylation of Esters under Mild Conditions

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Abstract: A mild and highly efficient catalytic hydrosilylation protocol for room-temperature ester reductions has been developed using diethylzinc as the catalyst. The methodology is operationally simple, displays high functional group tolerance and provides for a facile access to a broad range of different alcohols in excellent yields.

Functionalized alcohols play an important role as building blocks in modern organic synthesis, and are therefore frequently employed in academia, the pharmaceutical industry, and in the production of fine chemicals. A significant number of alcohol-containing compounds demonstrate high biological activity, whereby the hydroxy group often plays a significant role for the action of the specific compound. Hence, functionalized alcohols occur frequently in top-selling drugs in the current market (Figure 1).

The chemoselective reduction of esters is a straightforward route towards the formation of functionalized alcohols. Traditional moisture-sensitive aluminum and boron hydride reagents are still widely applied in ester reductions, despite the high hazard and the formation of significant amounts of waste.[1] The use of catalytic pathways are much more attractive from a safety and environmental point of view, and catalytic hydrogenation would be the ideal reduction method. Nevertheless, this method suffers from a number of drawbacks and it generally requires harsh reaction conditions, which sometimes leads to low functional-group tolerance.[2]

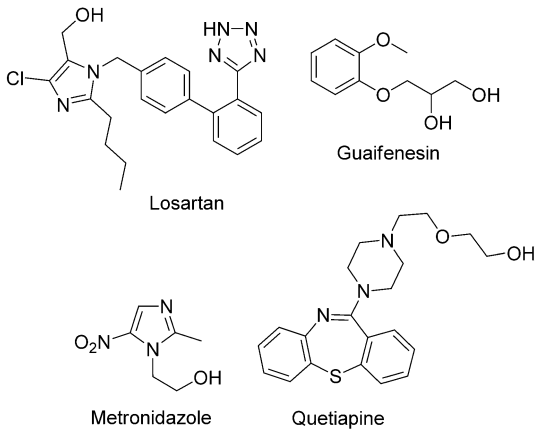

Figure 1. Top selling drugs containing hydroxyl groups.

An attractive alternative method for ester reduction is metal-catalyzed hydrosilylation. It allows for milder reaction conditions, and improved chemoselectivity has been demonstrated in some cases.[3] Catalytic ester hydrosilylation protocols were developed based on a range of different transition metals, such as Ti,[4] Mn,[5] Fe,[6] Mo,[7] V,[7a] Pd,[8] Ru,[9] Rh,[10] Ir,[11] In,[12] B[13] and Zn.[14] Nevertheless, some of these reported catalytic systems display drawbacks in terms of requiring highly toxic and expensive silanes, or show limitations in terms of a narrow substrate scope. The development of an efficient, inexpensive, highly selective, and environmentally benign system is still desirable.[15]

Zinc is vital for many biological functions in humans, animals, and plants, and plays a crucial role in more than 300 enzymes; thus zinc is classified as a biometal.[16] The high abundance of zinc, its low toxicity and moderate price make it a very attractive metal precursor for applications in catalysis.[17] To our knowledge, there are only two reports describing Zn-catalyzed hydrosilylation of esters.[14] These procedures required high reaction temperatures, as well as either catalyst pretreatment or the use of an expensive silane. We have previously reported on efficient Fe-catalyzed hydrosilylations of aldehydes, ketones,[18] and amides.[19] More recently we also demonstrated an organocatalytic method for the reduction of amides to the corresponding enamines, based on *t*BuOK and $(MeO)_3SiH$.[20] In an attempt to expand these methodologies to include hydrosilylation of esters, we screened a number of first-row transition metal complexes for this purpose and found that diethylzinc displayed interesting catalytic properties for this transformation. Herein we present an efficient, mild, and chemoselective catalytic protocol for the reduction of esters to alcohols, using the inexpensive and shelf-stable polymethylhydrosiloxane (PMHS) as the hydride source.[21]

