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Enantioselective synthesis of polycyclic ketones by desymmetrisation of bis(phenylsulfonyl)alkenes with chiral alcoholates. Control of the absolute configuration by a simple modification of the chiral auxiliary

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Abstract

Treatment of polycyclic bis(phenylsulfonyl)alkenes with chiral alcoholates, followed by acidic work-up, affords enantioselectively α-phenylsulfonyl ketones. The enantioselectivity is total with monomethylated hydrobenzoin and of opposite configuration with respect to that obtained with hydrobenzoin itself. Thus, starting from a bis(phenylsulfonyl)alkene, it is possible to obtain either the *R* or *S* polycyclic ketone by the use of the same chiral auxiliary (hydrobenzoin) and a simple modification (methylation of one of the hydroxy functions).

Keywords: desymmetrisation; asymmetric synthesis; polycyclic ketones; sulfones.

In standard asymmetric synthesis, the production of one or other enantiomer is usually accomplished by using one or other antipode of a chiral auxiliary. In practice, this is not always attainable because most chiral auxiliaries are of natural origin and available largely as only one enantiomer. It follows that, if the use of a chiral auxiliary leads, for example, to the enantiomer of *S* configuration, the production of the *R* enantiomer is not always convenient, and a completely different approach has to be frequently undertaken. To solve this problem, several strategies have been put forward that are often based on the change of a key substituent of the chiral auxiliary.[1] Here, we report on the switch of configuration that can be obtained in the recently reported procedure for the synthesis of chiral polycyclic ketones, based on the diastereoselective desymmetrisation of bis(phenylsulfonyl)alkenes.[2] As shown in Scheme 1, the change of configuration was observed when the desymmetrisation reaction, formerly reported with C_2-chiral diolates (upper part of Scheme 1), was performed with chiral alcoholates possessing the same backbone configuration (lower part of Scheme 1). The reaction with chiral alcoholates has the additional important advantage of leading directly to enantiomorphic α-phenylsulfonyl ketones (e.g. **4**) without

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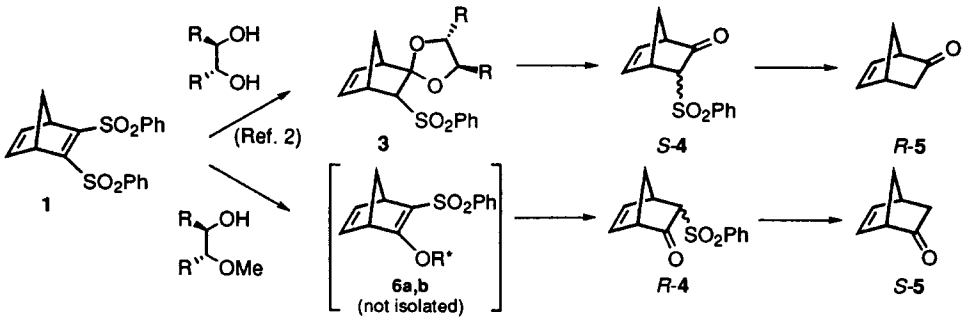
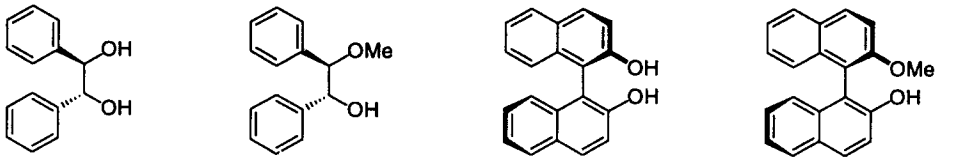
isolation of the diastereomorphic acetal of type **3** that is obtained with diolates. The phenylsulfonyl ketones produced afford polycyclic ketones such as **5** by reductive desulfonylation. When the reaction is totally stereoselective, ketosulfones **4** and ketones **5** are obtained as single enantiomers.



Scheme 1.

