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A Lewis acid-promoted reduction of acylsilanes to α -hydroxysilanes by diethylzinc

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ABSTRACT

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Acylsilanes and corresponding α -hydroxysilanes are interesting functional organometallic compounds exhibiting specific chemical properties and reactivities beside the usual ones of carbonyl derivatives, that allow for the generation of many synthetically and pharmaceutically useful compounds.^{1,2} It is noteworthy that the acylsilanes and α -hydroxysilanes function similarly to carbonyl and alcoholic compounds, but the inherent striking differences between carbon and silicon element allow for the chemistry of silicon's own.³ Therefore, acylsilanes and their derivatives have received increasing research interest in organosilicon chemistry and organic synthesis, and have been recognized as important synthons and valuable intermediates in the synthesis of complex molecules via a number of synthetically useful transformations.⁴

During our investigation of a new family of diol ligands, the Ar-BINMOLs, for the asymmetric 1,2-addition of diethylzinc to aldehydes, we observed that the treatment of various aromatic aldehydes afforded chiral secondary alcohols in excellent yields and enantioselectivities (Scheme 1, up to >99.9% *ee*).⁵

Despite many methods reported for the transformations of carbonyl compounds, there are a few based upon bulky silicon-based acylsilanes. In view of the great importance of acylsilanes in synthetic organic chemistry, we are interested in testing the notion that these chiral ligands could be employed for the asymmetric 1,2-addition to acylsilanes with diethylzinc and Grignard reagents



We report here the first example of the reduction of acylsilanes to α -hydroxysilanes, in which diethylzinc

was used as a highly reactive agent in the presence of Ti(OiPr)₄ or other Lewis acids. The reduction typ-

ically proceeds to give synthetically useful α -hydroxysilanes in good yields.

Scheme 1. Asymmetric 1,2-addition of diethylzinc.

as well. Therefore, we first examined the 1,2-addition of diethylzinc to acylsilane **1a** (Scheme 2). When treated with 2 equiv of diethylzinc in the presence of Ti(OiPr)₄ and BINMOL in Et₂O at room temperature for 12 h, no desired adduct **3a** but only reductive product, α -hydroxysilane **2a**, was obtained with completed conversion and in excellent yields (85% isolated yield).

Although transfer hydrogenation and general reduction of acylsilanes are straightforward methods to produce α -hydroxysilanes,⁶ there are very few examples on the reduction of acylsilanes via hydride transfer from organometallic compounds.⁷ On the basis of the above results, we envisioned that the use of diethylzinc as the reducing agent would offer the effective process for the synthesis of α -hydroxysilanes. To the best of our knowledge, there are no





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Scheme 2. 1,2-Addition of diethylzinc to acylsilane.

reports in the literature about the diethylzinc-induced hydride transfer reduction of acylsilanes. Therefore the development of an efficient procedure for the selective hydride transfer reduction of acylsilanes with new organometallic reagents is highly desirable.

Preliminary studies were carried out with the model reaction of (*tert*-butyldimethylsilyl)(phenyl)methanone **1a** and diethylzinc or Grignard reagent. After optimization of the solvent and temperature, this reaction was best carried out in Et₂O as solvent at room temperature, and the yield of α -hydroxysilane reached an excellent 86% isolated yield (Table 1, entry 1).⁸ Interestingly, the Grignard reagent, *i*-PrMgCl, was also effective and gave 40% isolated yield under the same reaction conditions (entry 2).^{6a} Notably, no addition of Ti(OiPr)₄ to this reaction resulted in only moderate yield (56% isolated yield, entry 3), thus the addition of Ti(OiPr)₄ was beneficial to the improvement of the conversion (see Scheme S2, Supplementary data).

Have established a new method to reduce acylsilane to α -hydroxysilane, the reaction of various acylsilanes was examined

Table 1

Ti-catalyzed reduction of acylsilanes in the presence of diethylzinc^a

R ⁴	Si R ³	$\begin{array}{c} \text{Ti}(C)\\ \text{R}^1 & \text{Et}_2 \\ \text{R}^2 & \text{Et} \end{array}$	0/Pr)₄ (1.0 e Zn (2.0 eq.) ′ ₂ O, 12 h, rt	q.) $R^4 \frac{\Gamma}{U}$	OH S ¹ R ³ R ² 2
Entry	\mathbb{R}^1	\mathbb{R}^2	R ³	R^4	Yield ^b (%)
1	Me	Me	t-Bu	Н	2a : 86
2	Me	Me	t-Bu	Н	2a : 40 ^c
3	Me	Me	t-Bu	Н	2a : 56 ^d
4	Me	Me	Me	Н	2b : 78
5	Me	Me	t-Bu	<i>m</i> -F	2c : 75
6	Et	Et	Et	Н	2d: 54
7	Ph	Ph	t-Bu	o-F	2e : 77
8	Ph	Ph	t-Bu	<i>m</i> -F	2f : 71
9	Ph	Ph	t-Bu	p-F	2g : 59
10	Ph	Ph	t-Bu	<i>m</i> -Me	2h : 67
11	Ph	Ph	t-Bu	p-Me	2i : 59
12	Ph	Ph	t-Bu	o-OMe	2j : 61
13	Ph	Ph	<i>t</i> -Bu	<i>m</i> -OMe	2k : 69
14	Ph	Ph	<i>t-</i> Bu	p-OMe	2l : 35(80) ^e

Note:

^a Unless otherwise stated, reactions were conducted using 1.0 mmol of **1**, diethyl zinc (2.0 mmol), and $Ti(Oi-Pr)_4$ (1.0 mmol), in Et₂O (4 mL). And the reactions were run for 12 h at room temperature unless otherwise noted.

