Highly Diastereoselective Reduction of 2-Acyl-1,3-oxathiane 3-Oxides Derived from (1*R*)-(+)-Camphor

Kwang-Youn Ko* and Kwang-Il Kim

Department of Chemistry, Ajou University, Suwon 442-749, Korea
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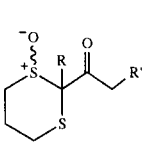
The diastereoselective addition of hydride reagents to ketones having a chiral auxiliary is a useful method of obtaining optically active alcohols.[1] One of the methods is based on chiral 2-acyl-1,3-oxathianes derived from (*R*)-(+)-pulegone.[2] In this case, the high diastereoselectivity observed in the reduction with chelating reducing agents such as L-Selectride® has been explained by invoking a Cram's chelate model, where the ring oxygen and the carbonyl oxygen take part in the chelation with metal cation. On the contrary, non-chelating agents such as diisobutylaluminum hydride (DIBAL-H) and *n*-Bu_4NBH_4 have been suggested to react according to a dipolar model.[2]

β-Ketosulfoxides react with DIBAL-H in a highly diastereoselective manner and the stereochemistry of this reduction has been explained by a chelate model involving the sulfoxide oxygen and the aluminum atom.[3] On the other hand, the sense of diastereoselectivity was reversed by the presence of $ZnCl_2$ in DIBAL-H reduction. In this context, Page studied the reduction of (±)-2-acyl-2-alkyl-1,3-dithiane 1-oxides **1** with DIBAL-H or DIBAL-H/$ZnCl_2$.[4] However, the stereochemical course in the addition of various hydride reagents to enantiopure 2-acyl-1,3-oxathiane 3-oxides **2** has not yet been reported in the literature. In these cases, the sulfoxide oxygen and the ring oxygen will compete with each other in chelation with metal ion and the degree and direction of diastereoselectivity will be governed by the relative chelating ability of two oxygen atoms. To probe into the difference in chelating ability of oxygen atoms in **2**, we studied a reduction of 2-benzoyl- **3a** (an aromatic ketone), 2-heptanoyl-1,3-oxathiane **3b** (an aliphatic ketone) and its 3-oxide analogs **4a, 4b** prepared from (1*R*)-(+)-camphor.



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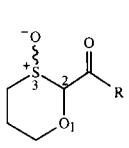

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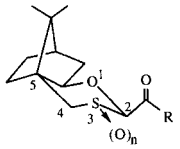
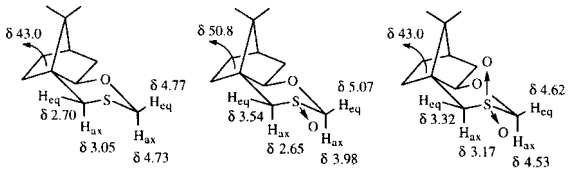
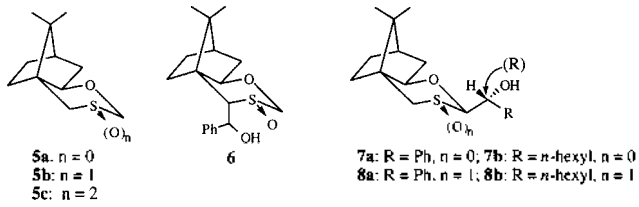


3a: R = Ph, n = 0; **3b**: R = *n*-hexyl, n = 0
4a: R = Ph, n = 1; **4b**: R = *n*-hexyl, n = 1

At first, we tried to prepare the ketone **4a** starting from the equatorial sulfoxide **5b**, which was obtained in 95% yield by *m*-chloroperbenzoic acid oxidation of the oxathiane **5a**.[5,6] However, lithiation of **5b** with *n*-BuLi (THF, − 78 °C) followed by treatment with benzaldehyde gave an unexpected alcohol **6** (77%), mp 177-178 °C, as a single diastereomer. The axial orientation was manifested by the presence of long-range coupling (*J*=1.5 Hz) between the equatorial protons at C-2 and C-4. Since lithiation of **5b** occurred at the C-4 position,[7] we resorted to the oxidation of the known phenyl ketone **3a**[5] with *m*-chloroperbenzoic acid and obtained the equatorial sulfoxide **4a** (95%).[8] Similarly, lithiation of **5a** with *n*-BuLi (THF-HMPA, − 78 °C) followed by treatment with heptanal gave a mixture of diastereomeric alcohols (*R*)-**7b** and (*S*)-**7b** in 89% yield, which was converted to ketone **3b** (68%) using Swern oxidation. Subsequent oxidation of **3b** with *m*-chloroperbenzoic acid gave the equatorial sulfoxide **4b** in 72% yield.



