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Dynamic Kinetic Resolution of Bis-Sulfinyl Chlorides: A General Enantiodivergent Synthesis of C_2-Symmetric Bis-Sulfinate Esters and Bis-Sulfoxides

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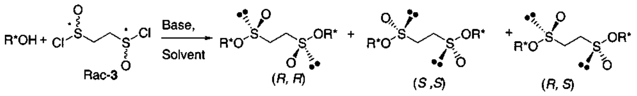
While the utilization of sulfoxides as chiral auxiliaries in highly asymmetric C−C bond formation in well documented,[1] their applications in catalytic asymmetric synthesis and in molecular recognition studies are scarce. Optically pure (o.p.) sulfoxides, especially C_2-symmetric bis-sulfoxides, offer unique features for their use as ligands in transition metal-catalyzed reactions as well as synthetic receptors. This is due to the inherent chirality of the coordinating sulfinyl sulfur atom[2] and its character as a strong hydrogen bond acceptor and weak Brönsted base.[3] Additionally, bidentate complexes of ruthenium(II) of various racemic ethane and propane bridged bis-sulfoxides have been shown recently to accumulate inside the cell and to interact with DNA, indicating their potential utilization as anticancer agents.[4] The main limitation for these applications is the absence of a general method able to yield compounds with two stereogenic sulfur atoms of known configuration.[5] We report here a general enantiodivergent approach to both isomers of C_2-symmetric ethane 1,2-bis-sulfoxides from the corresponding bis-sulfinate esters obtained by an *enantiodivergent dynamic kinetic resolution* of the starting bis-sulfinyl chlorides, (Scheme 1).

Condensation of 1 equiv (2 mmol) of glucose derived secondary carbinols, diacetone-D-glucose (DAGOH, **1**) or dicyclohexylidene-D-glucose (DCGOH, **2**), and 1 equiv (1 mmol) of ethane 1,2-bis-sulfinyl chloride[6] **3** in the presence of pyridine or Hunig's base gave 1,2-bis-sulfinate esters **4** and **5,** respectively, in high yield and high diastereoselectivity (Table 1). The diastereomeric ratio is easily determined by ^{1}H NMR analysis of the crude mixture in deuterated benzene,[7] based on the difference of the chemical shifts of the anomeric protons in the three possible diastereomeric sulfinate esters. As can be seen from Table 1, a major isomer is obtained in all the cases studied (higher than 80%). Taking into account that (i) only 1 equiv of the racemic ethane-1,2-bis-sulfinyl chloride has been used in all the runs, (ii) the conversion is occurring with nearly quantitative yield, and (iii) the diastereomeric ratio of the major diastereoisomer is always higher than 50%, we can affirm that the reaction is occurring via a dynamic kinetic resolution process,[8] rather than a simple kinetic resolution of the starting bis-sulfinyl chloride. The results given in Table 1 demonstrate unambiguously that the stereochemical outcome of the 1,2-bis-sulfinate ester synthesis for a given chiral auxiliary is tightly tied to the nature of the tertiary amine used to catalyze the reaction.[9] In the presence of pyridine, a high diastereoselection in favor of the C_2-symmetric (*R*,*R*) diastereoisomer (Table 1, entries 1 and 3) was observed. The (*R*,*R*) diastereoisomer is obtained in 84 mol % yield in the case of **5** (entry 3), together with the non-C_2-symmetric bis-sulfinate ester **5**-(*R*,*S*) (15%) and a small amount (1%) of the other C_2-symmetric diastereoisomer **5**-(*S*,*S*). A simple change of the tertiary amine used to catalyze the reaction from pyridine to *i*-Pr_2NEt shifts the diastereoselection in favor of the C_2-symmetric bis-sulfinate ester (*S*,*S*) (Table 1, entries 2 and 4) obtained in negligible amount in the former case. Only two of the three possible bis-sulfinate esters are obtained when Hunig's base is used as tertiary amine in up to a 88/12 ratio (*S*,*S*/*R*,*S*) in the case of bis-sulfinates **4**, and no trace of the major C_2-symmetric bis-sulfinate ester **4**-(*R*,*R*) formed with pyridine as base has been detected (Table 1, entry 2). Thus, the achiral base used is acting as a stereodirecting group allowing the synthesis of both bis-sulfinate esters with high diastereoselection. *To the best of our knowledge, this is the first report on an enantiodivergent dynamic kinetic resolution, with simultaneous creation of two chiral centers*. To test the potential of these sulfinate esters to transfer the chiral bis-sulfinyl ethane moiety and to determine their absolute configuration, various 1,2-bis-sulfoxides were synthesized (Scheme 2). Condensation of the

Table 1. Reaction of Ethane 1,2-Bis-Sulfinyl Chloride with Glucose-Derived Carbinols[a]



entry	alcohol[b] R*OH	base	solvent	major product[c]	diastereomeric ratio[d] (*R*,*R*):(*S*,*S*):(*R*,*S*)
1	DAGOH-**1**	pyridine	THF	**4**-(*R*,*R*)	82:1:17
2	DAGOH-**1**	*i*-Pr2NEt	toluene	**4**-(*S*,*S*)	0:88:12[e]
3	DCGOH-**2**	Pyridine	THF	**5**-(*R*,*R*)	84:1:15[f]
4	DCGOH-**2**	*i*-Pr2NEt	toluene	**5**-(*S*,*S*)	0:85:15

[a] All reactions were conducted in the indicated solvent at −75 °C; [b] DAGOH: diacetone-D-glucose, DCGOH: dicyclohexylidene-D-glucose; [c] Determined on ^{1}H NMR of the crude mixture; [d] Obtained in almost quantitative yield; [e] 60% yield for isolated **4**-(*S*,*S*); [f] 55% yield for isolated **5**-(*S*,*S*).

