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Chiral non-racemic dihydroxysulfones via hydrolytic kinetic resolutions—synthesis of oxacyclic ring systems using intramolecular acylation strategies

Chunyang Jin, Raina D. Ramirez and Aravamudan S. Gopalan*

Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces, NM 88003-8001, USA

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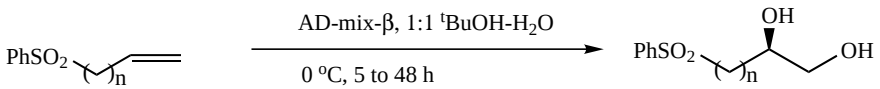
Abstract—A number of chiral non-racemic 1,2-dihydroxysulfones have been prepared in good yields and high enantiomeric excesses by hydrolytic kinetic resolution of the corresponding epoxysulfones with Jacobsen's (*S*,*S*)-salen(Co)III(OAc) catalyst. The intramolecular cyclization reactions of the acyl and ethoxycarbonyl derivatives of these dihydroxysulfones have been exploited to access a variety of functionalized chiral non-racemic cyclic ethers and lactones in good yields.

A major effort in our laboratory has been the development of asymmetric synthetic methods for the preparation of chiral hydroxysulfones and to exploit the intramolecular cyclization reactions of their derivatives to provide functionalized ring systems with stereochemical control.[1,2] The intramolecular cyclization reactions of some simple γ and δ acyloxysulfones have been shown to provide a convenient route for the preparation of a number of functionalized chiral non-racemic dihydrofurans and dihydropyrans.[1b] The corresponding cyclization reactions of the ethoxycarbonyl derivatives is also a valuable tool for the preparation of a variety of lactones and bicyclic lactones in good yields.[2]

A number of publications on the preparation of simple chiral hydroxysulfones using enzymatic reductions (for example baker's yeast) of the corresponding ketones or lipase catalyzed resolutions have appeared.[2,3] On the other hand, methodology to access chiral 1,2-dihydroxysulfones or other trifunctional hydroxysulfones are still very limited.[4] In this communication, we would like to report on a convenient way to make chiral 1,2-dihydroxysulfones using hydrolytic kinetic resolution of epoxysulfones with Jacobsen's (*S*,*S*)-salen(Co)III(OAc) catalyst. The usefulness of these dihydroxysulfones to the synthesis of a number of functionalized chiral cyclic ethers and lactones is also disclosed.

Asymmetric dihydroxylation (Sharpless AD) of terminal alkenes is a potentially useful and convenient method for accessing chiral non-racemic dihydroxysulfones.[5] However, the optical purities of the derived products are often not high in the Sharpless AD of 1-alkenes and the reaction is still being optimized.[6] The application of the Sharpless AD reaction to prepare chiral dihydroxysulfones of high optical purities was first investigated. A number of ω-phenylsulfonyl-1-alkenes **1a**–**d** were prepared and their oxidation reactions using commercially available AD-mix-β were studied (Eq. (1)). The enantiomeric excess of the diol products was determined by derivatization with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride followed by ^{19}F NMR spectral analysis. Unfortunately, in the case of the shorter chain alkenes **1a**–**c**, the diol products **2a**–**c** were obtained in good yields but unsatisfactory optical purities. Only the AD reaction of **1d** gave satisfactory yield and high optical purity of the corresponding product **2d**.



1a n=1
1b n=2
1c n=3
1d n=9

2a n=1, 88% yield, 42% ee
2b n=2, 92% yield, 53% ee
2c n=3, 82% yield, 37% ee
2d n=9, 98% yield, 92% ee

(1)

Keywords: hydrolytic kinetic resolution; dihydroxysulfone; intramolecular acylation; oxacyclic ring.
* Corresponding author. Tel.: +1 505 646 2589; fax: +1 505 646 2394; e-mail: agopalan@nmsu.edu

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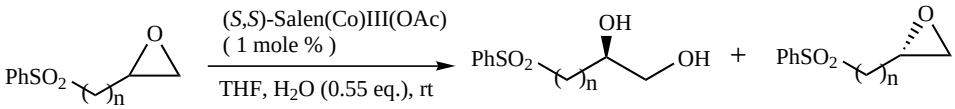
Recently, there has been much interest in the applications of the hydrolytic kinetic resolution (HKR) of terminal epoxides with Jacobsen's salen(Co)III(OAc) catalysts.[7,8] This method is versatile and is based on the enantioselective ring opening of a terminal epoxide by water or other simple nucleophiles in the presence of the chiral metal ligand catalyst. Access to either enantiomer of the desired dihydroxysulfones can be obtained with a simple change in the chiral catalyst. The application of this exciting method for the preparation of chiral dihydroxysulfones was then examined.



