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Li^+ and Na^+ switch of enantioselectivity in the desymmetrisation of polycyclic bis(phenylsulfonyl)alkenes by chiral alcohols

Sergio Cossu,* Ottorino De Lucchi,* Paola Peluso and Raffaella Volpicelli

Dipartimento di Chimica, Università Ca' Foscari Venezia, Dorsoduro 2137, I-30123 Venezia Italy

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Abstract

A complete switch of enantioselectivity is obtained in the desymmetrisation reaction of polycyclic bis(phenylsulfonyl)alkenes by the change of the base from *n*-BuLi to NaH, thus allowing convenient access to either enantiomer of polycyclic ketones with the same chiral auxiliary. © 2000 Published by Elsevier Science Ltd.

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The important issue of the preparation of either one of two enantiomers has been addressed several times in asymmetric synthesis. Such an operation is most simply achieved by changing the configuration of the chiral auxiliary (or ligand) but, since the chiral auxiliary is usually a natural compound (or a derivative), often only one enantiomer is readily available. We have reported on the efficient enantiotopic discrimination between carbon atoms of a double bond of C_s-symmetric bis(phenylsulfonyl)alkenes in reactions with sodium salt of chiral diols[1] and more recently of chiral alcohols.[2]

As reported for 2,3-bis(phenylsulfonyl)norbornadiene **1a**, chosen as the main test substrate (Scheme 1), and for bis(phenylsulfonyl)alkenes **1b–d**, the reaction with chiral alcoholates derived from *R*,*R*-(+)-1,2-diphenyl-2-methoxyethanol [*R*,*R*-(+)-hydrobenzoin monomethylether] (**2a**)[3a] and *R*-(+)-2-hydroxy-2′-methoxy-1,1′-binaphthalene [*R*-(+)-binaphthol monomethylether] (**2b**)[3b] followed by hydrolysis of the enolether species **3a**,**d**, gives the ketosulfones **4a**,**d**. These afford ketones **5a**,**d** by reductive desulfonylation (Scheme 1).[2] Enantiopure polycyclic ketones of this sort are key intermediates in the preparation of a number of important biologically active products:[4] the preparation of such compounds in optically active form is often troublesome through classical methodologies.[5]

* Corresponding author. E-mail: cossu@unive.it

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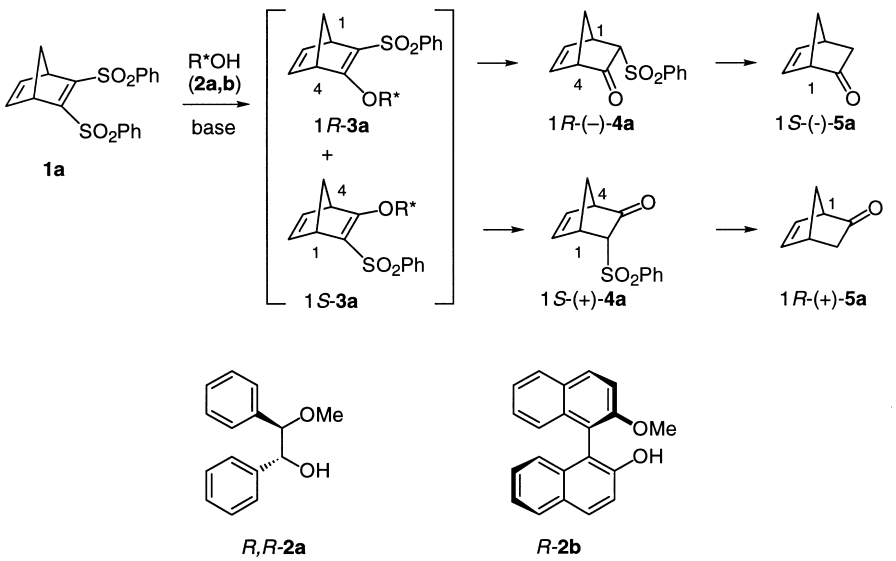
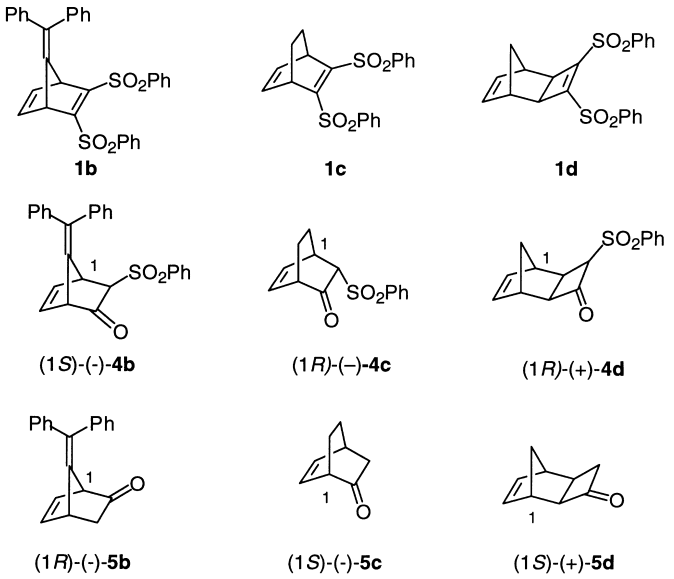


Scheme 1.

