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A GENERALIZATION OF THE BASE EFFECT ON THE DIASTEREOSELECTIVE SYNTHESIS OF SULFINIC AND PHOSPHINIC ESTERS

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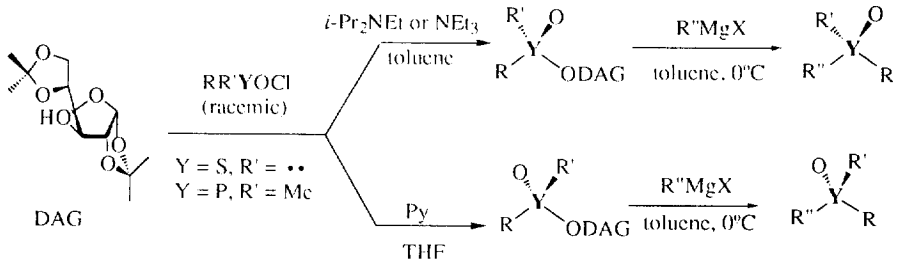
Abstract : Various chiral secondary alcohols have been used to study the dependence of the stereochemical outcome of sulfinate and phosphinate ester synthesis on the nature of the base used to catalyse the reaction. From this study it has been shown that the achiral stereodirecting base effect determined in the *DAG methodology* is a general behaviour in the asymmetric synthesis of sulfinate and phosphinate esters.

Some years ago we developed a general and practical route to both enantiomerically pure sulfoxides which we named "*DAG methodology* "[1] as it uses the glucose derivative diacetone-*D*-glucose (DAG) as inducer of chirality in the reaction of this alcohol with an alkane- or arenesulfinyl chloride to give the corresponding (R_S)- or (S_S)-sulfinate.[2] The *DAG methodology* is unique in its kind because the achiral base used to catalyse the reaction acts as chiral stereodirecting group. Most interestingly, we have shown the existence of two kinds of bases able to induce complete stereocontrol in the sulfinate synthesis and in opposite manner. In a predictable manner *pyridine like bases* induce mainly the formation of (R_S)-sulfinates, while *Hunig like bases* promote the synthesis of (S_S)-sulfinate as a single isomer in most cases, Scheme 1 (Y=S, R'=••).



Scheme 1

A simple inspection of the literature indicated that the methodologies reported for the synthesis of chiral sulfinate esters[3] work equally well for phosphinate esters,[4] showing identical behaviour for both types of compound. As anticipated, the achiral stereocontrolling base effect in the phosphinate synthesis has been observed in an identical manner to that in the sulfinate synthesis.[5] Using a single inducer of chirality, diacetone-*D*-glucose, both phosphinate esters, R_P and S_P, can be obtained in a predictable manner by a simple change of the base used, Scheme 1 (Y=P, R'=Me). Thus, the *DAG methodology* has been extended to the synthesis of optically pure P-chiral phosphine oxides which are precursors of P-chiral phosphines and diphosphines, important ligands for transition metal catalysis of enantioselective reactions. An important question is whether the achiral stereodirecting base effect observed with DAG is a particular case due to this alcohol or a general behaviour of secondary chiral carbinols. In order to answer this question and to get better

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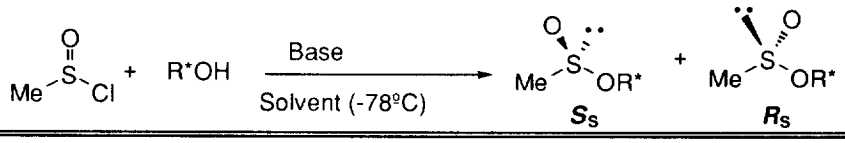
insight into the mechanism of the reaction, we report in this communication the generalization of the base effect in the synthesis of other chiral methanesulfinates and methyl phenyl phosphinates.

The reactivity of different chiral carbinols with methanesulfinyl chloride was checked up using the optimal conditions previously determined for DAG.[1]

Table 1: Reaction of methanesulfinyl chloride with different chiral secondary alcohols.

