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A CATALYTIC EFFECT OF $ZnCl_2$ DURING DIBAL REDUCTION OF ß-KETOSULFOXIDES.

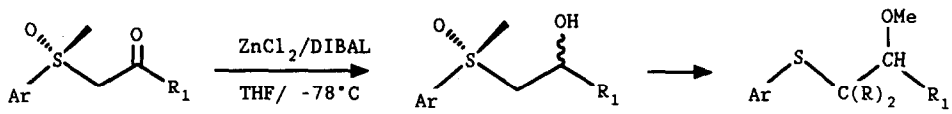
A. Solladié-Cavallo*, J. Suffert, A. Adib, G. Solladié

Département de chimie organique fine associé au CNRS,
EHICS, 1 rue Blaise Pascal, 67008 Strasbourg, France.

Summary : *High asymmetric inductions (>94/6) are obtained upon DIBAL reduction of ß-ketosulfoxides in the presence of non-stoichiometric amounts of $ZnCl_2$ (0.5 equiv. to 0.05 equiv.). Intramolecular hydride transfer and new chelated models are proposed to explain the observed stereoselectivity.*

Being concerned by the synthesis of optically pure chiral sulfides **3** as potential reagents for asymmetric epoxidation we became interested in the known (1-3) diastereoselective DIBAL and/or DIBAL/$ZnCl_2$ reduction of ß-ketosulfoxides.

Here we want to report that not only stoichiometric (1-3) but also non-stoichiometric quantities of $ZnCl_2$ can efficiently be used to affect highly diastereoselective reduction of ß-ketosulfoxides.



1a racemic Ar= R_1= Ph
1b (R_S) Ar=p-tolyl, R_1=C_8H_{17}
1c (R_S) Ar=p-tolyl, R_1=CH=CH-Ph

2a, 2b, 2c
(R_SR/R_SS)

3a-c

As shown in the Table, addition at -78°C of DIBAL into a THF solution of ß-ketosulfoxide **1a-1c** containing variable amounts of anhydrous $ZnCl_2$ leads to the ß-hydroxysulfoxides in 80 % to 95 % yield and diastereomeric excesses up to 94%.

The smaller asymmetric induction occasionally observed (lines 2,6,9) is probably due to the fact that, differences in reactivity towards DIBAL between the uncomplexed ß-ketosulfoxide and the activated (through electrophilic assistance) $ZnCl_2$-complexed ß-ketosulfoxide being too small, DIBAL molarity (compare lines 2 and 3) and its rate of addition become determining and must be optimized.

In the first model used to explain the stereoselectivity observed with DIBAL in the presence of $ZnCl_2$, the $ZnCl_2$-complexed ß-ketosulfoxide was postulated to undergo an intermolecular hydride attack whose favored-approach was explained from steric and stereoelectronic effects (1, 4).

Table: $ZnCl_2$/DIBAL reduction of ketosulfoxides **1a-c** to hydroxysulfoxides **2a-c** [≠]:

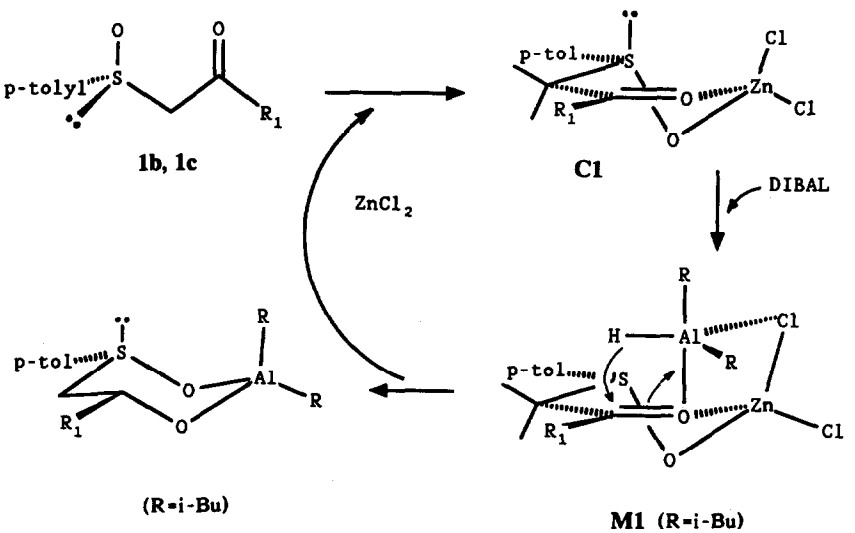
entry	starting compound	$ZnCl_2$ equiv.	DIBAL equiv.	Yield % *	R_SR / R_SS **
1	**1a**	0	1.4	85	<5 / >95
2	"	0.05	1.5	90	87 / 13
3	"	0.05.	1.1	85	94 / 6
4	"	0.1	1.1	90	97 / 3
5	**1b**	0	1.5	85	15 / 85
6	"	0.05	1.5	87	73 / 27
7	"	0.5	1.5	90	95 / 5
8	**1c**	0	1.5	>95	10 / 90
9	"	0.05	1.5	95	90 / 10
10	"	0.5	1.5	95	97 / 3

