An efficient protocol for the reduction of ketones with tin(II) complexes and PMHS

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Abstract

A mixture of tin(II) triflate/pybox and polymethylhydrosiloxane (PMHS) in methanol effects the efficient reduction of ketones; the use of an enantiomerically pure pybox ligand leads to moderate enantioselectivity. © 2000 Elsevier Science Ltd. All rights reserved.

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Polymethylhydrosiloxane (PMHS) is an attractive reducing reagent for environmentally benign reductive processes because it is inexpensive,[1] non-toxic[2,3] and stable to air and moisture. Such is its importance that we recently highlighted its use as a reducing agent in organic synthesis.[4] PMHS has featured in only a small number of methods for the asymmetric reduction of ketones—a fundamental and important process in organic synthesis. Asymmetric titanium catalysts have been developed by Halterman[5] and Buchwald for the reduction of ketones[6] and imines.[7] We have developed chiral quaternary ammonium fluoride catalysts.[8] Mimoun and co-workers have developed asymmetric zinc complexes.[9] We now report the first example of the enantioselective reduction of ketones using PMHS and an asymmetric tin species. The lack of such a protocol is surprising since tin complexes were the first catalysts to be used with PMHS to reduce ketones.[10,11] The product of these tin-based protocols is an alcohol whereas that of the titanium-, fluoride- and zinc-catalysed reactions is a silyl ether which must be subjected to a separate hydrolysis step, which in some cases can be somewhat extreme.

We chose to investigate a catalyst possessing both a tin–oxygen bond—capable of undergoing σ-bond metathesis with PMHS—and lacking tin-alkyl groups, which generally infer toxicity. Tin(II) triflate emerged as a good candidate. However, tin(II) triflate (200 mol%) alone in methanol with PMHS did not reduce acetophenone even after 48 hours at reflux. This appears an inauspicious start; nevertheless, we were hopeful that ligand accelerated catalysis[12] would prove useful. Reduction of acetophenone, in 98% yield, was achieved with a mixture of PMHS and

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TMEDA (10 mol%)/tin(II) triflate (10 mol%). Since pyridine[13] was also an effective ligand we investigated the use of 2,6-pyridine bis(2′-oxazoline) **1** (pybox).[14] Pybox is an excellent catalyst in combination with tin(II) triflate for the reduction of ketones (Scheme 1 and Table 1).
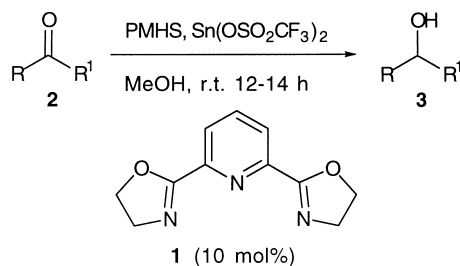
Scheme 1.

Table 1
Reduction of ketones **2** to alcohols **3** with tin(II) triflate (10 mol%)/**1** (10 mol%) and PMHS (200 mol%)

	R	R¹	Yield (%)
a	Ph	Me	98
b	Ph	CO_2Me	99
c	Ph	CO_2Et	99[a]
d	p-MeOC$_6$H$_4$	CO_2Me	99
e	p-MeC$_6$H$_4$	CO_2Me	96
f	p-NO$_2$C$_6$H$_4$	CO_2Me	98
g	1-Napthyl	CO_2Me	98
h	2-Napthyl	CO_2Me	96
i	Ph	CH$_2$-N-Phthalimide	98
j	p-MeOC$_6$H$_4$	CH$_2$-N-Phthalimide	88[c]
k	p-ClC$_6$H$_4$	CH$_2$-N-Phthalimide	89
l	p-NO$_2$C$_6$H$_4$	CH$_2$-N-Phthalimide	50[c]
m	CO_2Et	CF$_3$	75[b]
n	2-Thienyl	CO_2Et	98[b]

a. The ethyl ester was contaminated by the methyl ester **3c**:**3b**, 96:4; **3c** obtained in 99% when the reaction is conducted in ethanol; b. Reaction performed in ethanol; c. Reaction performed by Mr Raheel Ashraf, (MSc. project student, UMIST, 1999).

Acetophenone was reduced to **3a** in excellent yield with **1** (10 mol%)/tin(II) triflate (10 mol%). α-Ketoesters were also selectively reduced to the corresponding α-hydroxyesters in excellent yields. The reduction of ethyl ester **2c** was accompanied by a small amount of transesterification. The formation of the accompanying methyl ester **3b** was prevented by performing the reaction in ethanol. It is noteworthy that the reduction of methyl α-ketoesters by common reducing agents such as sodium borohydride is often complicated by the reduction of the ester group. Thus, the methodology represents a convenient way to reliably prepare α-hydroxyesters from their ketone counterparts. Reduction of α-N-phthalimidylacetophenone **2i** was again chemoselective with no evidence of reaction of the phthalimide group giving the alcohol **3i**. The efficient reduction of phthalimidylacetophenones **2i–l** illustrates that this is a potentially useful way to prepare 1,2-aminoalcohol derivatives from readily available starting materials. The tin residue can be removed simply by filtration of the reaction mixture through a plug of silica gel. This contrasts