3a n=1
3b n=2
3c n=3
3d n=9

2a-d **4a-d**

(2)

The (±)-epoxysulfones **3a–d** required for our study were easily made from the corresponding ω-phenylsulfonyl-1-alkenes by oxidation with *m*-CPBA in good yields. The HKR reaction of these epoxides was carried out as per published procedures.[7] The epoxide in THF was stirred at room temperature in the presence of (*S*,*S*)-salen(Co)III(OAc) catalyst (1.0 mol%) and H_2O (0.55 equiv.) (Eq. (2)). The progress of the reaction was monitored by TLC, and the reaction worked up after approximately 50% conversion (10–30 h). The products 1,2-diols and the unreacted epoxide starting materials were separated by silica-gel chromatography.[9] Subsequently, the optical purities of the diols **2a–d** were determined by analysis of their di-MTPA esters. Samples of the epoxides **4a–d** were first hydrolyzed to the corresponding diols with 0.5N NaOH in H_2O–^{t}BuOH (5:1) at 60°C[10] and then the optical purities were determined as described earlier. The absolute configurations of the products were determined by application of the models for the HKR reactions as well as comparisons with literature values of optical rotations in the case of known compounds.[4]

It is pleasing to note that a number of 1,2-dihydroxysulfones as well as the corresponding epoxides can be prepared in good yields and high optical purities using the HKR reactions (Table 1). The only exception is in the case of the epoxide **4a**. The enantiomeric excess of this compound could not be reliably established due to its conversion to γ-hydroxyvinyl sulfone upon treatment with sodium hydroxide. The epoxide **3a** is also unstable to the HKR reaction conditions and some formation of the γ-hydroxyvinyl sulfone was observed in the crude product mixture.

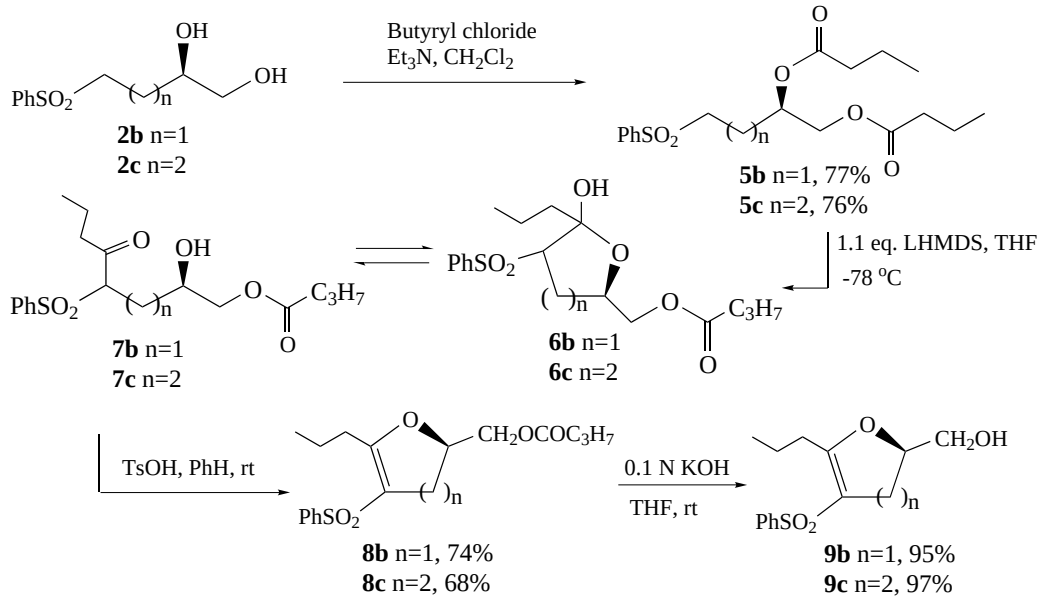
With these chiral non-racemic 1,2-dihydroxysulfones in hand, we were ready to examine the intramolecular cyclization reactions of their acyl and ethoxycarbonyl derivatives. The 1,2-di-acyloxysulfones **5b–c** were easily made by esterification of **2b–c** with excess butyryl chloride in the presence of Et_3N in CH_2Cl_2 (Scheme 1). In a representative sequence, the sulfone **5b** was treated with LHMDS (1.1 equiv.) in THF at −78°C for 3 h and then, the reaction quenched with saturated ammonium chloride at −78°C. The crude product that was isolated was an inseparable mixture of the lactol **6b** and the open chain hydroxy ketone **7b**.[1b] Dehydration of this mixture with TsOH in benzene gave the chiral dihydrofuran **8b**, as the only product in 74% yield after chromatographic purification. Clearly, the dominant pathway involves the cyclization of the sulfonyl carbanion of **5b** to give the five-membered ring rather than the six-membered ring product. Similarly, the cyclization reaction of **5c** followed by dehydration with TsOH gave dihydropyran **8c** rather than the corresponding seven-membered ring system in 68% yield. Basic hydrolysis of **8b** and **8c** gave **9b** ($[\alpha]_D = -66.8°$, *c* 1.7, $CHCl_3$) and **9c** ($[\alpha]_D = -117.2°$, *c* 1.5, $CHCl_3$), respectively.[11]