5a **5b** **5c**



5a: n = 0
5b: n = 1
5c: n = 2

6

7a: R = Ph, n = 0; **7b**: R = *n*-hexyl, n = 0
8a: R = Ph, n = 1; **8b**: R = *n*-hexyl, n = 1

Next, we studied the stereoselectivity of reduction of **3** and **4** as shown in Table 1. Phenyl ketone **3a** showed a usual dichotomy in the reduction: chelating reducing agents and non-chelating agents gave an epimeric carbinol as the major product, respectively. In the presence of $ZnCl_2$, DIBAL-H behaved as a chelating agent. Curiously, this well-known dichotomy[2] was not observed in the reduction of *n*-hexyl ketone **3b**; both chelating and non-chelating agents gave the same alcohol as a major product, which means that chelating agents react according to a dipolar model rather than a chelate model.

To determine the absolute configuration of the carbinol center, **7a** (94% de, from DIBAL-H reduction of **3a**) was oxidatively cleaved with NCS and $AgNO_3$ and the resulting aldehyde was reduced by $NaBH_4$ to give (*R*)-1-phenyl-1,2-ethanediol (78%, $[\alpha]_D^{20}$ − 35.0 (c=1.15, EtOH), lit.[9] for (*R*)-isomer, $[\alpha]_D^{25}$ − 39.7 (c=4.33, EtOH)). Similarly, **7b** (96% de, from DIBAL-H reduction of **3b**) was converted to (*R*)-1,2-octanediol (53%, $[\alpha]_D^{20}$ +16.3 (c=0.905, EtOH), lit.[2] for (*S*)-isomer, $[\alpha]_D^{20}$ − 15.2 (c=1.29, EtOH)). Then, it follows that DIBAL-H reduction of **3a** and **3b** give (*R*)-carbinols. On the other hand, reduction of **4a** with DIBAL-H and **4b** with LiAlH (O-*t*-Bu)[3] yielded (*R*)-carbinols **8a** and **8b**, respectively. This was inferred from the fact that reduction of sulfoxide groups in **8a** and **8b** with $NaBH_4$-$CoCl_2 \cdot 6H_2O$ in EtOH[10] gave sulfides **7a** and **7b**, whose ^{1}H-NMR spectrum was identical with that of the DIBAL-H reduction product of **3a** and **3b**.

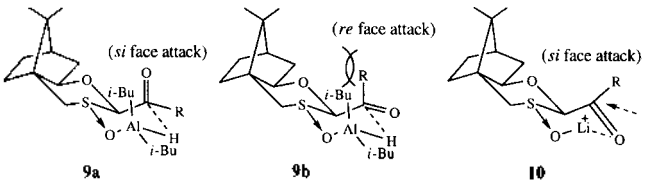
The formation of (*R*)-carbinols **8** in DIBAL-H reduction of **4** can be explained by a Solladié model **9a**, where a dsp^3

Table 1. Diastereoselectivity in the Reduction of 2-Acyl-1,3-oxathianes and Oxides[a]

Entry	Reagent	Solvent	Temp. (°C)	%de of sulfides **3a** / **3b**	%de of sulfoxides **4a** / **4b**
1	$NaBH_4$	EtOH	0	(*S*)10 (95) / (*R*)48 (89)	(*R*)46 (95) / (*R*)52 (93)
2	$LiBH_4$	THF	-78	(*S*)20 (95) / (*R*)40 (87)	(*R*)76 (95) / (*R*)60 (93)
3	$LiAlH_4$	THF	-78	(*S*)46 (95) / (*R*)46 (88)	(*R*)72 (95) / (*R*)74 (93)
3a	$LiAlH_4$	ether	-78	(*S*)66 (85) / (*S*)8 (70)	(*R*)77 (80) / (*R*)82 (82)
4	L-Selectride®	THF	-78	(*S*)42 (95) / (*R*)86 (78)	(*R*)96 (93) / (*R*)96 (70)
4a	L-Selectride® /12-crown-4[c]	THF	-78	b)	(*R*)96 (95) / (*R*)96 (90)
5	LiAlH(O-*t*-Bu)$_3$	THF	-78	(*S*)80 (95) / (*R*)62 (92)	(*R*)64 (90) / (*R*)96 (95)
5a	LiAlH(O-*t*-Bu)$_3$ /12-crown-4[c]	THF	-78	b)	(*R*)52 (90) / (*R*)96 (90)
6	*n*-Bu$_4$NBH$_4$	THF	0	(*R*)40 (98) / (*R*)65 (92)	(*R*)68 (96) / (*R*)65 (88)
7	DIBAL-H	THF	-78	(*R*)74 (94) / (*R*)78 (93)	(*R*)96 (95) / (*R*)24 (83)
	DIBAL-H	hexanes	-78	(*R*)94 (82) / (*R*)96 (88)	(*R*)96 (90) / (*R*)74 (87)
7a	DIBAL-H/$ZnCl_2$	THF	-78	(*S*)56 (63)[d] / b)	(*S*)14 (40)[d] / (*R*)10 (90)