** In weight of crude products, corrected from remaining starting aldehyde using* 200MHz ^{1}H NMR.
*** Diastereomer-ratios (±1%) are determined using* 200MHz ^{1}H NMR *of the* ABX *system.* [≠] *see ref.*6.

We now think that the hydride transfer occurs intramolecularly and that the DIBAL approach is Cl-directed as shown on Figure.

The $ZnCl_2$-chelated ß-ketosulfoxide adopts the favored twisted conformation C1 where the p-tolyl group is pseudo-equatorial when the absolute configuration at sulfur is *R*.

Figure :



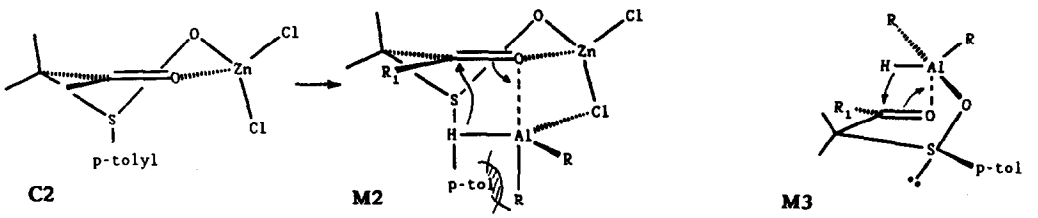
In the early stage of the reaction the approach of $HAl(i\text{-}Bu)_2$ is then directed by complexation with the geometrically well situated pseudo-axial chlorine leading to a bimetallic bridged-species where aluminum is dsp^3 hybridized (5). In this model of approach **M1**, the hydride is just in the right position to be transfered intramolecularly from the top leading to the *R* configuration at C-2, as observed.

In conformation **C2**, where the p-tolyl group has an unfavorable pseudo-axial position, the Cl-directed approach of $HAl(iBu)_2$ is now also greatly hindered by the p-tolyl group which explains the small contribution of the corresponding approach **M2** on the stereoselectivity (only 2% to 10% of the *S* configuration is observed)

The high asymmetric inductions obtained with non-stoichiometric amounts of $ZnCl_2$ (0.5 and 0.05 equiv.) suggest that, after hydride transfer, $ZnCl_2$ is displaced from the aluminum alkoxysulfoxide formed, being then able to complex remaining ß-ketosulfoxide.

Since Na^+ is not a Lewis acid and is not able to undergo a Cl-directed approach, model **M1** does not hold anymore in the case of $NaBH_4$ reduction of $ZnCl_2$-complexed ß-ketosulfoxides which explains the low stereoselectivity observed (4).

Considering again the Lewis acid character of Al^{+3} in $HAl(i\text{-}Bu)_2$ we now think that DIBAL reduction of ß-ketosulfoxide involves also in an early stage of the reaction a chelated dsp^3 hybridized aluminum as shown on model **M3** (where the p-tolyl group afford a favorable equatorial position). Model **M3** leads, through an already proposed intramolecular hydride transfer (4), to the *S* configuration at C-2, as observed (1-4).