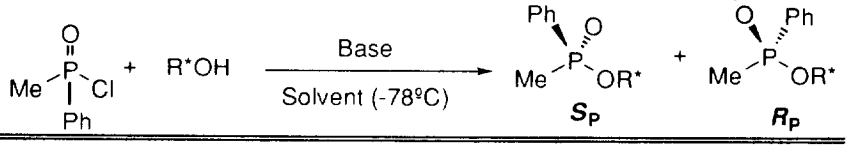


Entry	Alcohol	Base[a]	Yield (%)	Diast. Ratio[b] S_S/R_S	d. e. (%)
1	Diacetone-*D*-glucose	Pyridine	87	7/93	86
2		*i*-Pr$_2$NEt	90	≥98/≤2	≥96
3	Dicyclohexylidene-*D*-glucose	Pyridine	53	6/94	88
4		*i*-Pr$_2$NEt	92	≥98/≤2	≥96
5	[(1*S*)-*endo*]--(—)-Borneol	Pyridine	61	74/26	48
6		*i*-Pr$_2$NEt	68	38/62	24
7	(1*S*, 2*R*, 5*R*)--(+)-Isomenthol	Pyridine	86	65/35	30
8		*i*-Pr$_2$NEt	95	40/60	20
9	(1*S*, 2*R*, 3*S*, 5*R*)-(+)--Isopinocampheol	Pyridine	80	46/54	8
10		*i*-Pr$_2$NEt	92	65/35	30
11	(—)-Cholesterol	Pyridine	≥95	52/48	4
12		*i*-Pr$_2$NEt	≥95	47/53	6
13	(1*R*, 2*S*, 5*R*)--(—)-Menthol	Pyridine	≥95	28/72	44
14		*i*-Pr$_2$NEt	≥95	71/29	42
15	(*R*)-(—)-3,3-Dimethyl-2--hydroxy-γ-Butyrolactone	Pyridine	70	61/39	22
16		*i*-Pr$_2$NEt	74	49/51	2
17	Methyl (*S*)-(—)-Lactate	Pyridine	83	39/61	22
18		*i*-Pr$_2$NEt	87	54/46	8

[a]The solvents used were THF with pyridine and toluene with *i*-Pr$_2$NEt. [b]Determined by ^{1}H NMR analysis of the crude.

The results obtained, summarised in Table 1, show that the stereocourse of this reaction is tightly tied to the nature of the base used. The differences in the chemical shifts of various proton signals allowed determination of the diastereoisomeric ratio by ^{1}H NMR of the crude mixture.[6] The highest d.e. was obtained with dicyclohexylidene-*D*-glucose (DCG) as predicted from its structural similarity with DAG. The (*R*)-sulfinate was obtained as the major isomer with pyridine (88% d.e., entry 3) while the (*S*)-sulfinate was the only isomer detected with *i*-Pr2NEt (d.e. ≥ 96%, entry 4). (+)-Isopinocampheol, (—)-menthol, and methyl (*S*)-(—)-lactate showed a similar behaviour to DCG but the d.e.'s obtained were markedly lower. On the other hand,(—)-borneol, (+)-isomenthol, (—)-cholesterol and (*R*)-3,3-dimethyl-2-hydroxy-γ-butyrolactone yielded mainly the (*S*)-sulfinate as the major isomer with pyridine (entries 5, 7, 11 and 15) and the (*R*)-sulfinate with *i*-Pr2NEt (entries 6, 8, 12 and 16). Surprisingly, the lowest d.e.'s (4 % and 6%, entries 11 and 12) were obtained with (—)-cholesterol which was the first chiral alcohol used in the synthesis of optically pure methanesulfinates on route to optically pure methyl alkyl sulfoxides.[7] The absolute configuration of each sulfinate was assigned by transforming it into the known methyl *p*-tolyl sulfoxide, by treatment with the Grignard reagent, *p*-tolyl magnesium bromide, assuming that the displacement step occurs with complete inversion of configuration.[8]