nicely with the characteristically difficult removal of trialkyltin residues when tributyltin hydride is used as a reducing agent. We know from our own tests that tin(II) triflate is not cytotoxic (IC_{50} > 50 μM, K562 cell line) whereas Bu_3SnH, as expected, is considerably cytotoxic (IC_{50} < 1 μM).[15]
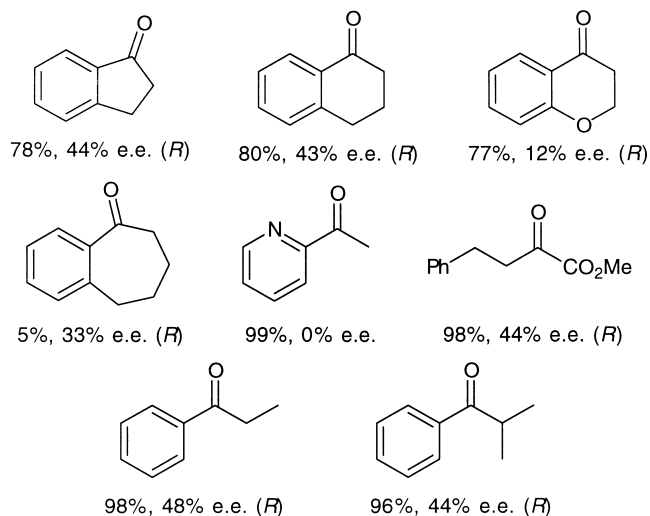
We had chosen to use pybox **1** since it would clearly form the prototype of an asymmetric system. The tin(II)-pybox complex **4**, prepared in dichloromethane using the method described by Evans and co-workers,[16] is a good catalyst for the asymmetric reduction of acetophenone, giving (*S*)-**3a** with moderate enantioselectivity[17] (Scheme 2, Table 2). We subsequently found that it is not necessary to isolate the pybox/tin(II) triflate complex. The components of the reaction mixture can simply be mixed in methanol and asymmetric reduction ensues with no significant change in reaction rate or enantioselectivity. The results using several other substituted pybox ligands, prepared using known methods,[18] are summarised in Table 2. The best result, both in terms of yield and enantioselectivity, was obtained with pybox **5a**. The bulkier ligands **5b** and **5c** gave both poorer conversions and enantioselectivities. The sense of enantioselectivity seems to be determined by the configuration of the chiral centre adjacent to the nitrogen atom of the oxazoline, which is closest to the reaction centre. The enantioselectivity of the system incorporating **5a** in the reduction of a series of other ketones is summarised in Scheme 3. The enantioselectivities of reduction of 1-indanone and α-tetralone are only a little lower than that of acetophenone. However, the reaction is clearly sensitive to the structure of the ketone as revealed by the sluggish reduction of benzosuberone and poor selectivity with 4-chromanone. The conversion of 2-acetylpyridine is high, but the lack of enantioselectivity possibly suggests that the reaction is catalysed by a non-pybox bound tin species.
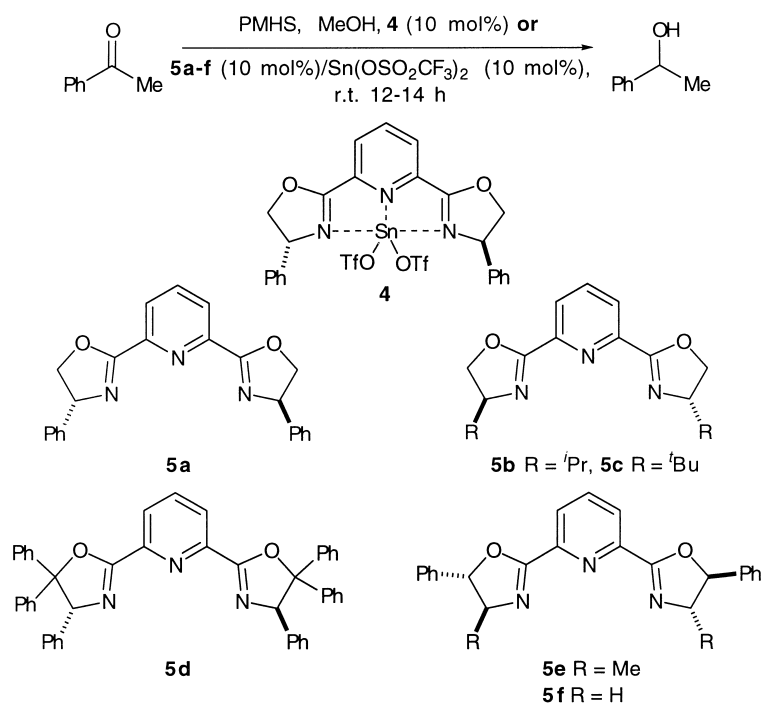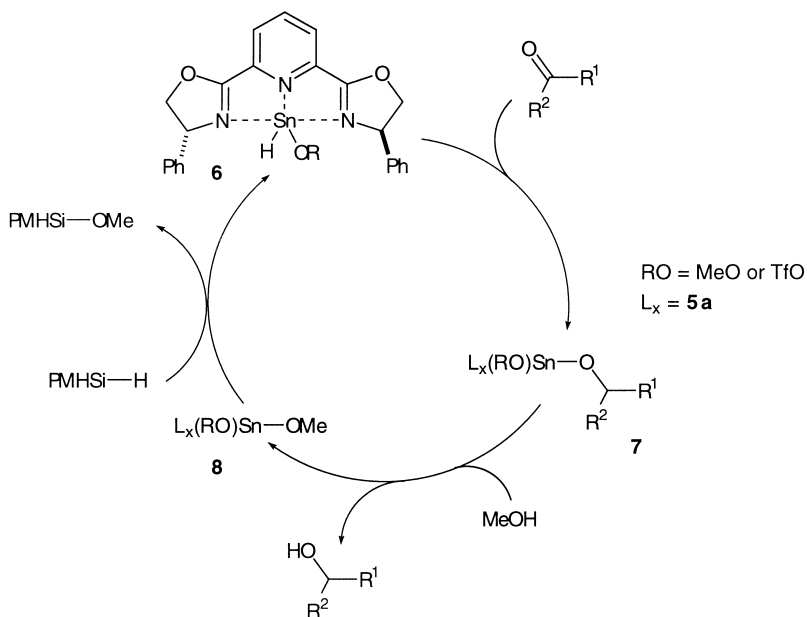

