INTRODUCTION

The asymmetric reduction of prochiral ketones is one of the most important, fundamental and practical reactions for producing non-racemic chiral alcohols, from which many industrially important chemicals such as pharmaceuticals, agrochemicals, and natural products. Asymmetric transformations invariably involve the conversion of two dimensional substrate into a three dimensional product. For prochiral ketones such as acetophenone reduction shown in scheme-1, addition to the back face gives 1-phenyl alcohol with R configuration, while addition to the back face gives alcohol with S configuration.

The problem, of course is that most common reducing agents, such as sodium borohydride or lithium aluminium hydride, react equally readily with either face. The most obvious solution to this problem is to use a hydride source which is itself enantiomerically pure in principal such as reagent will transfer the hydride to each face of the ketone through diastereoisomerically distinct transition state, which gives at least a fighting chance of an energy difference, and preference for addition to one face over the other.

The catalysts for the asymmetric reduction of ketones can be classified into two categories: chemical and biological methodologies. Presently, there are five chemical reagents which are extensively used in asymmetric reduction: Brown's DIP-chloride, Midland's Alpin-Borane, Corey's oxazaborolidines, Nyori's BINAL-H and BINAP-Ru complexes. In 1999, L. Sekhri and N. J. Lawrence utilized Corey's oxazaborilidine to obtain excellent yield and enantioselectivities for a variety of diphenylphosphinoyl alcohols. The biological catalysts used for these asymmetric reductions, isolated enzymes, microbes such as yeast and fungi, and plant cell cultures have also been used. Another category of biocatalyst backer's yeast, and vegetables, germinated plant has been applied to organic synthesis because these biocatalysts are easily obtainable from markets and...
easily manipulated by organic chemistry. In the other hand, Corriu and Co-workers have shown in 1980's that esters may be reduced with PMHS by fluoride or alkoxide-induced hydrosilylation20. They have also published several papers describing the related potassium and cesium fluoride catalysed triethoxysilane reduction of esters21-24.

Recently, N. J. Lawrence and Co-workers described the efficient reduction of esters to alcohols with polymethylhydrosiloxane (PMHS) (Me₃SiO[(CH₃)HSiO]ₙSiMe₃) in the presence of titanium (IV) isopropoxide or zirconium alkoxide25. This was followed by the description of the use of PMHS and catalytic fluoride26. More recently, L. Sekhri and Co-workers27 extend this method to reduce several aminoacids to the corresponding aminoalcohols with polymethylhydrosiloxane, PMHS, in the presence of catalytic tetrabutylammonium fluoride, TBAF.

We now report that the same transformation can be achieved but this time with PMHS and catalytic fluoride and biocatalyst baker’s yeast.

RESULTS AND DISCUSSION

The strategy we have adopted for this asymmetric reduction consists of the following steps:

It was, therefore decided to test whether the prochiral ketones could undergo the asymmetric reduction with baker’s yeast in the absence of TBAF and PMHS. Therefore the reaction was unsuccessful and unchanged ketone was recovered (100%).

The reaction was carried out on the same scale using TBAF and PMHS in the absence of baker’s yeast; the prochiral ketones were reduced in less than 1 min. with racemisation.

The reaction was repeated again on the same scale but using this time baker’s yeast with TBAF and PMHS, the reaction was completed after 3 min. (by t.l.c, silica, hexane/diethyl ether, 5:1 disappearance of ketone). High enantioselectivity is observed in the reduction of several aromatic ketones, in particular nitro, chloro, fluoro, methylacetoephonones.

This can be interpreted, in terms of the necessity of hydrogen sources such as TBAF and PMHS to perform the asymmetric reduction.

Our protocol has several advantages since PMHS is cheap and baker’s yeast is easily obtainable from markets and easily manipulated by organic chemistry. The protocol is an efficient method for the convenient reduction of prochiral aromatic ketones such as 1a, 1b, 1c, 1d and 1e to the corresponding (R)-alcohols with > 80% yield and good enantioselectivities (up to 70% ee) (Scheme-2).

Cyclic ketones are also reduced with high levels of stereoselectivity with PMHS in the presence of TBAF and baker’s yeast, in particular 4-methylcyclohexanone (trans: cis 84:16) (Scheme-3).

High stereoselectivity is also observed in the reduction of 2-cyanobenzaldehyde and anti-imine was obtained in 71% as shown in (Scheme-4):

In summary, we have shown that polymethylhydrosiloxane in combination with catalytic TBAF is an excellent reducing agent for the mild reduction of aminoacids.

EXPERIMENTAL

All 300 MHz ¹H and 75 MHz ¹³C NMR spectra were run on a Bruker AC 200 NMR spectrometer. Both ¹H NMR ¹³C spectra were recorded using CHCl₃ as internal standard.