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(1) For reviews on the synthesis and utilization in C−C bond formation of chiral sulfoxides see: (a) Solladié, G. *Synthesis* **1981**, 185. (b) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717. (c) Kagan, H. B.; Diter, P. *Organosulfur Chemistry*; Page, P. C. B., Ed.; Academic Press: New York, 1998; Vol. 2, p 1. (d) Khiar, N.; Fernández, I.; Alcudia, A.; Alcudia, F. *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAI Press Inc.; Stamford, 2000; Vol. 2, Chapter 3.

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(7) Anomeric proton chemical shifts (in ppm) for the three diastereisomers of 1,2-bis-sulfinate esters **4** and **5** in C_6D_6 at 500 MHz: **4**-(*S*,*S*), 5.76; **4**-(*R*,*R*), 5.82; **4**-(*R*,*S*), 5.79 and 5.84; **5**-(*S*,*S*), 5.82; **5**-(*R*,*R*), 5.87; **5**-(*R*,*S*), 5.83 and 5.89.

(8) For reviews on DKR see: (a) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475. (b) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. (c) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, 447. (d) Stecher, H.; Faber, K. *Synthesis* **1997**, 1. (e) El Gihani, M. T.; Williams, J. M. *Curr. Op. Chem. Biol.* **1999**, *3*, 11.

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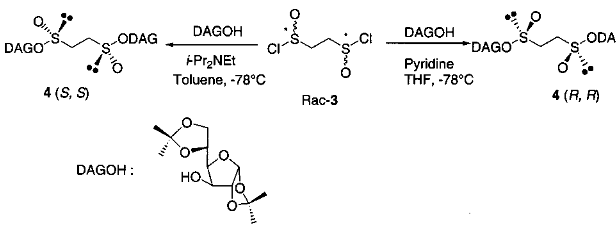
Scheme 1. Enantiodivergent Dynamic Kinetic Resolution of Ethane 1,2-Bis-Sulfinyl Chloride **3**



Scheme 2. Enantiodivergent Dynamic Kinetic Resolution Route to Optically Pure C_2-Symmetric Bis-Sulfoxides

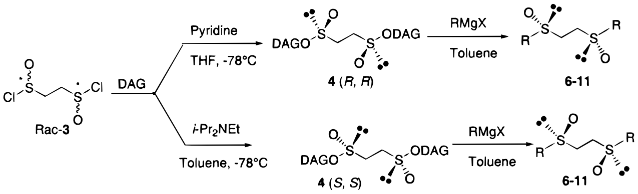
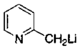
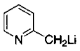


Table 2. Synthesis of Optically Active C_2-Symmetric Bis-Sulfinylethane, $RS(O)CH_2CH_2S(O)R$, from Chiral Ethane-1,2-bis-sulfinate Esters and RM[a]

	Bis-Sulfinate			Bis-Sulfoxide				
Entry	Comp	Conf. at S[b]	RM	Comp	Yield (%)[c]	de (%)	Config. (ee,%)	$[\alpha]_D$ (*c*, Solvent)[ref]
1	**4**	(*R, R*)	MeMgI	**6**	40	>98	*S, S* (>98)	+281 (*c* 0.5, EtOH)[5a]
2	**4**	(*R, R*)	^tBuMgCl	**7**	46	>98	*R, R* (>98)	+245 (*c* 0.5, EtOH)
3	**4**	(*R, R*)	*o*-AnMgI	**8**	52	>98	*R, R* (>98)	+650 (*c* 0.5, $CHCl_3$)[5c]
4	**4**	(*S, S*)	TolMgBr	**9**	54	86	*S, S* (>98)	-272 (*c* 0.5 MeOH)[5b]
5	**4**	(*R, R*)		**10**	60	64	*S, S* (>98)	+105 (*c* 1.0, $CHCl_3$)
6	**5**	(*S, S*)		**10**	50	70	*R, R* (>98)	-110 (*c* 0.8, $CHCl_3$)
7	**4**	(*R, R*)	$^tBuO_2CCH_2Li$	**11**	60	>98	*S, S* (>98)	+137 (*c* 1.0, $CHCl_3$)
8	**5**	(*S, S*)	$^tBuO_2CCH_2Li$	**11**	70	>98	*R, R* (>98)	-138 (*c* 1.0, $CHCl_3$)

[a] All reactions were carried out by adding 2 equiv of the organometallic reagent to a 0.05 M solution of the 1,2-bis-sulfinate ester in toluene. [b] Configuration of the major isomer. [c] Isolated yield after flash chromatography.

