Pergamon

Tetrahedron Letters, Vol. 35, No. 29, pp. 5303-5306, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00987-2

The Effect of Zinc(II)Bromide on the Reduction of a Chiral, non-Racemic, Benzylidene Sulphinamide Derived from a Recoverable, Cyclic Sulphinamide.

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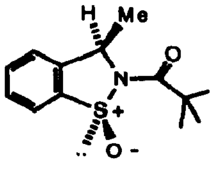
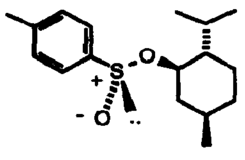
Abstract: The addition of zinc(II)bromide reverses the diastereoselectivity of the diisobutyl-aluminium hydride (DIBAL-H) reduction of benzylidene sulphinamide $R_{(S)}R$-(-)-4. The same reversal is not observed in the reactions of analogues lacking an amide side chain.

In a series of recent publications we have described the preparation and synthetic applications of the chiral, non-racemic, cyclic sulphinamide $S_{(S)}R$-(+)-**1**.[1] This reagent may be converted into chiral sulphoxides *via* reactions with nucleophiles such as Grignard reagents or the enolates of esters or ketones. In each case inversion of configuration at sulphur is observed. Sulphinamide $S_{(S)}R$-(+)-**1** has several advantages over the more commonly used 1R,2S,5R-(-)-menthyl-(S)-p-toluenesulphinate **2**.[1] It is readily available in either homochiral form from inexpensive starting materials and is not prone to epimerisation at sulphur during use or in storage and most significantly, it has been demonstrated to be recyclable after use.[1c]



$S_{(S)}R$-(+)-**1**

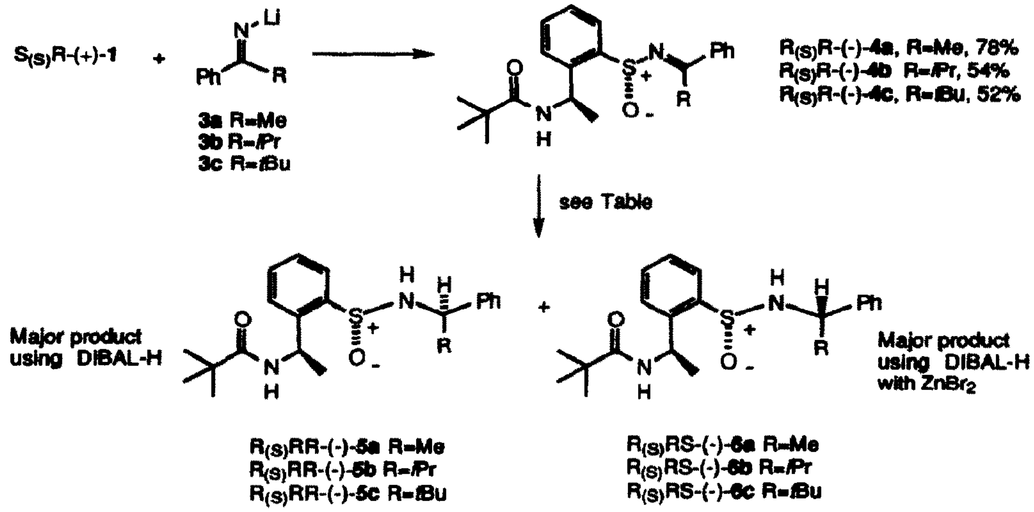


S-**2**

The chemistry of this versatile compound has been extended to the asymmetric synthesis of α-methylbenzylamine from benzylidene sulphinamide $R_{(S)}R$-(-)-**4a** which is formed from the reaction between lithio-imine **3a** and $S_{(S)}R$-(+)-**1**.[3] Subsequent reduction of the sulphinylimine $R_{(S)}R$-(-)-**4a** results in the formation of the diastereomeric products $R_{(S)}RR$-(-)-**5a** and $R_{(S)}RS$-(-)-**6a**. The highest diastereoselectivity was obtained using DIBAL-H in THF at -23°C which gave $R_{(S)}RR$-(-)-**5a** as the major product (Table).[3] The diastereoisomeric sulphinylamine products were treated with methanolic trifluoroacetic acid to obtain the corresponding optically enriched amine.[3]

The use of chelating agents to change or enhance the selectivity of a reduction is well known.[4] For instance, zinc(II)bromide has been used to reverse the selectivity in the DIBAL-H reduction of β-ketosulphoxides.[5] In this paper we report the effect of zinc(II)bromide on the DIBAL-H reductions of benzylidene sulphinamides $R_{(S)}R$-(-)-4.

Scheme 1



Treatment of $R_{(S)}R$-(-)-4a with 1 equivalent of zinc(II)bromide at room temperature, followed by two equivalents of DIBAL-H, resulted in the formation of the diastereoisomeric products $R_{(S)}RR$-(-)-5a and $R_{(S)}RS$-(-)-6a. The selectivity of the reduction, compared to the DIBAL-H reduction, was completely reversed yielding $R_{(S)}RS$-(-)-6a as the predominate isomer, as assessed by HPLC and high field ^{1}H-NMR analysis (Table).