Standard procedure

Three-necked round bottomed flask was fitted with magnetic stirrer bar, a reflux condenser, and an addition funnel. The flask was then charged with a mixture of prochiral ketone (1 mmol) and bread yeast (1g) tetrabutylammonium fluoride (0.02 mmol) in dry tetrahydrofuran (10 ml). The remaining neck was sealed with a septum and nitrogen line attached. A solution of polymethylhydrosiloxane (1.5 mmol) in 10 ml of THF was poured into the addition funnel and added dropwise over 30 min resulting in vigorous evolution of hydrogen. After addition of polymethylhydrosiloxane was completed and gas
Scheme 1.

\[ \text{Me Ph} \begin{array}{c} \text{H} \\ \text{add hydrogen to front face} \end{array} \begin{array}{c} \text{Me Ph} \\ \text{add hydrogen to back face} \end{array} \text{HO} \]

\text{S-configuratin} \quad \text{Acetophenone} \quad \text{R-configuration}

\text{Scheme 2.}

\[ \begin{array}{c} \text{CH}_3 \\ \text{1. PMHS, TBAF (cat.) and Baker's yeast} \\ \text{2. NaOH, H}_2\text{O} \end{array} \]

\begin{align*}
&\text{R} \\
&\text{1a (R= 4-H)} \\
&\text{1b (R = Cl)} \\
&\text{1c (R = NO}_2\text{)} \\
&\text{1d (R = 4-Me)} \\
&\text{1e (R = 4-F)} \\
&\text{2a (R = 4-H)} \\
&\text{2b (R = Cl)} \\
&\text{2c (R = NO}_2\text{)} \\
&\text{2d (R = 4-Me)} \\
&\text{2e (R = 4-F)}
\end{align*}

\text{Scheme 3.}

\[ \begin{array}{c} \text{Me} \\ \text{PMHS, TBAF (cat.) and Baker's yeast} \\ \text{NaOH} \end{array} \]

\[ \begin{array}{c} \text{Me} \\ \text{3a} \end{array} \]

\[ \begin{array}{c} \text{Me} \\ \text{OH} \end{array} \text{trans (87%) } + \text{ cis (13%) } \]

\[ \begin{array}{c} \text{Me} \\ \text{3b: trans (87%)} \\
\text{Me} \\
\text{3c: cis (13%)} \end{array} \]

\[ \begin{array}{c} \text{Me} \\ \text{4a} \end{array} \]

\[ \begin{array}{c} \text{Me} \\ \text{OH} \end{array} \text{trans (80%) } + \text{ cis (20%) } \]

\[ \begin{array}{c} \text{Me} \\
\text{4b: cis (20%)} \end{array} \]
evolution had ceased, the reaction was completed after 3 min. (by TLC, silica, hexane/diethyl ether, 5:1 disappearance of ketone). The mixture was stirred for further one hour and 3N NaOH (10 ml) was added cautiously until the mixture became clear. After stirring for 4 hours, the combined organic solution was passed through a short pad of Florisil, and the THF was removed by rotavapor and the remaining solution extracted with (3x20ml) ether. The combined organic extracts were washed with water, dried (MgSO₄) and evaporated in vacuo. The residue was purified by chromatography on silica gel (pet. Ether 40-60°C/diethyl ether, 4:2) or distillation if necessary. Typical pure yield after purification is (54%). The alcohols 2a, 2b, 2c and 2d are identified by the following spectroscopic data:

**p-Phenylethanol 2a**  
(83% yield); ¹H (CDCl₃, 300 MHz): δ (ppm): 1.4 (3H, d, CH₃CHOH-), 3.0 (1H, br. s, OH), 4.8 (1H, q, -CHOH), 7.1-7.3 (5H, m, Ar-H).

**4-Chlorophenylethanol 2b**  
(96% yield); ¹H (CDCl₃, 300 MHz): δ (ppm): 1.3 (3H, d, CH₃CHOH-), 3.5 (1H, br.s, OH), 4.7 (1H, q, -CHOH), 7.0-7.3 (4H, m, Ar-H); ¹³C (CDCl₃, 75MHz): δ (ppm) = 28.03 (CH₃CHOH), 69.54 (-CHOH), 126.93 (CH, Ar), 128.25 (CH, Ar), 132.94 (C, Ar), 144.44 (C, Ar).

**4-Nitrophenylethanol 2c**  
(90% yield); ¹H (CDCl₃, 300 MHz): δ (ppm): 1.4 (3H, d, CH₃CHOH-), 2.6 (1H, br.s, OH), 4.9 (1H, q, -CHOH), 7.4 (2H, d, Ar-H), 8.1 (2H, d, Ar-H); ¹³C (CDCl₃, 75MHz): δ (ppm) = 25.27 (CH₃CHOH), 69.27 (-CHOH), 123.56 (CH, Ar), 126.04 (CH, Ar), 146.86 (C, Ar), 153.28 (C, Ar).