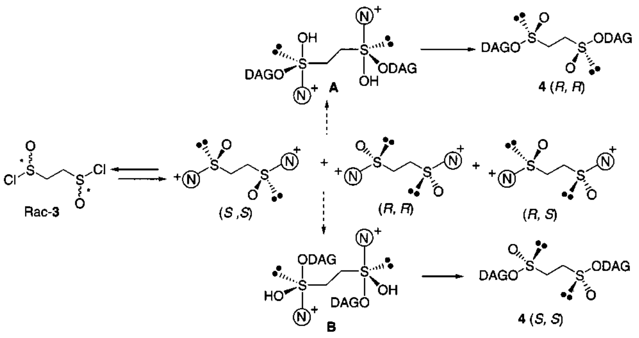


Figure 1. Possible pathways for the enantiodivergent dynamic kinetic resolution of racemic bis-sulfinyl chlorides **3**.

Grignard reagents on the crude sulfinate esters mixture led to the corresponding enantiomerically pure C_2-symmetric bis-sulfoxide together with the *meso* compound, easily separable by column chromatography. Various bis-alkyl, bis-aryl, and functionalized bis-sulfoxides have been obtained with high ee and dr in modest to good yields (Table 2). The modest yield obtained in the case of simple dialkyl and diaryl sulfoxides can be rationalized by a competing elimination reaction occurring after the first displacement step, as a consequence of the basisity of the protons α to the sulfoxide group. In accordance with this assumption are the good yields observed in the case of functionalized bis-sulfoxides (entries 7 and 8, Table 2), where the favored carbanion formation α to the sulfoxide and the ester group inhibits the elimination reaction.[10]

Since the absolute configuration of (*S,S*)-bis-(*p*-tolylsulfinyl) ethane **9** is known and the displacement step occurs with inversion of configuration at the sulfinyl sulfur,[11] the absolute configuration of the starting 1,2-bis-sulfinate ester can be determined. Thus, the major product obtained using pyridine as base should be (*R,R*), while the major isomer obtained with Hunig's base should have the (*S,S*) absolute configuration at the sulfinyl sulfurs. The diastereomeric ratio of the final bis-sulfoxides reflects exactly the diastereomeric ratio of the intermediate bis-sulfinate esters,[12] as was expected.

The stereodirecting base effect can be ascertained by assuming that 1,2-ethane bis-sulfinamides (Figure 1) formed from ethane 1,2-bis-sufinyl chlorides are the *active sulfur species* which interact with the chiral alcohol. As has been proposed for most dynamic kinetic resolution processes reported to date,[13] the enantiodivergent dynamic kinetic resolution of bis-sulfinyl chlorides can be rationalized by a continuous racemization process of two bis-sulfinamide intermediates along with the formation of a major bis-sulfinate ester from the third bis-sulfinamide, induced by the chiral secondary alcohol. Nevertheless, as the sulfur atom can undergo pseudorotation during the reaction, the EDKR reported here can be also explained by the formation of bis-sulfurane intermediates with two pentavalent sulfur atoms. Depending on whether the base used is pyridine or *i*-Pr_2NEt all the bis-sulfurane intermediates evolve by a Berry pseudorotation[14] process to bis-sulfurane **A** or bis-sulfurane **B** (Figure 1) which yields (*R,R*)- or (*S,S*)-bis-sulfinate ester respectively by extrusion of the amine.

The method reported here represents the first example of an enantiodivergent dynamic kinetic resolution with the simultaneous creation of two chiral centers. We are confident that the generality of this route will stimulate the synthetic utilization of C_2-symmetric compounds with two stereogenic sulfur atoms in general, and C_2-symmetric bis-sulfoxides in particular, in fields such as in asymmetric synthesis as ligands of transition metals, as well as in molecular recognition as chiral synthetic receptors. These aspects are currently being sought in our group.

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Supporting Information Available: Experimental procedure for the preparation of **3**−**11**; characterization data of **4**−**11**; ^1H NMR spectra of crude 1,2-bis-sulfinate esters **4** and **5**; fragments of the ^1H NMR spectra showing the assignation of the signals corresponding to the anomeric protons in the crude mixtures for the three diastereomers of **4** and **5**; ^1H and ^{13}C NMR spectra of optically pure bis-sulfinate esters **4**-(*S,S*) and **5**-(*S,S*) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Also in accord with this assumption is the detection in the ^1HNMR spectra of the crude mixture of signals at 5.8−6.7 ppm corresponding to the vinyl sulfoxides.

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(12) The result of the displacement step is always a mixture of a C_2-symmetric bis-sulfoxide and the corresponding *meso* diatereoisomer. The enantiomeric excess of the former should be very high taking into account that in the bis-sulfinate ester mixture, the minor bis-sulfinate ester leading to the C_2-symmetric bis-sulfoxide enantiomer is always present in negligible amount (0 to 1%, Table 1).

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