The initial experiments revealed that a series of different zinc organometallic derivatives displayed high catalytic activity for the hydrosilylation of esters. Due to the commercial availability and low cost of diethylzinc (1.0 M solution in hexanes), it was selected for further screening. Isopropyl 2-phenylacetate was chosen as a model substrate for the optimization of the reaction, which was conducted in a 0.5 M THF solution using

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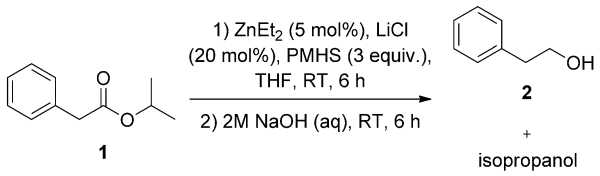
3 equivalents of PMHS as the hydride source. In the initial screening, it was also observed that the presence of LiCl was crucial for the reaction, as, in the absence of LiCl, the reduction did not proceed at all (see the Supporting Information). Furthermore, no ester reduction was observed when the reaction was performed with LiCl present, but without diethylzinc. The optimal amount of LiCl was established to be 20 mol%, and, in combination with 5 mol% of $ZnEt_2$, 2-phenylethanol **2** was obtained in excellent yield (Scheme 1 and Table 1, entry 1).



Scheme 1. Hydrosilylation of isopropyl 2-phenylacetate catalyzed by $ZnEt_2$.

Diethyl ether and toluene were also evaluated as solvents. However, no product formation was observed, which might be due to the poor solubility of LiCl in these solvents.

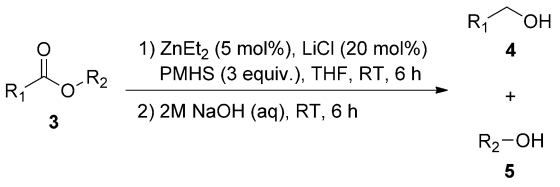
With the optimized conditions in hand, we performed an evaluation of a series of substrates with different functional and protective groups (Table 1). The majority of the investigated reactions afforded the corresponding alcohols in excellent yields, and functional groups such as alkene, alkyne, halide, and nitro groups were all tolerated (Table 1, entries 6, 7, 9, 10, and 17–19). The mild reaction conditions enabled efficient and selective acyl deprotection of an alcohol and the stereocenter of (*R*)-(−)-methyl 2-methoxy-2-phenylacetate was not affected during the reduction (Table 1, entries 11 and 25). Moreover, we demonstrated that the method is applicable for the ring opening of a lactone and the reduction of a tristearate compound, both of which gave the corresponding alcohols in excellent yields (Table 1, entries 21 and 24).

Substrates containing a pyridine moiety or a cyano group were more challenging, and the products were obtained in 80 and 68% yields, respectively (Table 1, entries 20 and 22). A slightly lower reactivity was also seen in the case of the highly sterically hindered substrate methyl 2,2,2-triphenylacetate; the corresponding alcohol was obtained in 90% yield (Table 1, Entry 27).

A few limitations to the $ZnEt_2$-catalyzed hydrosilylation protocol were discovered during the substrate evaluation (Figure 2). Compounds containing acidic protons, such as hydroxyl group (**6**), secondary amide (**7**), and N-Boc protected primary amine (**8**), did not react under these conditions. To further investigate the chemoselectivity of the system, ester compounds containing tertiary amide (**9**) and ketone (**10**) functionalities were screened. Unfortunately, the esters could not be reduced selectively due to the competitive reductive processes of the other carbonyl functionalities and mixtures of products were obtained.

Since we observed reduction of the ketone in the evaluation of compound **10**, we decided to employ the $ZnEt_2$-catalyzed method for the reduction of other carbonyl compounds

Table 1. Substrate evaluation for the reduction of esters catalyzed by $ZnEt_2$.