2,3-Bis(phenylsulfonyl)norbornadiene **1** was prepared on a large scale (up to 0.5 mol) by cycloaddition reactions of (*E*)-1-chloro-1,2-bis(phenylsulfonyl)ethylene to cyclopentadiene, followed by dehydrochlorination.[3] Reasoning that hydrobenzoin and binaphthol have already been shown to be very selective,[2] the monomethylated alcohols **2a′** and **2b′** were tested: they were obtained by monomethylation of the respective diols using the recent procedure that allows for minimisation of the dimethylated derivative.[4] The presence of a C_2 symmetry axis in the starting chiral diols (either hydrobenzoin and binaphthol) is important to avoid partitioning of the methylated products into two structurally different isomers.



The reaction of bis(phenylsulfonyl)norbornadiene **1** was performed in THF at −78°C with an equimolar amount of the sodium salts of alcohols **2a′** and **2b′** obtained using an equimolar amount of NaH (60% dispersion in mineral oil), and afforded the enol ether intermediates **6a,b**. The intrinsic instability of such enol ethers towards moisture did not permit their isolation in a pure state as they were partially converted into the ketosulfone **4**. Consequently, the ethereal solution of the crude reaction mixture containing the enol ethers **6**, was treated directly with a three-fold excess of 3 M HCl at room temperature, extracted with dichloromethane, dried over sodium sulfate and recrystallised from diethyl ether to obtain, in a one-pot procedure, the ketosulfone **4** separated from the chiral auxiliary that remained in solution. The latter auxiliaries could be recovered in excellent yields by rotoevaporation of the mother liquors with no loss of enantiomeric excess.

The enantioselectivity of the reaction was determined by chiral HPLC analysis of the ketosulfone **4** (Chiracel OD-H column, eluent: hexane:*i*-PrOH:MeOH 91:6:3 with CF_3COOH 0.1%). The enantiomeric excesses, together with yields and absolute configurations of the ketosulfone **4** obtained with alcohols **2a,′b′** and, for comparison, those obtained with diols **2a,b** are reported in Table 1. The reaction with (*R,R*)-hydrobenzoin monomethyl ether **2a′** (entry 2 in Table 1) proved totally stereoselective affording exclusively the ketosulfone **4** as the (*R*)-enantiomer [$[\alpha]_D^{23}$ −257 (c=1.0, $CHCl_3$)]. Most notably, the absolute configuration of **4** obtained from (*R,R*)-hydrobenzoin **2a** itself (upper part of Scheme 1, entry 1 in Table 1) and its monomethylated derivative **2a′** (lower part of Scheme 1, entry 2 in Table 1) are

Table 1
Yields,[5] enantiomeric excesses and absolute configurations of **4**[6] as obtained from the reaction of **1** with the sodium diolates **2a**,**b**[2] and alcoholates of **2a**,'**b**'

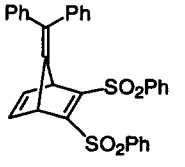
#	Diol/Alcohol	Yield (%)	Enantiomeric excess(%)[a]	Absolute Configuration[b]
1	**2a**	84[c]	>98	(+)-(*S*)
2	**2a'**	70[d]	>98	(–)-(*R*)
3	**2b**	92[e]	>98[e]	(*R*)[e]
4	**2b'**	68[d]	55	(+)-(*S*)

[a]Determined by chiral HPLC on Chiralcel OD-H. The ee's refer to both epimers of **4** (Ref. 5).[b]The stereochemistry of **4** was assigned by comparisation with a sample of known absolute stereochemistry (X-ray crystallography) and optical rotation (Ref. 2). [c]Overall yields of a two step procedure (see Ref. 2). [d]**General Procedure:** To a solution of alcohol (1 mmol) in dry THF (2 mL), maintained at 0 °C under argon atmosphere, was added NaH 60% dispersion in mineral oil (1 mmol). After 30 min disulfone **1** (1 mmol) in dry THF (1 mL) was added at -78°C. The solution was stirred at r.t. for 24 hours, H_2O added, extracted with Et_2O, dried over $MgSO_4$ and concentrated *in vacuo*. [e]Data refers to the ketoacetal **3** (Ref. 2).

opposite. In the case of (*R*)-binaphthol, such a switch of configuration changing from **2b** and **2b'** (entries 3 and 4 in Table 1) is also observed but the ee of the ketosulfone **4** as obtained from **2b'** is poorer than that observed with hydrobenzoin.

