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Enantioselective Synthesis of α-Hydroxy Thioesters *via* Oxazaborolidine-Mediated Reduction of α-Phenylthio Enones

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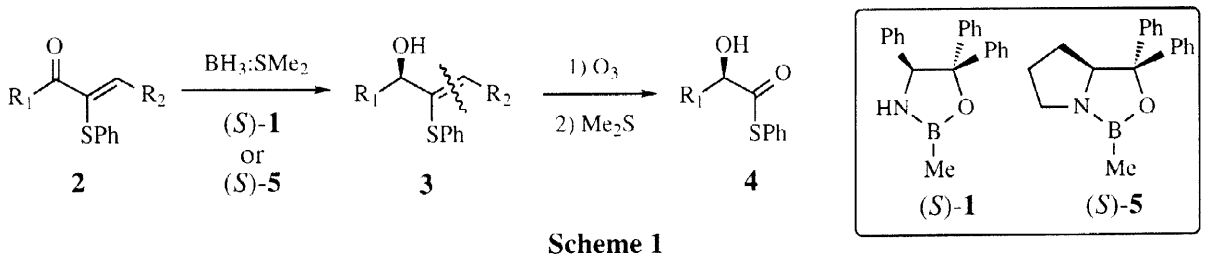
Abstract: α-Phenylthio-α,β-alkenones (**2**), readily available by Pd(II)-catalysed coupling of (*E*)-1-phenylthio-1-tributylstannylhex-1-ene with the corresponding acid chlorides, have been treated with borane in the presence of phenylglycine- or proline-derived oxazaborolidines to afford 2-phenylthio-2-alken-1-ols (**3**) with good to excellent enantioselectivities. Ozonolysis of **3** provides a new and efficient route to chiral α-hydroxy thioesters **4**. © 1998 Elsevier Science Ltd. All rights reserved.

Enantiomerically pure α-hydroxy acids and esters are important building blocks for the construction of chiral ligands and natural products,[1] so that many methods have been reported for their preparation.[2] The related thioesters (thiol esters) have received much less attention,[3] despite the fact that thioesters are suitable intermediates for several functional group manipulations and C–C bond-forming reactions.[4] In this connection, Aggarwal *et al.*[4a] have very recently reported on transformations of chiral aromatic α-hydroxy thioesters into a range of functional groups including acids, amides, esters and ketones without racemisation. Thus, a practical and straight route to chiral α-hydroxy thioesters would be desirable.

Recently, we have reported the enantioselective reduction of α,β-unsaturated ketones with BH_3:SMe_2 catalysed by (*R*)- and (*S*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidines, (*R*)- and (*S*)-**1**.[5] This study showed that in such reductions the ethylenic moiety behaves as a group "larger" than a saturated chain, specially if the double bond is α-branched, leading to highly enantioenriched allylic alcohols. In the light of these precedents we envisioned that α,β-unsaturated ketones bearing an SPh group linked to the α-position (such a **2**, Scheme 1) are appropriate substrates to be converted into allylic alcohols (**3**) by BH_3:SMe_2 in the presence of oxazaborolidines. These alcohols are, in turn, potentially useful intermediates since they are amenable to be transformed into other functionalities, including α-hydroxy thioesters (**4**). We wish to report herein that this strategy emerges as a general and efficient way to these compounds.



Scheme 1

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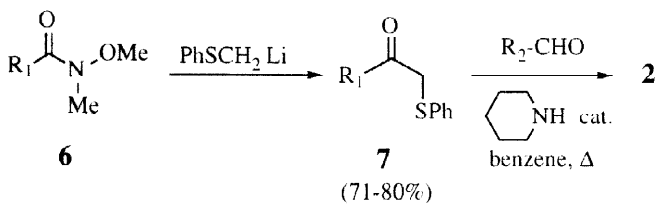
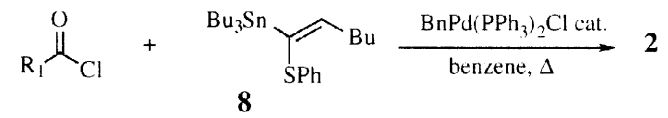
Preparation of ketones 2. Although some α-phenylthio enones (**2**) have been used as Michael acceptors, Diels-Alder dienophiles, extended enolate anions, and annelating agents, reported synthetic approaches to **2** suffer from serious limitations such as lack of generality or relatively long reaction sequences.[6] For instance, when Weinreb amides **6** were converted to (phenylthio)methyl ketones **7** and subsequently subjected to piperidine-catalysed condensation with aldehydes in refluxing benzene,[6a] good yields were