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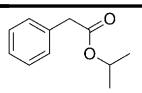
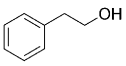
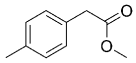
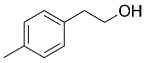
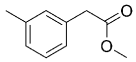
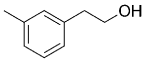
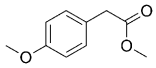
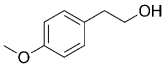
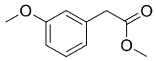
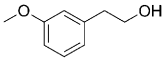
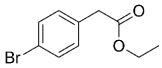
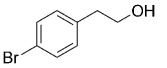
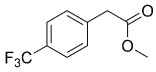
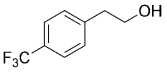
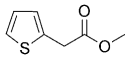
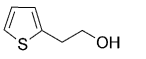
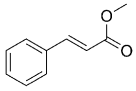
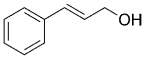
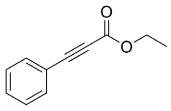
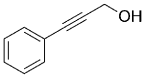
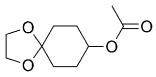
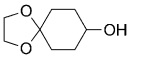
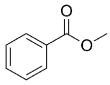
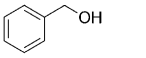
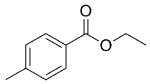
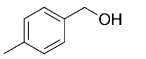
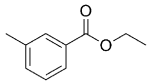
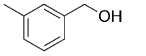
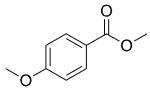
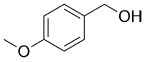
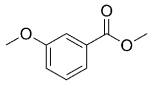
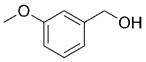
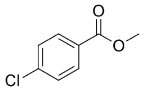
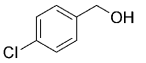
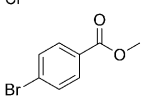
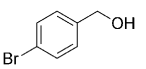
1			98
2			98
3			98
4			98
5			98
6			98
7			98
8			98
9			98
10			98
11			98
12			98
13			98
14			98
15			98
16			98
17			98
18			98

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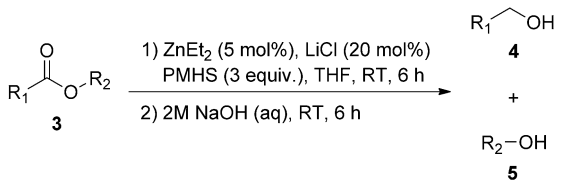

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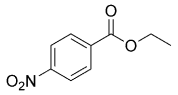
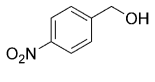
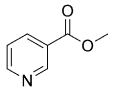
19			97
20			80
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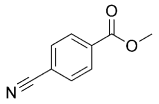
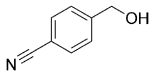
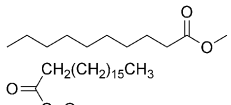
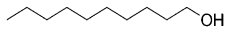
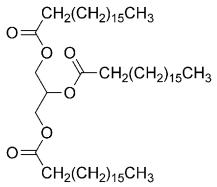
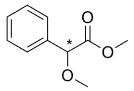
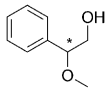
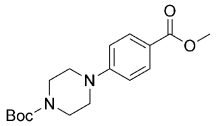
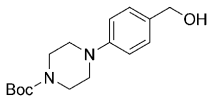
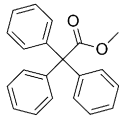
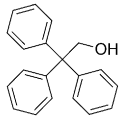
22			68
23			98
24		$CH_3(CH_2)_{16}CH_2OH$	98[c]
25			98 (*ee* 95%)
26			98
27			90[c]

[a] Reaction conditions: $ZnEt_2$ (5 mol%), LiCl (20 mol%), PMHS (3 equiv), THF (2 mL), ester (1.0 mmol), 6 h at RT; [b] yield of isolated product; [c] because of negligible solubility of the ester precursors, the reaction was performed in 4 mL of THF.