Here, we present an unusual, complete switch of enantioselectivity which was observed on changing the counterion of the base used to generate the nucleophile from **2a**,**b** from Na^+ to Li^+. To the best of our knowledge, only a few other reports in the literature concern drastic changes in selectivity on varying the counterion.[6]

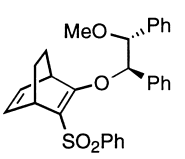


Treatment of the bis(phenylsulfonyl)alkenes **1a**–**d** with an equimolar amount of alcohols **2a**,**b** and *n*-BuLi (1 equiv. of a 2.5 M solution in hexanes) in THF leads to enol ether intermediates (e.g. **3a**), whose isolation and full characterisation proved possible only in a few cases (i.e. for **3c** and **3d**), while in the other cases they were partially converted into the ketosulfones **4a**–**d** during

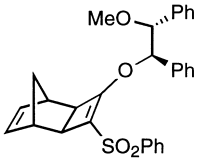
Table 1
Reaction of **1a–d** with lithium and sodium salts of alcohols **2a,b** in THF. Yields, enantiomeric excesses and absolute configuration of the resulting ketosulfones **4a–d**

#	1a-d	2a,b	Method	Yield(%)	E.e(%)[7]	Abs.Conf.[8]
1	**1a**	**2a**	*n*-BuLi	72	98	1*S*-(+)
2	**1a**	**2a**	NaH	70	98	1*R*-(-)
3	**1a**	**2a**	NaH/LiCl	70	97	1*S*-(+)
4	**1a**	**2a**	*n*-BuLi/TMEDA	70	70	1*S*-(+)
5	**1a**	**2b**	*n*-BuLi	75	55	1*S*-(+)
6	**1a**	**2b**	NaH	68	55	1*R*-(-)
7	**1b**	**2a**	*n*-BuLi	72	17	1*S*-(-)
8	**1b**	**2a**	NaH	68	47	1*R*-(+)
9	**1c**	**2a**	*n*-BuLi	68	25	1*R*-(-)
10	**1c**	**2a**	NaH	75	0	-
11	**1d**	**2a**	*n*-BuLi	75	98	1*R*-(+)
12	**1d**	**2a**	NaH	85	98	1*R*-(+)

purification (the configuration of the structures shown refers to the reaction obtained with *n*-BuLi and **2a** as chiral alcohol).



1*S*-(–)-**3c**



1*S*-(–)-**3d**

In view of this fact and for the sake of consistency, the ethereal solution of the crude reaction mixtures containing the enol ethers was directly treated with 3 M HCl at room temperature to deliver ketosulfones **4a–d**: after purification,[2] the chiral auxiliaries were recovered without loss of optical activity. The efficiency of the stereoselective process was determined by measuring the enantiomeric excesses of the ketosulfones **4a–d** by HPLC (Chiralcel OD-H). The results obtained using either NaH and *n*BuLi, including yields, e.e. and absolute configurations are reported in Table 1.

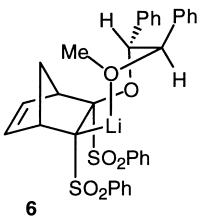
As shown in rows 1 and 2 of Table 1, a total reversal of selectivity was observed upon varying the counterion from sodium to lithium. Despite the minor stereoselectivity, the change of configurations confirmed with the substrates **1b,c** (lines 7–10 of Table 1); in the case of **1d** high stereselectivity was observed without change of configuration (lines 11 and 12 of Table 1).

The change of configuration was also observed on changing the counterion from sodium to lithium when 2-hydroxy-2′-methoxy-1,1′-binaphthalene **2b** is employed as the chiral alcohol (lines 5 and 6 of Table 1).

The effect of additives, such as LiCl and TMEDA were examined. The NaH promoted reaction in THF, in the presence of LiCl (twofold excess, row 3, Table 1) gave the same selectivity observed in the reaction employing *n*-BuLi as base. The use of TMEDA (1 equiv., **2a** lithium salt,

row 4, Table 1) provides an intermediate result leading to a decreased enantiomeric excess of ketosulfone **4a**.

The stark difference in stereoselectivity observed on changing from lithium to sodium can be tentatively rationalised by considering the steric effects of the reactive species and the different complexing ability of the metals. Taking into account the propensity of the lithium ion to form coordinated species, we speculate that the *re* face attack is due to the formation of thermodynamically preferred intermediate **6** with both phenyl rings in the pseudoequatorial conformation. At variance, the sodium ion, which is notoriously less prone to coordination, leads to an attack on the *si* face because of the kinetic preference of the nucleophile to enter through the least sterically hindered trajectory as indicated in **7**. In both cases it is assumed that the attack of the nucleophile occurs on the *exo* face of the substrate as it is largely known for this system.



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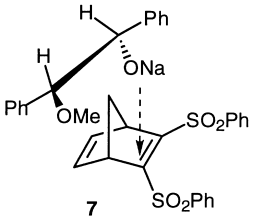

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In conclusion, we have provided an example of preparation of either one of the enantiomer of polycyclic ketone **5a** by the simple change of the counterion and we have speculated that this fact is due to the different coordinative behaviours of a lithium and a sodium cation.

Acknowledgements

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8. The stereochemistry of all ketosulfones **4a**,**d** are assigned by comparison of the HPLC and optical rotation data with those of samples of known absolute configuration (X-ray crystallography, NMR).