a	R_1 = Me, R_2 = Ph	75%
b	R_1 = Me, R_2 = 2-furoyl	75%
c	R_1 = Ph[CH_2]$_2$, R_2 = Ph	70%
d	R_1 = Ph[CH_2]$_2$, R_2 = Bu	60%
e	R_1 = cyclohexyl, R_2 = Bu	30%
f	R_1 = Bu^t, R_2 = Bu	<10%



d	R_1 = Ph[CH_2]$_2$, R_2 = Bu	87%
e	R_1 = cyclohexyl, R_2 = Bu	75%
f	R_1 = Bu^t, R_2 = Bu	79%
g	R_1 = Me, R_2 = Bu	65%

Scheme 2

obtained with aromatic aldehydes or unbranched ketones but yields dropped in the more hindered cases (see Scheme 2). Looking for a more general method to obtain ketones **2**, we tried the Pd-catalysed coupling of the readily available (*E*)-1-phenylthio-1-tributylstannylhex-1-ene (**8**) with acid chlorides.[7] In this way, good yields of **2** were obtained *even in the more hindered case* (**2f**).[8]

Reduction of ketones 2. Reductions were performed by slow addition (~30 min) of the ketone (1 mmol) to a solution of BH_3:SMe_2 (1 mmol) and 0.2–1.0 mmol of **1** or **5**, ~1 M in THF, under Ar at 0 °C. The results are summarized in Table 1.

Table 1. Reduction of Ketones **2** with BH_3:SMe_2

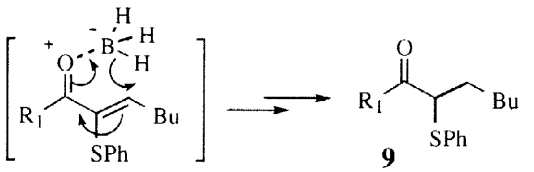
entry	ketone	catalyst	alcohol[a]	e.e. (%)[b]	yield (%)[b]
1	**2a**	(*S*)-**1**	(*R*)-**3a**	95[d] (93)	93 (80)
2	**2b**	(*S*)-**1**	(*R*)-**3b**	97[c] (96)	99 (95)
3	**2c**	(*S*)-**1**	(*R*)-**3c**	93[c]	86
4	**2d**	(*S*)-**1**	(*R*)-**3d**	97[c]	73
5	**2d**	(*S*)-**5**	(*R*)-**3d**	96[c]	98
6	**2e**	(*S*)-**1**	(*S*)-**3e**	82[d]	37[e]
7	**2e**	(*S*)-**5**	(*S*)-**3e**	89[d]	61[e]
8	**2f**	(*S*)-**5**	(*S*)-**3f**	96[d]	54[f]
9	**2g**	(*S*)-**1**	(*R*)-**3g**	96[d] (94)	95 (96)
10	**2g**	(*S*)-**5**	(*R*)-**3g**	98[d] (98)	90 (85)

[a] Absolute configuration was established by chemical correlation (ref. 10). [b] Values are referred to 1 equiv. of **1** or **5**. Within parentheses, values using 0.2 mmol of catalyst. [c]Determined by HPLC analysis of the alcohol (**3b** and **3d**) or its acetate (**3c**) with a Chiracel OD-H chiral column. [d]Determined by HPLC and/or ^{19}F NMR analysis of the corresponding Mosher esters. [e]1-Cyclohexyl-2-phenylthio-1-heptanone was also isolated (entry 6, 54%; entry 7, 32%). [f]Starting material (~40%) was recovered as well as a trace of 2,2-dimethyl-4-phenylthiononan-3-one.