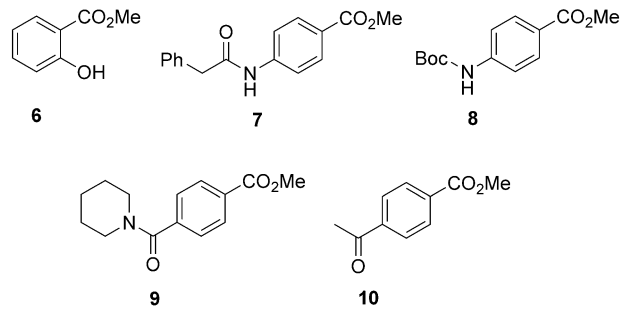
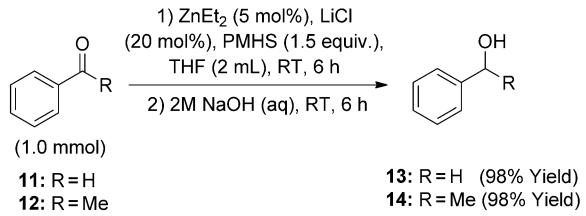


Figure 2. Functional group limitations and investigation of chemoselectivity.

(Scheme 2). Benzaldehyde **11** and acetophenone **12** were efficiently reduced, and the $ZnEt_2$-based catalytic system provided excellent yields of the isolated corresponding alcohols **13** and **14**. The reactions were performed under standard conditions. However, we were able to lower the amount of PMHS to 1.5 equivalents. Amides constitute a most challenging functional group to reduce and, in parallel to this work, we have developed a catalytic protocol based on $ZnEt_2$ for the hydrosilylation of tertiary amides.



Scheme 2. Reduction of aldehydes and ketones catalyzed by $ZnEt_2$.

In conclusion, we have developed a catalytic protocol that is mild, highly efficient and versatile, and serves as a competitive alternative to the traditional stoichiometric aluminum and boron hydride reagents used for the reduction of esters. The herein-presented catalytic system, based on inexpensive and commercially available $ZnEt_2$ in combination with LiCl, displays an impressive tolerance to a wide range of functional groups such as halides, ethers, nitro- and cyano groups, multiple bonds, heterocyclic moieties, acetal and N-Boc protecting groups. The majority of the alcohol products were obtained in excellent yields and the catalytic system allowed for a mild preparative method for acyl deprotection of alcohols, reductive opening of lactones into diols, and reductive hydrolysis of lipids into the corresponding alcohols. Ketones and tertiary amides did not survive under the conditions reported. However, ketone and aldehyde substrates were readily reduced using a decreased amount of PMHS. Although the nature of the active catalyst is currently not clear, further investigations are being pursued.

Experimental Section

General procedure for the catalytic reduction of esters

The corresponding esters (1.0 mmol) were added to a 10 mL vial equipped with a septum and a stirring bar, and the atmosphere was exchanged to argon. Freshly prepared LiCl solution in dry THF (0.1 M, 2.0 mL), $ZnEt_2$ solution in hexanes (1.0 M, 0.05 mL), and PMHS (3.0 equiv, 0.18 mL) were added. The resulting mixture was stirred for 6 h at room temperature. The reaction was then quenched with 2 M aqueous NaOH solution (10 mL), stirred for 8 h, and subsequently extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure (for details, see the Supporting Information).

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The Knut and Alice Wallenberg Foundation, and Swedish Research Council are gratefully acknowledged for financial support. We would also like to thank Dr. Fredrik Tinnis for fruitful discussions while finishing this work.

Keywords: alcohols · esters · hydrosilylation · reduction · zinc

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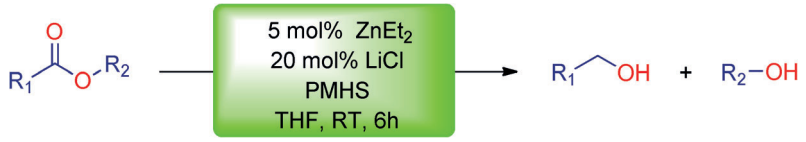

Hydrosilylation

*O. O. Kovalenko, H. Adolfsson**

■■ – ■■

Highly Efficient and Chemoselective Zinc-Catalyzed Hydrosilylation of Esters under Mild Conditions

A mild and highly efficient catalytic hydrosilylation protocol for room-temperature ester reductions has been developed using diethylzinc as the catalyst. The methodology is operationally simple, displays high functional group tolerance and provides for a facile access to a broad range of different alcohols in excellent yields.