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3) Kosugi H., Konta H., Uda H., *JCS Chem. Comm.*, 1985, 211

4) Carreno C., Garcia Ruano J.L., Martin A.M., Pedregal A., Rodriguez J.H., Rubio A., Sanchez J., Solladié G., *J. Org. Chem.* 1990, *55*, 2120

5) Trigonal-bipyramidal structures (dsp^3) is often encountered for transient species in alkyl-aluminum

compounds and Cl is well known to be a bridging-ligand in various type of complexes (see "Advances Inorganic Chemistry " F.A. Cotton and G. Wilkinson, Interscience Publ., J. Wiley & Sons 1972)

6) ^{1}H NMR of compound 1a-c and 2a-c, Bruker WP 200 SY, $CDCl_3$/TMS, δppm.

1a : 4.29 (d, 1H, CH_2, A part of an AB, J=14Hz); 4.56 (d, 1H, CH_2, B part of an AB, J=14Hz); 7.5 (m, 6H, Harom); 7.7 (m, 2H, Harom); 7.89 (d, 2H, Harom).

1b : 0.88 (t, 3H, Me); 1.24 (b, 12H, $(CH_2)_6$); 1.51 (t, 2H, CH_2); 4.42 (s, 3H, Me); 3.73 (d, 1H, CH_2, A part of an AB, J=13Hz); 3.88 (d, 1H, CH_2, B part of an AB, J=13Hz); 7.34 (d, 2H, Harom); 7.54 (d, 2H, Harom).

1c : 2.4 (s, 3H, Me); 4.02 (d, 1H, CH_2, A part of an AB, J=13Hz); 4.22 (d, 1H, CH_2, B part of an AB, J=13Hz); 6.7 (d, 1H, CH=, J=16Hz); 7.5 (m, 10H, Harom + CH=).

2a (RR) : 3.0 (dd, 1H, CH_2, A part of an ABX, J=13Hz, J=2.5Hz); 3.2 (dd, 1H, CH_2, B part of an ABX, J=13Hz, J=9.5Hz); 5.42 (dd, 1H, X part of an ABX, J=9.5Hz, J=2.5Hz); 7.2-7.7 (m, 10H, Harom).

2a (RS) : 2.85 (dd, 1H, CH_2, A part of an ABX, J=13Hz, J=3Hz); 3.3 (dd, 1H CH_2, B part of an ABX, J=13Hz, J=10Hz); 5.25 (dd, 1H, X part of an ABX); 7.1-7.8 (m, 10H, Harom).

2b (RR) : 0.95 (t, 3H, Me); 1.2 (b, 12H, $(CH_2)_6$); 1.4 (b, 2H, CH_2); 2.4 (s, 3H, Me); 2.77 (dd, 1H, CH_2, A part of an ABX, J=13Hz, J=2.5Hz); 2.95 (dd, 1H, CH_2, B part of an ABX, J=13Hz, J=9Hz); 4.31 (m, 1H, X part); 7.32 (d, 2H, Harom); 7.55 (d, 2H, Harom).

2b (RS) : 0.9 (t, 3H, Me); 1.22 (b, 12H, $(CH_2)_6$); 1.41 (b, 2H, CH_2); 2.41 (s, 3H, Me); 2.65 (dd, 1H, CH_2, A part of an ABX, J=13Hz, J=2Hz); 3.0 (dd, 1H, CH_2, B part of an ABX, J=13Hz, J=9Hz); 4.12 (m, 1H, X part); 7.32 (d, 2H, Harom); 7.51 (d, 2H, Harom).

2c (RR) : 2.4 (s, 3H, Me); 2.95 (dd, 1H, CH_2, A part of an ABMXY, J=13Hz, J=3Hz); 3.1 (dd, 1H, CH_2, B part of an ABMXY, J=13Hz, J=9Hz); 5.0 (m, 1H, M part); 6.2 (dd, 1H, CH=, X part, J=16Hz, J=6Hz); 6.7 (d, 1H, CH=, Y part, J=16Hz); 7.27 (m, 7H, Harom); 7.57 (d, 2H, Harom).

2c (rs) : 2.42 (s, 3H, Me); 2.85 (dd, 1H, CH_2, A part of an ABMXY, J=13Hz, J=3Hz); 3.17 (dd, 1H, CH_2, B part of an ABMXY, J=13Hz, J=9Hz); 4.9 (m, 1H, M part); 6.16 (dd, 1H, CH=, X part, J=16Hz, J=6Hz); 6.65 (dd, 1H, CH=, Y part, J=16Hz, J=1.5Hz); 7.31 (m, 7H, Harom); 7.57 (d, 2H, Harom).

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