It is worth noting that:

(i) Excellent selectivities and good chemical yields were achieved in a few minutes for the reactions involving methyl ketones (entries 1, 2, 9, and 10 of Table 1) even when only 0.2 equiv. of **1** or **5** were used.

(ii) On the other hand, for linear enones (entries 3, 4, and 5) at least an equimolar amount of oxazaborolidine was required to achieve good chemical yields, otherwise competitive 1,4 reduction by borane to saturated ketones **9** becomes important (Scheme 3).



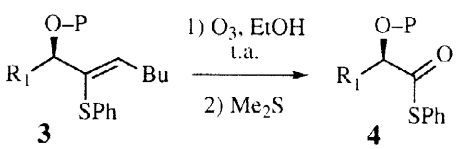
9

Scheme 3

(iii) Cyclohexyl ketone **2e** (entries 6 and 7) was reduced more slowly (further 30–40 min were required) and gave only moderate yields even in the presence of 1 equiv. of catalyst.[9]

(iv) Finally, more sterically demanding ketone **2f** (entry 8) was reduced in moderate yield under similar conditions but with excellent enantioselectivity.

Ozonolysis of alcohols 3. To our satisfaction, a set of alcohols **3** (or their acetate and benzyl ether derivatives) were cleany converted into α-hydroxy thioesters **4**, without significant loss of optical purity,[10] by treatment with ozone in EtOH. Apparently, the SPh group was not affected. It is also worth noting that the process is compatible with the *O*-benzyl protecting group if excess of ozone is avoided.



3 **4**

R_1 = Me	P = Ac	85%
R_1 = Me	P = CH_2Ph	85%
R_1 = CH_2CH_2Ph	P = H	84%
R_1 = Cyclohexyl	P = H	79%
R_1 = Bu^t	P = H	75%

Scheme 4

In conclusion, we have achieved an efficient oxazaborolidine-mediated reduction of α-phenylthio enones –readily available from the corresponding acid chlorides– to highly enantioenriched allylic alcohols **4**. We have described herein the conversion of these potentially useful intermediates into α-hydroxy thioesters **6** with practically complete retention of chirality. Transformations of chiral alcohols **4** to other building blocks are in course.

Acknowledgements

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8. An attempt to obtain a simpler ketone, **2** (R_1 = $PhCH_2CH_2$, R_2 = H), by using tributyl(α-phenylthiovinyl)tin and 3-phenylpropionyl chloride, failed; the major product seemed to be the previously reported ketone dimer (ref. 6c).
9. Some experiments carried out in our laboratory demonstrated that borane itself reacts with ketones **2** to give mixtures of 1,4- and 1,2-reduction products. For instance, treatment of **2e** with BH_3:SMe_2 (2 equiv.) for 45 min at 0 °C gave 47% of **9e** and 33% of **3e**. On the other hand, it is timely to point out that, in our hands, ketone **2e** was reluctant to undergo reduction with neat Alpine-Borane® or (–)-DIP-Chloride®.
10. Determinations of absolute configuration of α-hydroxy thioesters **4** (R_1 = CH_2CH_2Ph, cyclohexyl, and Bu^t) and, therefore, their parent allylic alcohols **3**, were carried out by reduction to 1,2-diols ($NaBH_4$ in MeOH, 0 °C) and comparison of the sign of the specific rotation with that given in the literature (R_1 = CH_2CH_2Ph: Jeong, K.-S.; Sjö, P.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 3833; R_1 = cyclohexyl and Bu^t: Ko, K.-Y.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1333). On the other hand, treatment of *S*-phenyl (α-acetoxi)thiopropionate with morpholine gave the corresponding amide, which was correlated with that derived from commercial (–)-methyl lactate. Based on this correlation through their corresponding thioesters, the absolute configurations of alcohols **3a**, **3b**, and **3f** were established.