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The Asymmetric Reduction Of Ketones Using Chiral Ammonium Fluoride Salts And Silanes

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Abstract: Acetophenone and substituted arylalkyl ketones are reduced with moderate to good enantioselectivity by silanes bearing alkoxyl or siloxy groups and chiral ammonium fluoride salts derived from cinchona alkaloids.

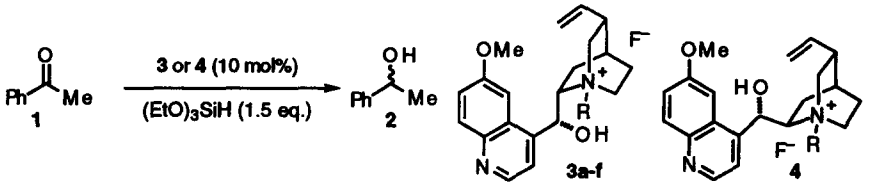
As part of an ongoing programme, we have been developing catalysts for the reduction of carbonyl compounds with silanes bearing alkoxyl or siloxy groups. The ultimate aim of the research being the development of an asymmetric catalyst capable of effecting enantioselective hydride transfer from polymethylhydrosiloxane (PMHS) to prochiral ketones. (PMHS){Me_3SiO–[$(CH_3)HSiO]_nSiMe_3$} is a cheap, commercially available non-toxic silane making it an attractive reducing reagent for organic synthesis.[1] We[2] and Buchwald[3] recently described the efficient reduction of esters to alcohols with PMHS in the presence of titanium(IV) isopropoxide or zirconium alkoxides. This type of process has recently been rendered asymmetric by the use of titanium(IV) isopropoxide modified with enantiomerically pure 1,1'-bi-2-naphthol; in the best case acetophenone was reduced with triethoxysilane, and (*R*)-BINOL-Ti(O^iPr)$_2$ as the catalyst, with moderate enantioselectivity (e.e. 55%).[4] Similar results were obtained with titanium catalysts bearing chiral amine and alcohol ligands.[5] Although we too have pursued the use of titanium catalysts we have also investigated the use of nucleophilic catalysis to promote the reduction of ketones with PMHS.[6] The asymmetric modification of such processes has proved fruitful and we report our initial findings herein.

The use of nucleophilic catalysts for the reduction of carbonyl compounds with PMHS and alkoxysilanes has been pioneered by Corriu and co-workers. They have shown that various metal fluoride or alkoxide salts are capable of promoting the efficient hydrosilylation of ketones.[7] In related papers the use of alkoxides in combination with triethoxysilane has been studied by the groups of Hosomi[8,9] and Izumi.[10,11] Although these processes have been made asymmetric, the catalyst loading is high and the enantioselectivity only modest.

As part of our studies on the reduction of carbonyl compounds with PMHS and other alkoxysilanes, we found that tetrabutylammonium fluoride (TBAF)(0.001 mol%) is a remarkable homogeneous catalyst for the hydrosilylation of ketones. This use of PMHS/TBAF reagent for the reduction of selected ketones has also recently been reported by Kobayashi *et al.*[12] The asymmetric modification of this process by the use of a chiral fluoride catalyst was attractive particularly since this approach had successfully been used for the asymmetric

trifluoromethylation of aldehydes.[13] The catalyst used in this process, *N*-benzylcinchononium fluoride **6** has also been used to promote the reaction between silylenol ethers and aldehydes.[14]