Table 2: Reaction of methyl phenyl phosphinyl chloride with different chiral secondary alcohols.[a]



Entry	Alcohol	Base[b]	Diast. Ratio[c] S_P/R_P	d. e. (%)
1	Diacetone-*D*-glucose	Pyridine	25/75	50
2		NEt3	97/3	94
3	Dicyclohexylidene-*D*--glucose	Pyridine	30/70	40
4		NEt3	95/5	90
5	[(1*S*)-endo]-(—)--Borneol	Pyridine	75/25	50
6		NEt3	58/42	16
7	(1*S*, 2*R*, 5*R*)-(+)--Isomenthol	Pyridine	58/42	16
8		NEt3	13/87	74
9	(1*S*, 2*S*, 3*S*, 5*R*)-(+)--Isopinocampheol	Pyridine	44/56	12
10		NEt3	57/43	14

[a]Reactions were stopped when all the alcohol had reacted, obtaining the phosphinate esters in nearly quantitative yield.[b]The solvents used were THF with pyridine and toluene with NEt3. [c]Determined by ^{1}H NMR analysis of the crude.

Having demonstrated that the stereochemical outcome for the formation of sulfinate esters is base dependent we turned our attention to generalization of this effect in the phosphinate ester synthesis. The results of this study are summarised in Table 2. As before, the d.e.'s were calculated by ^{1}H NMR spectroscopy of the crude mixture[6] and the absolute configuration at the phosphorus atom in the major isomer by transforming it into a known phosphine oxide.[5] The highest d.e. was obtained, again, with the *D*-glucose derivatives DAG and DCG. Moreover, in all the cases studied, the achiral stereocontrolling effect of the base was observed, indicating once again a similar stereochemical behaviour of sulfinate and phosphinate esters. Thus, the *DAG methodology* is not limited to sulfinate esters but also to phosphinate synthesis.

In conclusion, the results presented here demonstrate unambigously that the stereochemical outcome of the sulfinate and phosphinate ester synthesis is highly dependent up on the nature of the base used and that we are dealing with a general stereochemical behaviour in this kind of synthesis. We do believe that this effect is a consequence of the participation of an hypervalent sulfur and phosphorus atom. In our proposed mechanism,[1a] a Berry pseudorotation of the alleged sulfurane or phosphorane intermediate would account for the stereoselectivity observed.

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2. The *DAG methodology* is emerging as the method of choice for the synthesis of optically pure sulfoxides, especially those which in general can not be obtained by the methods reported in the literature. See for example: (a) El Ouazzani, H; Khiar, N; Fernández, I.; Alcudia, F. *J. Org.Chem.* **1997**, *62*, 287. (b) García Ruano, J.L.; Fernández, I.; Del Prado Catalina, M.; Alcudia Cruz, A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407. (c) Hase, N.; Watanabe, Y.; Toru, T. *J. Org. Chem.* **1998**, *63*, 3899. (d) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B.J.; Ellman, J.A. *J. Am. Chem. Soc.* **1998**, *120*, 8011. (e) Gautier, N.; Noiret, N.; Nugier-Chauvin, C.; Patin, H. *Tetrahedron: Asymmetry* **1997**, *8*, 501. (f) Díaz Buezo, N.; Alonso, I.; Carretero, J.C. *J Am. Chem. Soc.* **1998**, *120*, 7129.

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6. All the spectroscopic data (NMR and Mass Spectrometry) were in good agreement with the proposed structures. All the NMR data (^{1}H and ^{13}C) were unambigously assigned by recording DQF-COSY, TOCSY, HSQC, HMBC and NOESY (or ROESY) 2D experiments from the crude sulphinates or phosphinates mixtures.

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9. See for example: Mislow, K. *Acc. Chem. Res.* **1970**, *3* , 321.