[a] Determined by ^{1}H NMR on the crude products. Yields (%) are shown in the parenthesis. [b] Not determined. [c] Molar ratio of ketone, reducing agent, and crown ether=1 : 3 : 5. [d] Incomplete reaction.

hybridized aluminum chelates with the sulfoxide oxygen, positioning itself in a chair-like conformation.[3,4] An intramolecular hydride transfer to the *si* face of ketones will lead to the formation of (*R*)-carbinols **8**, which was confirmed as described above. Alternative model **9b** will be disfavored due to the steric interaction between the phenyl or alkyl group and the isobutyl group. The stereochemistry of reduction by chelating reducing agents suggests that the sulfoxide oxygen, rather than the ring oxygen takes part in chelation with metal ion, as shown in model **10**. Here, an intermolecular hydride addition from the less hindered *si* face of carbonyl group will give the carbinol of observed stereochemistry. Effect of crown ether on the diastereoselectivity was briefly investigated as shown in Table 1. The presence of crown ether did not affect the degree of high stereoselectivity observed in L-Selectride® reduction of **4a** or LiAlH (O-*t*-Bu)$_3$ reduction of **4b**. However, the moderate diastereoselectivity observed in LiAlH (O-*t*-Bu)$_3$ reduction of **4a** grew worse by the presence of a crown ether. These results suggest that a stronger chelation of lithium cation with sulfoxide oxygen, which is little perturbed by the crown ether, leads to a higher selectivity. In the presence of $ZnCl_2$, DIBAL-H showed either a reveral of stereochemistry or a decreased selectivity. However, the stereoselectivity was marginal.



9a **9b** **10**

In summary, chelating reducing agents such as L-Selectride® can reduce 2-acyl-1,3-oxathiane 3-oxides **4** in a high diastereoselectivity through a chelate process involving the sulfoxide oxygen rather than the ring oxygen. DIBAL-H gives the same epimeric carbinols *via* a Solladié model.[11]

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References

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5. Eliel, E. L.; Frazee, W. J. *J. Org. Chem.* **1979**, *44*, 3598-3599.
6. Formation of the equatorial sulfoxide is based on the assumption that oxygen is transferred from the less hindered direction. In ^{1}H NMR spectrum the α-proton which is trans to the sulfoxide oxygen appears at lower field than the α-proton which is *cis* to oxygen (Casey, F. A.; Dailey, Jr., O. D.; Hernandez, O.; Tucker, J. R. *J. Org. Chem.* **1976**, *41*, 3975-3979.). Also, upon formation of an equatorial sulfoxide from 1,3-dithianes, C(5) undergoes a downfield shift whereas the same carbon of the axial sulfoxide suffers an upfield shift (Koskimies, J. K. *Reactions of sulfur-stabilized carbanions with electrophiles: 2-lithio-1,3-dithiane sulfoxides and 2-lithio-1,3-oxathianes: some highly stereoselective reactions*, University of North Carolina at Chapel Hill, 1976.). According to these criteria, NMR data shown below suggest the equatorial orientation of sulfoxide group in **4b**.
7. It can be speculated that the sulfoxide group directs the lithiation in such a way that the carbon-lithium bond is formed *cis* to the sulfur-oxygen bond, due to the chelating (stabilizing) effect of *cis* oxygen. For a similar case, see Casey, F. A.; Dailey, Jr., O. D.; Hernandez, O. *J. Org. Chem.* **1976**, *41*, 3979-3983. Axial lithiation at the C-2 position in **5b** would not occur owing to the unfavorable stereoelectronic effect (two orbital-four electron repulsive interaction) imposed by the ring

oxygen (Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press: Boca Raton, 1995; pp. 208-209.).
8. Equatorial orientation of the sulfoxide oxygen could be inferred from the NMR data (see Ref. 6). For ketone **3a** the axial proton at C-2, *cis* to oxygen suffered an upfield shift from δ 5.97 ppm to δ 5.37 ppm upon oxidation. Also, C-5 of sulfoxide **4a** appeared at lower field than C-5 of sulfide **3a** (δ 50.8, 42.9 ppm, respectively).
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11. Addition of CH_3MgBr to sulfide **3b** and sulfoxide **4b** proceeded with a high (96% de) and moderate (40% de) diastereoselectivities, respectively. Even though the absolute configuration of the Grignard addition product has not been determined yet, the lower selectivity in Grignard addition to **4b** suggests that Mg ion chelates with ring oxygen more strongly than Li ion does.

