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Enantiotopic Group Differentiation and Kinetic Resolution: Asymmetric Reduction of *meso*-1,3-Dihalides

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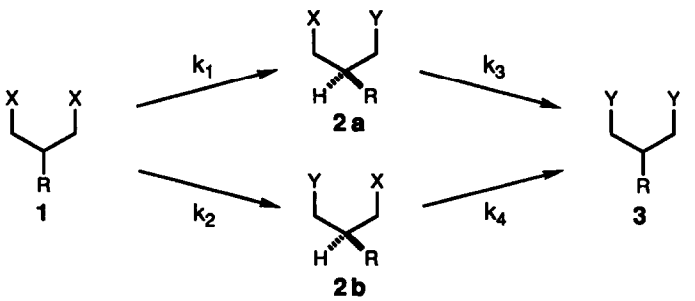
Key Words: enantiotopic group differentiation; kinetic resolution; asymmetric reduction

Abstract: Asymmetric reduction of 1,3-dihalides derived from glycerol occurs with moderate levels of enantiotopic group differentiation. A concomitant kinetic resolution increases the enantiomeric purity of the initial product.

The use of enantiotopic group differentiation for asymmetric synthesis has long been recognized[1] but, although there are many examples of such differentiation by enzymes,[2,3] there have been relatively few "chemical" examples.[4] Chemical examples in which a concomitant kinetic resolution occurs to enhance the enantiomeric purity of the intermediate (as has been shown to occur with some enzyme catalyzed reactions[5]) are even rarer. The scarcity of such examples is at least partially due to the fact that a second reaction cannot take place with most enantiotopic group differentiation processes (*e.g.* anhydride openings,[6] epoxide deprotonations,[7] and ketone deprotonations[8]) that have been studied. In a seminal contribution, Schreiber showed that divinylcarbinols undergo Sharpless epoxidation to afford monoepoxides whose enantiomeric purity increases as the reaction progresses.[9] However, there are few other non-enzymic systems which are as enantioselective as the Sharpless epoxidation. It would be of interest to demonstrate that non-enzymatic systems that show only modest initial selectivities might be useful for the preparation of compounds in high enantiomeric purity if a kinetic resolution also occurs to increase the enantiomeric purity of the intermediate.[10]

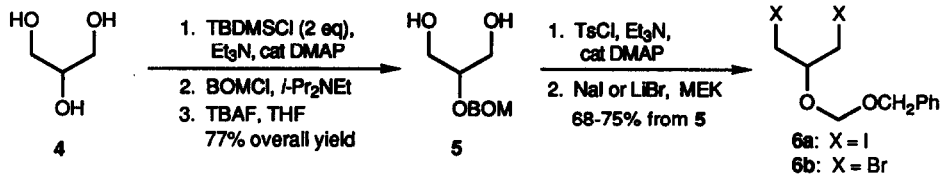
Scheme 1



Asymmetric reductions of carbonyl compounds, processes involving enantiofacial selectivity, have received considerable attention,[11] but there appear to be no reports of asymmetric reductions of meso-dihalides, processes dependent upon enantiotopic group differentiation. We felt that the reduction of meso-dihalides with asymmetric reducing agents might be interesting systems to test the anticipated changes in enantiomeric purity of the intermediate **2** (Scheme 1) with time and to determine whether such an approach might constitute a viable access to compounds of high enantiomeric purity.[12] In principle, as long as $k_1 > k_2$, unequal amounts of **2a** and **2b** would be formed; in addition, if $k_4 > k_3$ (*i.e.* the more reactive group in **1** is also more reactive in **2**), one would anticipate that the relative amounts of **2a** and **2b** would increase with time. While the conversion of **2**→**3** decreases the yield of **2**, an increase in enantiomeric purity is anticipated.

The glycerol derivatives **6a** and **6b** (Scheme 2) were chosen as substrates since it was expected that coordination by the OBOM group might help to enhance the ability of the chiral reducing agent to differentiate between the two enantiotopic -CH_2X groups. Preparation of the dihalides was straightforward and provided **6** in 52-58% overall yield from glycerol (**4**).[13]