We prepared the *N*-benzylquininium fluoride **3a**, by treatment of commercial *N*-benzylquininium chloride with Amberlyst A-26 (OH^- form) followed by treatment with 1N HF and evaporation of the solvent. The reduction of acetophenone **1** with trimethoxysilane and **3a** (10 mol%) at room temperature was moderately selective, giving (*R*)-phenethyl alcohol as the major product (scheme 1, table 1). A series of fluoride salts **3b-f** were also made by quaternization of the quinuclidine nitrogen atom with the appropriate alkyl halide, followed by halogen exchange, as above. The results in table 1 clearly illustrate that the enantioselectivity in the hydrosilylation reaction is very strongly dependent upon the R group. It is gratifying to note that the selectivity observed with **3a**, prepared from commercially available *N*-benzylquinidinium chloride, is only slightly lower than the best in the quinine series (obtained with **3f**). The pseudo-enantiomeric fluoride salt **4** prepared from quinidine gave the product alcohol with the opposite configuration to that obtained with **3a**. When a fluoride salt was prepared from cinchonine (**3a** lacking the methoxyl group) the reaction showed no enantioselectivity. THF was the best solvent when **3a** was used as the catalyst (enantioselectivities in the reaction **1** → **2**; THF, 51%; 1,2-dimethoxyethane, 51%; diethyl ether, 44%; toluene, 40%; 1,4-dioxane, 36%; dichloromethane 16%). The effect of temperature on the enantioselectivity of the reaction is not dramatic. At lower temperatures (-78 °C) we found the reactions to be too slow to be useful. However, in these cases where low conversions were observed the enantioselectivity was also lower (e.g. for **1** → **2**; 9% conversion after 4 h, 32 % e.e). The best stereoselectivity was observed for reactions performed at room temperature.



Scheme 1

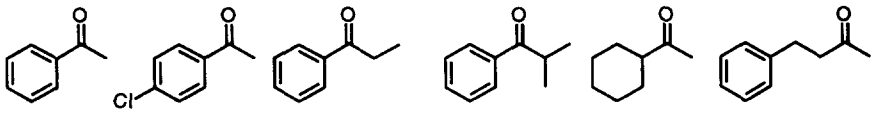
Table 1: Enantioselectivities in the reduction of acetophenone **1** with $(CH_3O)_3SiH$ and chiral fluoride catalysts **3** and **4**.

F⁻ salt	R	Yield (%)	e.e. (%)
3a	Benzyl	100	51 (*R*)
3b	4-^{t}BuC$_6$H$_4$CH$_2$	72	0
3c	Me	86	36 (*R*)
3d	4-CF$_3$C$_6$H$_4$CH$_2$	100	5 (*R*)
3e	3-CF$_3$C$_6$H$_4$CH$_2$	90	39 (*R*)
3f	4-NO$_2$C$_6$H$_4$CH$_2$	100	53 (*R*)
4	Benzyl	100	62 (*S*)

The enantiomeric excess was determined by gas chromatography using a Chiraldex G-TA column; the absolute configuration of the major product was confirmed by comparison with the retention times of commercial (Lancaster) (*R*) and (*S*)-phenethyl alcohol.

We next examined the selectivity in the *N*-benzylquininium fluoride **3a** catalysed trimethoxysilane reduction of other ketones (scheme 2). It is clear that the enantioselectivity is slightly improved when the methyl group of acetophenone is replaced by a larger group i.e. e.e's of 65% are obtained in the reduction of propiophenone and isobutyrophenone. It seems that the presence of an aryl group adjacent to the carbonyl group is necessary for

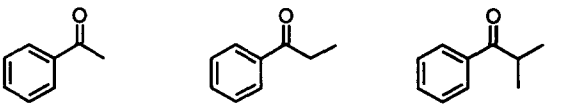
good enantioselection. There is a marked decrease in enantioselectivity in the reduction of cyclohexyl methyl ketone and 1-phenylbutan-3-one. This perhaps indicates that the stereoselectivity is derived from an interaction between the chiral cation and the ketone involving the aryl group.



51%	35%	65%	65%	11%	11%
(*R*)(94%)	(*R*)(68%)	(*R*)(83%)	(*R*)(86%)	(*R*)(68%)	(*R*)(97%)

Scheme 2 : Enantioselectivities‡ in the reaction with trimethoxysilane (1.5 eq.) and **3a** (10 mol%). Total yields and the absolute configuration of the major product are given in parenthesis. ‡ The enantiomeric excess of the alcohols or their acetates was determined by gas chromatography using a Chiraldex G-TA column.