Intramolecular cyclization to give the larger ring systems (for example six rather than five) can be achieved by use of protected monoacyl derivatives of dihydroxysulfones **2b–c**. The primary alcohol of **2b–c** can be selectively esterified by reaction with butyryl chloride (1.0 equiv.) and Et_3N (1.0 equiv.) using dibutyltin oxide (0.02 equiv.) as a catalyst (Scheme 2).[12] These reactions gave **10b–c** in good yields with excellent selectivities (>15:1 for mono to di). Then the secondary alcohol was protected by treatment with TBDMS or TBDPS chlo-

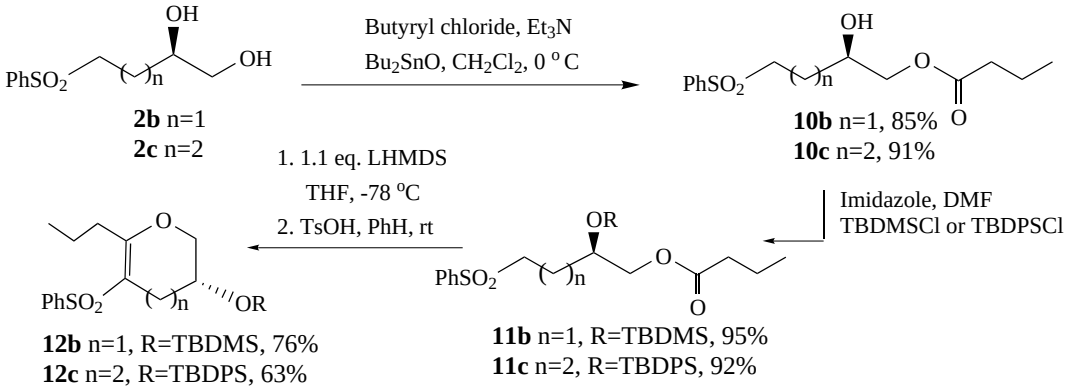
Table 1. Hydrolytic kinetic resolution of terminal epoxysulfones

Substrates	Diols **2a–d**		$[\alpha]_D$, *c* (g/dL)	Epoxides **4a–d**		$[\alpha]_D$, *c* (g/dL)
	Yield (%)	ee (%)[a]	EtOH	Yield (%)	ee (%)[b]	$CHCl_3$
3a	32	95	+21.0°, 1.4	50	–	−3.8°, 3.3
3b	44	94	+23.2°, 1.4	48	95	−24.4°, 3.1
3c	44	94	+20.5°, 1.4	48	92	−19.5°, 3.1
3d	44	>98	+9.1°, 1.4	49	91	−4.9°, 3.3

[a] Enantiomeric excesses were determined by ^{19}F NMR analysis of the corresponding di-MTPA esters.
[b] The epoxides were analyzed after conversion to diols.[10]