Scheme 2

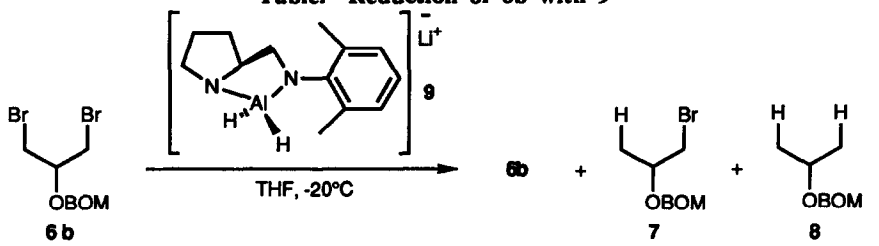


Of the chiral reducing agents available, it was expected that only those based on $LiAlH_4$ (as opposed to BH_3 or $NaBH_4$) would be capable of reducing alkyl halides. Initial experiments with BINAL-H[16] and dibromide **6b** revealed the reactions to be very sluggish; for example, treatment of **6b** with BINAL-H (2 eq, THF) at rt for 24 h provided mostly starting material (80% by GC), mono-reduced product **7** (18%), and fully reduced material **8** (2%, see Table for structures). A reagent derived from $LiAlH_4$ and *N*-methylephedrine with *N*-ethylaniline[17] proved to be completely unreactive towards **6b**. Reductions with a reagent derived from $LiAlH_4$ and (S)-2-(2,6-xylidinomethyl)pyrrolidine[18] (which might be expected to be more reactive than other chiral modifications of $LiAlH_4$ since two hydrides still remain on the aluminate) proceeded much more readily; in fact, **6b** was almost completely consumed after 2 h at -30°C on treatment with this $LiAlH_4$-diamine reagent. Thus, we chose to study reductions of **6** with this reagent in more detail.

When **6b** was allowed to react with reducing agent **9**, the product distribution and the enantiomeric purity of the mono-reduced product **7** changed as the reaction progressed. Results of experiments carried out in THF (2 eq **9**, -20°C) are summarized in the Table. The results in the Table suggest that the reduction of **6b**→**7** occurs much more readily than the subsequent **7**→**8** reduction. Thus, **7** is by far the major product after 1 h (entry 3). Control experiments using limiting amounts of $LiAlH_4$ also gave **7** as the major product. It is not clear how the second bromide facilitates the reduction of the first one but the outcome may be synthetically useful for the mono-reduction of similar dibromides. While conversion of **7**→**8** is slow, it does occur, and it does so such that the enantiomeric purity of **7** increases as the reaction progresses. The initial

selectivity (entry 1, where very little **8** has been formed) is rather modest, but the subsequent kinetic resolution of **7** increases its enantiomeric purity; after prolonged reaction times, it may be isolated with reasonable enantiomeric purity albeit in poor yield (entry 6). In other words, this system behaves essentially as expected.

Table. Reduction of 6b with 9



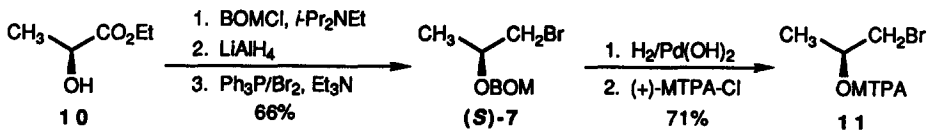
Entry	Time (min)	Product Distribution[a] **6b : 7 : 8**	Yield of 7[b] (%)	% ee of 7[c]
1	30	29 : 69 : 2	55	25
2	50	10 : 86: 4	69	42
3	60	3 : 91 : 6	74	53
4	90	-- : 77 : 23	62	60
5	130	-- : 60 : 40	48	74
6	240	-- : 18 : 82	17	87

a Mole ratios based on isolated yields.
b Isolated yield after flash chromatography.
c Determined by ^{1}H NMR analysis of the derived [H_2/Pd(OH)$_2$ then MTPA-Cl, Et_3N, cat DMAP] MTPA esters.[19]

Comparable results were obtained using DME as solvent while reactions in ether (the solvent best suited for asymmetric reductions of carbonyl compounds with **9**[20]) were much slower and less stereoselective. With diiodide **6a**, similar reaction profiles were observed but analysis was complicated by the formation of substantial (up to 25%) amounts of the BOM ether of cyclopropanol, a product that presumably arises from SET processes.[21]

The absolute configuration of **7** was established by correlation with material of known absolute configuration (Scheme 3). A sample of (*S*)-**7** was prepared from ethyl (*S*)-lactate and further transformed into MTPA ester **11**. This material was identical to the minor diastereomer produced (by hydrogenolysis followed by esterification) from **7** isolated from the reduction mixtures; thus the reaction of **6b** with **9** produces (**R**)-**7** as the major enantiomer.

Scheme 3



$[\alpha]_D^{24} = 4.5$ (c 0.7, $CHCl_3$)

These results show for the first time that the asymmetric reduction of meso dihalides with chiral reducing agents is possible. With the system investigated, only modest selectivity was observed. Significantly, however, the enantiomeric purity of the mono-reduced product increased as the reaction progressed. Further investigations in this area may lead to systems which are more selective, and capable of producing substances of high enantiomeric purity.

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