Scheme 2.

Table 2
Reduction of acetophenone to alcohols **3a** with tin(II) triflate
(10 mol%)/**5a**–**f** (10 mol%), and PMHS (200 mol%)

	Conversion (%)	e.e. (%)
a	95	58 (*R*)
b	78	54 (*S*)
c	50	13 (*S*)
d	30	44 (*R*)
e	50	58 (*R*)
f	82	0

78%, 44% e.e. (*R*)   80%, 43% e.e. (*R*)   77%, 12% e.e. (*R*)

5%, 33% e.e. (*R*)   99%, 0% e.e.   98%, 44% e.e. (*R*)

98%, 48% e.e. (*R*)   96%, 44% e.e. (*R*)

Scheme 3. Enantioselectivity in the reduction with PMHS and Sn(OSO$_2$CF$_3$)$_2$ (10 mol%)/**5a** (10 mol%), MeOH, rt, 12–14 h

We propose a reaction cycle similar to those described by Lipowitz and Bowman[11] and Fu and co-workers (Scheme 4).[19] Reduction of the species **8** which possesses a tin–oxygen bond by PMHS to the tin hydride **6** occurs via a known process[20] involving σ-bond metathesis. We believe that it is a hydride such as **6** which reduces the ketone in an ionic fashion, thereby producing the tin oxide **7**. Methanolysis of this species generates the tin methoxide **8** and ensures that the tin hydride is regenerated, since a secondary tin–alkoxy group is not reduced by the PMHS.[21] This appears to be the rate limiting step. We have found that the reaction can be carried out conveniently in a variety of solvents if 2 equivalents of methanol are included as an additive. Methanol for this purpose is better than both ethanol and isopropanol; no reaction is observed in the latter case. We are currently seeking proof that **6**, a rare example of a chiral tin hydride,[22] is indeed the actual reducing agent in the catalytic cycle. The system we describe is broadly related to the method developed by Mukaiyama and co-workers.[23] They found that ketones can be reduced with good enantioselectivity by a reagent prepared from DIBAlH and a chiral diamine such as (*S*)-1-methyl-2-(piperidinomethyl)pyrrolidine. However, the system is not catalytic with respect to the tin species and involves the use of the reactive terminal reducing agent DIBAlH. These drawbacks are not present in our system.

Scheme 4.

In summary, we have found that the combination of tin(II) triflate/pybox is an efficient catalyst for the direct synthesis of alcohols by the PMHS reduction of ketones. Asymmetric modification of the system has led to a conceptually novel way to enantioselectively reduce ketones, which with improvement may prove useful.

General procedure: The pybox ligand (50 μmol) in methanol (0.25 cm^3) is added to a slurry of tin(II) triflate (21 mg, 50 μmol) in dry methanol (0.25 cm^3) under an atmosphere of argon at room temperature. The resulting yellow homogeneous solution is stirred at room temperature for 2 min before sequential addition of the ketone (0.5 mmol) in dry methanol (0.25 cm^3) and PMHS (1 mmol). The resulting mixture is stirred at room temperature until complete (TLC). The solvent is removed in vacuo to yield the alcohol after chromatography or distillation.

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