Tetrahedron Letters, Vol.31, No.51, pp 7415-7418, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

ENANTIOSELECTIVE REDUCTIONS OF 2-ACYL-1,3-DITHIANES USING THE COREY OXAZABOROLIDINE CATALYST

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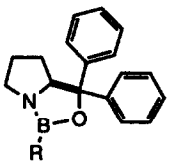
Summary: The enantioselective reduction of acyl dithianes has been achieved using the oxazaborolidine catalyst **1b**. The dithiane group can then be hydrolyzed to the ketone or removed reductively.

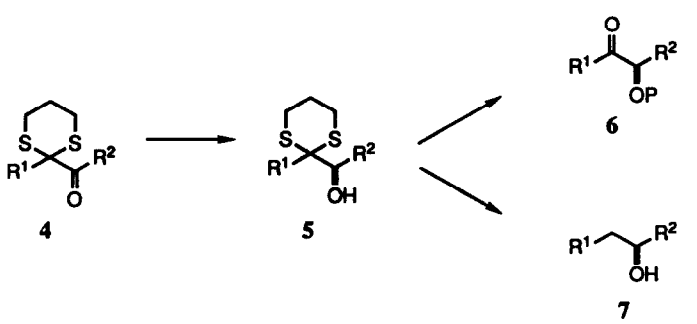
The oxazaborolidine catalysts, such as **1**, developed by Corey,[1] have been shown to be state of the art in asymmetric reductions. Similar pathways of reduction are also possibly involved in the chirally modified borohydride procedure of Itsuno.[2] High enantioselectivity in the reduction of ketones (**2**) is reliably achieved when R1 is aryl or tertiary alkyl and R2 is a small alkyl group.



1a R = Butyl
1b R = Phenyl

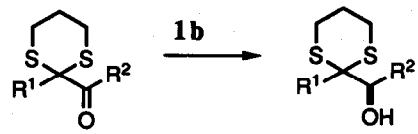
2 **3**

We envisioned that an acyl dithiane, **4**, would encompass the structural requirements necessary for good asymmetric induction. Furthermore, the alcohol product, **5**, could be subsequently transformed[3] into useful products such as **6** and **7**, which would be inaccessible via direct reduction. The transformation of **4** to **5** has been shown to be possible by microbial reduction[4], however, good yields are obtained only when R1 is hydrogen. Additionally, long reaction times are required (1-5 days) and the synthesis of only one of the enantiomers of the alcohol is viable by this route. The present method would allow for the preparation of both enantiomers since both antipodes of **1** are accessible.[2]



4 **5** **6** **7**

To test this theory, acyl dithianes **4(a-g)** were prepared by standard methods.[5,6] The catalyst chosen for the reductions was the B-phenyl catalyst **1b**. Although it was not reported in the Corey work, we found **1b** to be equal or superior to the B-alkyl derivatives at a substantially lower cost. As standard conditions, the reductions were carried out using 15 mol % of the catalyst and 60 mol % of borane at room temperature.[7] The results are tabulated below.



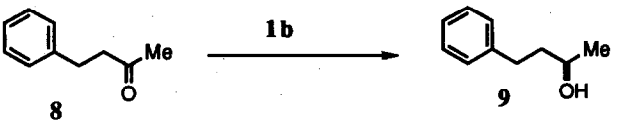
4 **5**

Ketone	R1	R2	Product	%ee#
4a	Methyl	Me	**5a**	94
4b	Propyl	Me	**5b**	93
4c	Benzyl	Me	**5c**	96
4d	Phenyl	Me	**5d**	90
4e	Phenyl	Et	**5e**	60
4f	$TBSOCH_2$	Me	**5f**	95
4g	$-CH_2CH_2CH_2CH_2-$		**5g**	>96

#%ee's were determined by analysis of the ^1H and/or ^{19}F NMR spectra of the corresponding Mosher esters.[8] The absolute configuration of alcohol **5d** was determined by conversion to a known compound (*vide infra*). The remaining structural assignments were made by analogy.

As can be seen from the table, very high enantioselectivities were observed in all of the methyl ketone examples. In general, the reductions were complete within 30 minutes and the yields were excellent (>95%). A dramatic decrease in selectivity was seen in the ethyl ketone case, **4e**, which also required a long reaction time (~24 h). It is reasonable to assume that this decrease in enantioselectivity could have resulted from a competitive non-catalyzed borane reduction pathway.[2] The reduction of the cyclic acyl 1,3-dithiane **4g**[9] was also studied and the (R)-alcohol **5g** was isolated in very high enantiomeric purity. None of the (S) isomer, as its Mosher ester, could be detected by NMR.