^b Isolated yields.

^c *i*-PrMgCl was used as reductant instead of Et₂Zn.

^d No addition of Ti(Oi-Pr)₄.

^e GC yield in parenthesis.

under the optimized conditions (Table 1). As shown in Table 1, the evaluation of substrate scopes revealed that the reduction with both electron-neutral and electron-rich aryl acyl silanes with TMS-, TBS-, and TBDPS-groups proceeded equally well. Notably, the reduction is excellent in completed conversion, simultaneously with almost no by-product, and the somewhat lower yields arise from purification with column chromatography, for example, there are no obvious differences in the conversion of reduction with *para*-methoxyl substituted aromatic acylsilane compared to *ortho*- and *meta*-substituted analogues, however, the stability of the corresponding α -hydroxysilane is different so that the isolated yields were obtained from 35% to 69% (entries 12–14). The major by-products are silanol and benzyl alcohol arising from silical gel-induced desilylation.

Hence, on the basis of the above results, we envisioned that the use of a chiral ligand or an auxiliary would offer the possibility of enantioselective reduction. We first examined the enantioselective reduction with diethylzinc with known BINOL and Ar-BINMOLs⁵ (1.0 equiv) using (*tert*-butyldimethylsilyl)(phenyl)methanone **1a** as the substrate. Unfortunately, although the reduction occurred smoothly in high yields, no enantioselectivity was observed. Other auxiliaries, such as cinchona alkaloids, also gave low levels of enantioselectivity (up to 5% *ee*). In our screening experiments, only **L3** was found to give slight improvement to the promising levels of asymmetric induction (21% *ee*) in the presence of large amount of diethylzinc (Scheme 3).⁹

As Ti(OiPr)₄ has been proved to be an efficient promoter or catalyst for the reduction of acylsilane **1a** in the presence of diethylzinc, we choose a series of Lewis acids to catalyze the reduction of the acylsilane. As shown in Table 2, experimental results showed the reaction of acylsilane **1a** with Et₂Zn in the presence of these Lewis acids gave simply the reduction product **2a** in different yields (25–90%). When the reaction conducted in the presence of catalytic



Scheme 3. Asymmetric reduction of acylsilane 1a in the presence of Ar-BINMOL derivatives (L3).

Table 2	
Lewis acid-catalyzed reduction of acylsilanes in the presence of diethylzinc ^a	

Entry	Lewis acid	Time (h)	Yield ^b (%)
1	YCl ₃	24	90
2	YbCl ₃	24	25
3	LaCl ₃	24	72
4	FeCl ₃	24	67
5	Ni(OAc) ₂	24	83
6	RhCl ₃	24	29
7	RhCl ₃ (PPh ₃) ₂	24	51
8	RuCl ₃	24	45
9	$Al(OiPr)_3$	10	90

Note:

^a Unless otherwise stated, reactions were conducted using 1.0 mmol of **1a**, diethyl zinc (2.0 mmol), and Lewis acid (0.1 mmol, 10 mol %), in Et_2O (4 mL).

^b Isolated yields.



Figure 1. Proposed transition state in the reduction.

amount of YCl₃, Ni(OAc)₂, or Al(OiPr)₃, the corresponding α -hydroxysilane **2a** was obtained in excellent isolated yields (entries 1, 5, and 9). In the treatment of acylsilane **1a** with Et₂Zn in the presence of YbCl₃ and RhCl₃, poor yields were observed. From these studies, it was clear that some Lewis acids showed effective catalytic activity in the hydride transfer reduction of acylsilane with diethylzinc. Encouraged by these results, we examined the enantioselective reduction of acylsilane (**1a**) was used as model substrate and cinchona alkaloids as chiral ligands. However, only Ni(OAc)₂ gave only 6% *ee*¹⁰ in the presence of cinchonine (110 mol %).

Although the mechanism of the reduction with Et_2Zn is unclear at present, it could be interpreted probably as being the result of a H-transfer process via a six-membered transition state (Fig. 1).^{7a} The current model for the reduction of acylsilane involves the coordination of the carbonyl moiety in the molecule to metal center/ zinc and subsequent β -hydride shift and extrusion of ethylene.

In conclusion, we report here the first example of the reduction of acylsilanes to α -hydroxysilanes, in which diethylzinc was used as a reducing agent in the presence of Ti(OiPr)₄ or other Lewis acids. The reduction typically proceeds in good yields. Further research on the asymmetric reduction with organozinc compounds is currently under way in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.059.

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- 8. General procedure for reduction of acylsilane **1a** to α -hydroxysilane **2a**: Under dry nitrogen atmosphere, Ti(OiPr)₄ (1.0 mmol) and 2.0 mmol of Et₂Zn (1.0 M solution in hexane) were mixed in 4 mL of Et₂O at room temperature. After 10 min, acylsilane **1a** (1.0 mmol) was added and then the reaction was carried out at room temperature for 12 h. The reaction was quenched with 1 N HCl. The aqueous phase was extracted with ethyl acetate, dried over Na₂SO₄, filtered, and concentrated. The product was known (e.g., see: Ref. 6k) and purified by chromatography (86% isolated yield was obtained).
- 9. 4.0 or 2.0 equiv of Et₂Zn resulted in poor conversion.
- 10. Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H column). When 1 equiv of cinchonine (CN) was chiral auxiliary, 6% ee of α -hydroxysilane **2a** was obtained. And other cinchona alkaloids (CD, QN, QD) resulted in poorer enantioselectivities. When *N*-(2-amino-1,2-diphenylethyl)-4-methylbenzenesulfonamide (Ts-DPEN) was used as a ligand, only 4% ee was observed in this reaction.