Liquid Chromatographic Resolution of *N*-1- and 2-Naphthylamide Derivatives of 2-Aryloxypropionic Acids

Wonjae Lee

LG Chemical Ltd., Research Park, P.O. Box 61 Yu Sung, Science Town, Taejon 305-380, Korea
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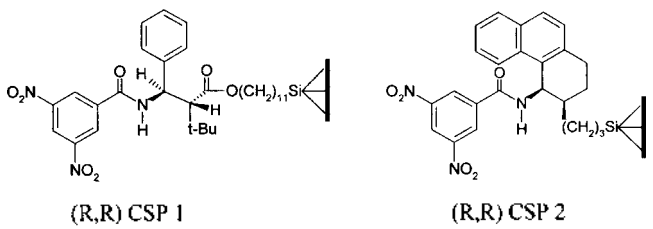
2-Aryloxypropionic acids and their ester or amide derivatives have proven to be essential herbicides and some of them are sold as the racemic mixtures.[1,2] It has been reported that the R-isomers show the herbicidal activity, the S-isomers being inactive.[3] Therefore, a few of these compounds are marketed as the single R-enantiomers.[1] Also, the most biologically active 2-aryloxypropionic acids and their derivatives have been developed. Owing to the importance of determining the enantiomeric purity of these compounds and to the dependence of their biological activities on stereochemistry, a number of studies for the resolution of 2-aryloxypropionic acids and/or their derivatives have been reported. Gas chromatographic chiral stationary phases (CSPs) based on modified cyclodextrins to resolve the ester derivatives of three 2-aryloxypropionic acids were reported.[4] Several liquid chromatographic methods using CSPs derived from *N*-3,5-dinitrobenzoylphenylglycine,[5-8] α_1-acid glycoprotein,[6,8] tartaric acid,[9] cellulose derivatives[10] and diaminocyclohexane[11,12] were investigated to separate the enantiomers of these various analytes. Recently, brush-type synthetic CSPs[13] 1 and 2 (Figure 1) were also employed to resolve several 2-aryloxypropionic acids and their derivatives.[14] Although these compounds showed generally good enantioseparation on CSPs 1 and 2, some analytes showed poor resolution, as seen in Table 1.[14] For example, 2-(2,4-dichlorophenoxy) propionic acid,[2,8] one of the important herbicides of this class in Europe and 2-(2-chlorophenoxy)propionic acid showed little enantioselectivity on CSPs 1 and 2 in the previous study. Even the enantiomers of their ester or *N*-n-butyl amide derivatives were poorly resolved on CSP 1 and/or CSP 2. In these cases, derivatization of the analyte with a proper achiral reagent which sometimes provides the necessary interaction sites for chiral recognition may improve the resolution.[15]



(R,R) CSP 1 (R,R) CSP 2

Figure 1. Structures of commercially available CSPs 1 and 2 used in this study.

Therefore, racemic 2-aryloxypropionic acids were derivatized with a strong π-basic 1- or 2-naphthylamine which is expected to allow an enantioselective π-π interaction with a π-acidic 3,5-dinitrobenzoyl (DNB) group of CSP. In this study, the enantioseparation of 2-aryloxypropionic acids as their *N*-1- and 2-naphthylamide derivatives was investigated on CSP 1 or CSP 2. The presence of *N*-naphthyl derivatizing moiety serves also to provide strong UV adsorption to aid detection, which affords an advantage of a lower limit of detection of 2-aryloxypropionic acids.

As good enantioseparation of the *N*-1- and 2-naphthylamide derivatives of 2-aryloxypropionic acids is observed on CSP 1, chromatographic data of these analytes on CSP 1 are presented in Tables 2 and 3. The enantiomers of *N*-1-naphthylamide derivatives of 2-aryloxypropionic acids were base-line separated on CSP 1 in all cases. Especially, fairly good enantioselectivity (α=1.37-1.66) was observed for the resolution of *N*-1-naphthylamide derivatives of 2-(2,4-dichloro- and 2-chlorophenoxy)propionic acids. The separation factors of the enantiomers of all analytes are superior to those of the corresponding *N*-n-butyl amides.[14] The degree of enantioselectivity of the *N*-1-naphthylamide derivatives of 2-aryloxypropionic acids is greater than that of the corresponding *N*-2-naphthylamide derivatives. These observed results are considered to arise from the