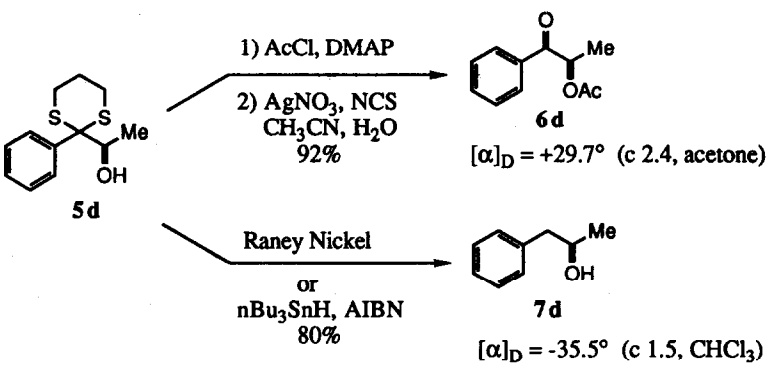
To prove that the dithiane had a controlling effect on the reaction, ketone **8**, the des-dithiane derivative of **4c**, was reduced under the standard conditions. The ketone reduced cleanly and rapidly, albeit in only 43% ee. This result supports the concept that the bulky dithiane group enhances the enantioselectivity of the reduction since the reaction of **4c** under the same conditions afforded **5c** in 96% ee.



8 **9**

43% ee

Finally, to demonstrate the versatility of the alcohol products, **5**, the dithiane group was removed both hydrolytically and reductively. For conversion to the ketone, it was found that protection of the alcohol was required prior to the hydrolysis reaction, (4.5 equiv $AgNO_3$, 4.0 equiv NCS in 80% CH_3CN/H_2O)[10]. In this manner, compound **6d** was prepared in high yield. Compound **7d** could be prepared from **5d** by reduction with either Raney nickel (10 equiv, EtOH, 50°C) or nBu_3SnH (3 equiv, cat AIBN in refluxing toluene)[11]. These reactions also confirm the stereochemical assignment of the compounds since optical rotation data has been reported for both **6d**[12a] and **7d**[12b]. Both compounds were converted to their corresponding Mosher esters (**6d** required prior deprotection) and it was verified that no racemization had occurred.



5d

6d

$[\alpha]_D = +29.7°$ (c 2.4, acetone)

7d

$[\alpha]_D = -35.5°$ (c 1.5, $CHCl_3$)

In conclusion, it has been demonstrated that both cyclic and acyclic 2-acyl-1,3-dithianes can be reduced enantioselectively using an oxazaborolidine catalyst. One must use caution when applying this methodology beyond methyl ketones since a drop in selectivity was seen with the ethyl ketone example. The compounds can be transformed into useful products such as optically active secondary alcohols and α-hydroxy ketones.

References and Notes

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2) a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc. Chem. Commun.* 469 (1983). b) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc. Perkin Trans. I.* 2039 (1985). c) Itsuno, S.; Sakurai, Y.; Ito, K. ; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **60**, 395 (1987).

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5) See Ref. 4b and: Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **4**, 1075 (1965).

6) Satisfactory 300 MHz ^{1}H NMR and mass spectral data has been obtained on all new compounds.

7) The procedures for the preparation of the catalyst and for the reductions were identical to those reported in references 2c and 2e.

8) The Mosher esters were prepared by treating the optically active alcohols with Mosher acid chloride and DMAP in methylene chloride for 1 h. The esters of all the racemic alcohols were also prepared for comparison. See Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **34**, 2543 (1969).

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12) a) For (S) enantiomer of **6d**: $[\alpha]_D$ = -25 (c 1.3, acetone) Ohta, H.; Ikemoto, M.; II, H.; Okamoto, Y.; Tsuchihashi, G. *Chem. Lett.* 1169 (1986). b) For (S) enantiomer of **7d**: $[\alpha]_D$ = +39.2 (c 4.76, $CHCl_3$) Golding, B. T.; Hall, D. R.; Sakrikar, S. *J. Chem. Soc. Perkin Trans. I* 1214 (1973).

(Received in USA 4 October 1990)