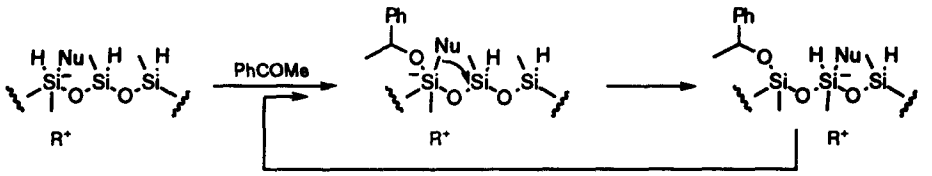
When the silane was changed from trimethoxysilane to tris(trimethylsiloxy)silane (Aldrich) there was a significant increase in enantioselectivity (scheme 3). This enhancement is presumably due the larger size of the silane. The reactions were however significantly slower with this silane, generally taking 28 hours for completion. The reactions with trimethoxysilane were normally complete within 8 h.



$(MeO)_3SiH$	**51%** (94%)	**[62%** (89%)]	**65%** (83%)	**65%** (88%)
$(Me_3SiO)_3SiH$	**65%** (78%)	**[78%** (99%)]	**71%** (81%)	**71%** (81%)
PMHS	**28%** (98%)	**[26%** (89%)]	**36%** (91%)	**36%** (91%)

Scheme 3 : Enantioselectivities in the reaction with different silanes (1.5 eq.) and **3a** (10 mol%). The yield (%) is given in parenthesis; in cases where **3a** was used (*R*)-**2** was in excess. As shown in [] parentheses, when **4** was the catalyst (*S*)-**2** was in excess.

When PMHS was used, there was a drop in enantioselectivity for all three ketones. Nevertheless, in these cases we observed an unexpected and phenomenal increased reaction rate. We have also shown that the TBAF catalysed reduction of ketones involving PMHS is much faster than the corresponding reaction involving monomeric silanes. For example, acetophenone is reduced in less than 1 min. using PMHS. However, when the monomeric diethoxymethylsilane is used under identical conditions, the reaction is only 60% complete after one hour. We believe that this impressive rate acceleration is due to the intramolecular 1,3-transfer of nucleophile[15] from the silicate to the adjacent silicon atom, as outlined in scheme 4; a process that is repeated over and over again as the nucleophile travels along the polymer backbone. The corresponding process of nucleophile transfer in an intermolecular sense is presumably much slower. The nucleophile involved in this catalysis may, in principle, be the initial anion from NuR, or the hydride or alkoxide groups present on the polymer backbone. If the product alkoxide is the catalyst its own chirality might influence the stereoselectivity of the hydride transfer to the ketone. However, we showed that this is not an important factor controlling the enantioselectivity of the process. When the lithium salt of (*R*)-phenethyl alcohol (10 mol%) is used as the catalyst in the PMHS reduction of acetophenone the product has an e.e. of only 9%. Clearly the enantioselectivity of the process is governed by the chiral counter-ion. We are currently studying this new process, which we call "zipper" catalysis, in detail.



Scheme 4 : Proposed mechanism of nucleophile-promoted "zipper catalysis".

We have also found that *N*-benzylquininium hydroxide is equally as good as **3a** for promoting the asymmetric reduction of ketones. For example acetophenone is reduced with trimethoxysilane, tris(trimethylsiloxy)silane and PMHS (1.5 eq.) and the chiral hydroxide salt (10 mol%) with e.e.'s of 46%, 65% and 25% respectively. This is significant as the fluoride salts are actually prepared from their corresponding hydroxide salts.

In summary, we have shown that the asymmetric hydrosilylation of ketones can be achieved in a new process with moderate to good enantioselectivity using chiral fluoride salts.

Standard procedure: To a stirred mixture of ester/ketone/aldehyde (1 mmol) and fluoride salt **3** or **4**† (0.02 mmol) in dry tetrahydrofuran (2 ml) was added the silane (1.5 mmol). The mixture was stirred at room temperature until the reaction was complete (by t.l.c.). Sodium hydroxide (5 ml of a 3N solution) was added dropwise. After stirring vigorously overnight the solution was extracted with diethyl ether (3 × 15 ml). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2) or distillation if necessary.

† Salts **3** and **4** were prepared according to reference 14, and used immediately without purification.

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15 The nucleophile involved in the "zipper" catalysis may, in principle, be the initial anion from NuR, or the hydride or alkoxide groups present on the polymer backbone. The intramolecular transfer need not be to the adjacent silicon atom. It is possible that 1,5- or indeed other types of intramolecular transfer are operating.

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