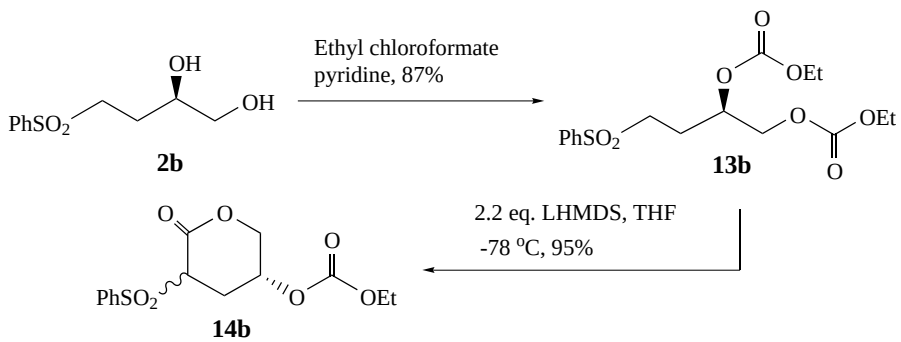
Scheme 1.



Scheme 2.

ride to give **11b** or **11c** in high yields. Treatment of **11b** with LHMDS (1.1 equiv.) in THF at −78°C for 2 h gave a mixture of lactol and the open chain hydroxy ketone. Subsequent dehydration of the mixture with TsOH in benzene gave the chiral dihydropyran **12b** ($[\alpha]_D = +33.6°$, *c* 1.1, EtOH) in 76% yield. The cyclization reaction of **11c** followed by dehydration gave the chiral seven-membered cylic ether **12c** ($[\alpha]_D = -70.7°$, *c* 1.1, EtOH) in 63% yield.

The intramolecular cyclization reaction of diethoxycarbonyl derivative of chiral 1,2-dihyroxysulfone **2b** has also been studied and gave some surprising results. The sulfone substrate **13b** was treated with 2.2 equiv. of LHMDS at −78°C and quenched after 1 h with saturated ammonium chloride (Scheme 3). Unexpectedly, a diastereomeric mixture of δ-lactone **14b** (1:1) was isolated as the only product in 95% yield.[13] In this case, cyclization occured to give the larger ring δ-lactone



Scheme 3.

system and no γ-lactone was detected in the product mixture. This result is opposite to that observed in the cyclization of the corresponding diacyl derivative **5b**, which favored the formation of the smaller ring. Further investigations are necessary to understand the observed ring selectivity in this cyclization.

In conclusion, Jacobsen's hydrolytic kinetic resolution provides an attractive method for the preparation of a number of chiral non-racemic 1,2-dihydroxysulfones in high ee. Furthermore, the intramolecular cyclization reactions of the acyl derivatives of these dihydroxysulfones are valuable for the preparation of a number of functionalized chiral non-racemic cyclic ethers in good yields. The intramolecular cyclization of ethoxycarbonyl derivative **13b** also proceeds efficiently but gives the functionalized δ-lactone as the only product in good yield. By proper choice of protecting groups, these cyclizations can be controlled to form various ring systems enhancing the synthetic utility of dihydroxysulfones. Finally, applications to the preparation of macrocyclic ring systems using this methodology are under investigation.

Acknowledgements

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11. Compound **9b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90–7.45 (m, 5H), 4.80–4.60 (m, 1H), 3.73–3.50 (m, 2H), 2.86 (t, $J=12.1$ Hz, 1H), 2.73–2.54 (m, 3H), 2.23 (br, 1H), 1.62 (tq, $J=7.7$, 7.7 Hz, 2H), 0.96 (t, $J=7.0$ Hz, 3H). Anal. calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43%. Found: C, 59.46; H, 6.60%.
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13. Compound **14b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.95–7.55 (m, 5H), 5.06 (dddd, $J=10.0$, 7.8, 6.1, 3.9 Hz, 0.5H), 4.82–4.58 (m, 1.5H), 4.31–3.93 (m, 4H), 2.72–2.40 (m, 2H), 1.09 (t, $J=7.1$ Hz, 1.5H), 1.08 (t, $J=7.2$ Hz, 1.5H). Anal. calcd for $C_{14}H_{16}O_7S$: C, 51.21; H, 4.91%. Found: C, 50.99; H, 4.85%.