The use of standard chiral auxiliaries containing an alcoholic functionality such as (–)-menthol, (1*R*)-*endo*-(+)-fenchyl alcohol and (+)-isopinocampheol proved unrewarding. Even chiral alcohols notoriously known to afford high levels of stereoselection because of their concave structures such as (–)-8-phenylmenthol and (+)-(1*S*,2*R*)-*trans*-2-phenylcyclohexanol were ineffective in this desymmetrisation reaction giving rise to only modest selectivities (ee 5–23%).

The desymmetrisation reaction of hydrobenzoin **2a** and its monomethyl derivative **2a'** was also tested on the other vicinal bis(phenylsulfonyl)alkenes **7–9** in order to test the generality of the reaction and to confirm the switch in configuration. The bis(phenylsulfonyl)alkenes **7–9** were obtained by cycloaddition reactions of (*E*)-1-chloro-1,2-bis(phenylsulfonyl)ethylene to diphenylfulvene, 1,3-cyclohexadiene and quadricyclane, respectively, followed by dehydrochlorination[3] and the desymmetrisation reaction afforded ketosulfones **10–12** represented below. Only in the case of the diphenylfulvene derivative **7**, was the switch in configuration on changing the diol **2a** to its monomethylated alcohol **2a'** confirmed, although the stereoselectivity obtained with the alcohol proved poorer than that observed with the diol (Table 2). In the [2.2.2]-system **8** the reaction with **2a'** gave a racemic ketosulfone, while no changes were observed in the tricyclic system **9**. These results suggest a strong dependence of the stereoselectivity of the reaction on the steric hindrance of the bridge skeleton of bis(phenylsulfonyl)alkenes used.



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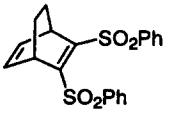

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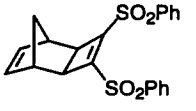

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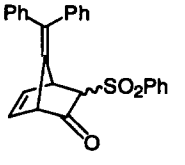

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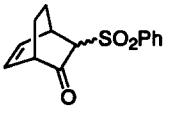

11 (and enantiomer)

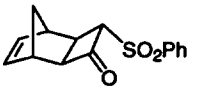

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Table 2
Yields,[5] enantiomeric excesses and absolute configurations of **10–12**[6] as obtained from the desymmetrisation of bis(phenylsulfonyl)alkenes **7–9** with **2a** and **2a'**

#	Substrate	Diol/Alcohol	Yield (%)	Enantiomeric excess(%)[a]	Absolute Configuration[b]
1	**7**	**2a**	92[c]	92	(–)-(*S*)
2	**7**	**2a'**	68	47	(+)-(*R*)
3	**8**	**2a**	92[c]	95	(-)-(*R*)
4	**8**	**2a'**	75	0	–
5	**9**	**2a**	63[c]	>98	(+)-(*R*)
6	**9**	**2a'**	85	>98	(+)-(*R*)

[a]Determined by chiral HPLC on Chiralcel OD-H. [b]The stereochemistry of all ketosulfones was assigned by comparisation with a sample of known absolute stereochemistry (X-ray crystallography) and optical rotation (Ref. 2). [c]Overall yields of a two step procedure (see Ref. 2).

In our mind, the present procedure with monomethylated hydrobenzoin **2a'** represents a definite improvement over that reported with hydrobenzoin itself **2a** for obtaining enantiopure polycyclic ketones such as **5** because of yields, efficiency and simplicity of operations.[2] It also represents, in general, a convenient method of preparation of such ketones in optically pure form.[7–10] Derivatives of **5** are key intermediates in the preparation of a number of compounds including biologically active natural products,[11] antibiotics,[12] prostaglandins,[13] drugs used in cancer[14] and AIDS therapy.[15]

Acknowledgements

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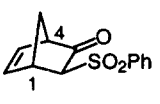
5. It is important to point out that the ketosulfone **4** is obtained in most cases as a mixture of epimers at the carbon atom of the sulfonyl group. In other words the product is obtained as a variable mixture of the *exo* (e.g. **i**) or *endo* isomers (e.g. **ii**).



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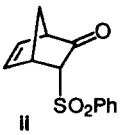

ii

The ratio between these two epimers is not dependent on the stereoselectivity of the desymmetrisation reaction and it is not considered in our discussion.
6. The absolute configuration given to the polycyclic ketosulfones refers to carbon atom 1 in the von Baeyer nomenclature rules.
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