Table

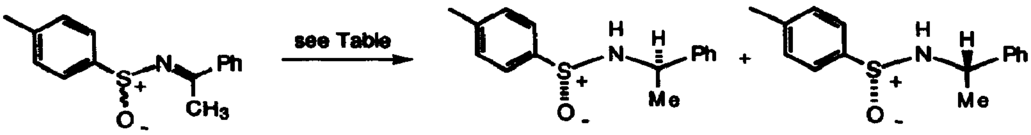
Compound	Reagents	Yield	d.e.	Major Isomer
4a	DIBAL-H, THF, -23°C	98%	86%	**5a**
4a	$ZnBr_2$/DIBAL-H, THF, RT	94%	92%	**6a**
4b	DIBAL-H, THF, -23°C	86%	71%	**5b**
4b	$ZnBr_2$/DIBAL-H, THF, RT	62%	88%	**6b**
4c	DIBAL-H, THF, -23°C	82%	85%	**5c**
4c	$ZnBr_2$/DIBAL-H, THF, RT	58%	62%	**6c**
7	DIBAL-H, THF, -23°C	89%	65%	**8**
7	$ZnBr_2$/DIBAL-H, THF, RT	81%	14%	**8**

Reaction of lithio-imines **3b** and **3c** with R$_{(S)}$S-(+)-**1** gave the expected imines **4b** and **4c** respectively. Reduction of **4b** and **4c** with either DIBAL-H or DIBAL-H/zinc(II)bromide gave products in which the same pattern of selectivity is observed as for the reductions of **4a**. In the case of reduction products **5b** to **6c** the relative stereochemistries have been assigned on the basis of the known result with **4a**.[3]

Such an effect, to our knowledge, has not been reported for a benzylidene sulphinamide. To examine whether this reversal of the selectivity is general for the reduction of such compounds, the racemic p-tolyl derivative (±)-**7** was prepared *via* published procedures. The sulphenylimine was prepared from p-tolyl disulphide, acetophenone and ammonia using the method of Davis[6] and was subsequently oxidised with mCPBA to give (±)-**7**.[7]

The DIBAL-H reduction of (±)-**7**, at room temperature, resulted in the formation of a diastereoisomeric mixture of (±)-**8** and (±)-**9** in 89% yield and 65% diastereoisomeric excess (d.e.) in favour of (±)-**8**.[8] The zinc(II)bromide mediated DIBAL-H reduction resulted in a decrease in the diastereoselectivity of formation of (±)-**8** to just 14% d.e. One must assume that the amide side chain of R$_{(S)}$R-(-)-**4a** is important in controlling the stereochemical outcome of the zinc(II)bromide/DIBAL-H reduction. How the amide moiety is involved is unclear. It is possible that the amide and sulphinylimine functionalities coordinate with the zinc ion prior to hydride addition.

Scheme 2



(±)-**7**

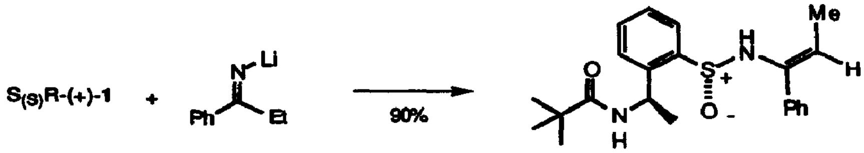
(±)-R$_{(S)}$R(S$_{(S)}$S)-**8**

(±)-R$_{(S)}$S(S$_{(S)}$R)-**9**

Major product using DIBAL-H or DIBAL-H with ZnBr$_2$

Although addition of lithio-imines **3a** to **3c** gave the expected imines **4a** to **4c** respectively, addition of anion **3d** gave the enamine **10** in 90% yield (Scheme 3). An X-ray crystallographic study of this product confirmed that the new double bond possessed Z-stereochemistry.[9] Presumably, in contrast to **4a** the extra methyl group must lend sufficient extra stabilisation to favour this isomer over the imine. In **4b** the enamine will be destabilised by the necessity for the phenyl and methyl groups to be oriented *cis*- to each other.

Scheme 3



3d

10

In conclusion, we have demonstrated that zinc(II)bromide/DIBAL-H is a complementary method to the DIBAL-H reduction of $R_{(S)}R$-(-)-4. This reaction is high yielding with good diastereoselectivity and is not a general method for other benzylidiene sulphinamides such as (±)-7, that do not possess an amide side chain. Further examples and the mechanism, which is under investigation, will be reported in due course.

Acknowledgment

The authors would like to thank the SERC and Roche Products Ltd. for a CASE award (DRJH) and Mr. J. A. Whatley and Mrs. H. Simmonite (Roche) for their assistance with HPLC and high field NMR analysis. We also thank Dr. J. Ballantine of the SERC Mass Spectrometry service at Swansea for analyses of certain intermediates by FAB techniques.

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(*Received in UK* 11 *May* 1994; *accepted* 20 *May* 1994)