**p-Tolylethanol 2d**  
(92% yield). ¹H (CDCl₃, 300 MHz): δ (ppm): 1.3 (3H, d, CH₃CHOH-), 2.3 (3H, s, 4-CH₃C₆H₄-), 3.0 (1H, br. s, OH), 4.7 (1H, q, -CHOH), 7.0-7.2 (4H, m, Ar-H); ¹³C (CDCl₃, 75MHz): δ (ppm) = 21.22

**Scheme 4.**
(CH₃CHOH⁻), 25.21 (4-CH₃C₆H₄⁻), 20.25 (-CHOH), 125.51 (CH, Ar), 129.25 (CH, Ar), 137.15 (C, Ar).

4-Fluorophenylethanol 2e

(86% yield); ¹H (CDCl₃, 300 MHz): δ (ppm): 1.4 (3H, d, CH₃CHOH⁻), 3.2 (1H, br.s, OH), 4.8 (1H, q, -CHOH), 6.8-7.0 (2H, m, Ar-H), 7.1-7.3 (2H, m, Ar-H).

Trans-2-methylcyclohexanol 3b

(84% yield, 87% trans); ¹H (CDCl₃, 300 MHz): δ (ppm): 0.9 (3H, d, J= 6.4Hz, CH₃), 1.2 (4H, m, -CH₂CH₂-), 1.5 (2H, m, -CH₂-), 2.3 (1H, m, -CHCH₃), 2.6 (1H, br.s, OH), 3.9 (1H, m, -CHOH); ¹³C (CDCl₃, 75MHz): δ (ppm) = 13.99 (CH₃), 20.71 (CH₂), 24.12 (CH₂), 25.54 (CH₂), 28.67 (CH₂), 38.41 (-CHCH₃), 70.94 (-CHOH).

Cis-2-methylcyclohexanol 3c

(84% yield, 13% cis); ¹H (CDCl₃, 300 MHz): δ (ppm): 0.8 (3H, d, J= 6.4Hz, CH₃), 1.0-1.6 (6H, m, -CH₂CH₂CH₂-), 1.8 (1H, m, -CHCH₃), 2.2 (1H, br.s, OH), 3.0 (1H, m, -CHOH); ¹³C (CDCl₃, 75MHz): δ (ppm) = 18.97 (CH₃), 24.27 (CH₂), 25.27 (CH₂), 26.16 (CH₂), 28.86 (CH₂), 33.44 (-CHCH₃), 70.89 (-CHOH).

Trans-3-methylcyclohexanol 4b

(84% yield, 80% trans); ¹H (CDCl₃, 300 MHz): δ (ppm): 0.9 (3H, d, J= 6.4Hz, CH₃), 1.0-1.6 (6H, m, -CH₂CH₂CH₂-), 1.8 (1H, m, -CHCH₃), 2.2 (1H, br.s, OH), 3.0 (1H, m, -CHOH); ¹³C (CDCl₃, 75MHz): δ (ppm) = 18.97 (CH₃), 24.27 (CH₂), 25.27 (CH₂), 26.16 (CH₂), 28.86 (CH₂), 33.44 (-CHCH₃), 70.89 (-CHOH).

Cis-3-methylcyclohexanol 4c

(84% yield, 20% cis); ¹H (CDCl₃, 300 MHz): δ (ppm): 0.8 (3H, d, J= 6.4Hz, CH₃), 1.1-1.6 (6H, m, -CH₂CH₂CH₂-), 2.3 (1H, m, -CHCH₃), 3.2 (1H, br.s, OH), 3.6 (1H, m, -CHOH); ¹³C (CDCl₃, 75MHz): δ (ppm) = 16.64 (CH₃), 20.80 (CH₂), 25.29 (CH₂), 28.68 (CH₂), 30.22 (CH₂), 33.66 (-CHCH₃), 76.38 (-CHOH).

Imine (anti) 4b

85% yield (71% anti); ¹H (CDCl₃, 300 MHz):
δ (ppm): 4.7 (2H, s, CH₂), 6.4 (1H, br.s, NH), 7.1-7.4 (3H, m, Ar-H), 7.5 (1H, d, Ar-H); ¹³C (CDCl₃, 75MHz): δ (ppm) = 61.45 (CH₂), 109.88 (C), 121.55 (CH), 127.10 (CH), 128.45 (CH), 133.12 (CH), 143.90 (C), 169.23 (CN); M/Z (FAB): 134 [M+H⁺]+100, 129 (25), 119 (20), 116 (35), 107 (20), 95 (18), 93 (20), 97 (18), 93 (20), 91 (63), 89 (18).

Imine (syn) 4c

85% yield (29% syn); ¹H (CDCl₃, 300 MHz):
δ (ppm): 5.1 (2H, s, CH₂), 6.4 (1H, br.s, NH), 7.1-7.4 (3H, m, Ar-H), 7.7 (1H, d, Ar-H); ¹³C (CDCl₃, 75MHz): δ (ppm) = 71.62 (CH₂), 117.37 (C), 123.27 (CH), 127.55 (CH), 132.75 (CH), 133.91 (CH), 145.82 (C), 169.23 (CN).

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REFERENCES


