Enantioselective Catalytic Oxidation of (Arylthio)- or (Alkylthio)methylphosphonates as a Route to Enantiomeric Pure Aryl Alkyl or Dialkyl Sulfoxides

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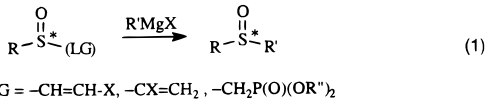
Received August 10, 1998

Chiral nonracemic sulfoxides are enjoying a deserved popularity among organic chemists due to the number of reactions in which they can be used for the transfer of chirality.[1,2] As a consequence, the search for new methods leading to enantiomerically pure sulfoxides represents a synthetic theme of high interest. Despite these efforts, after almost forty years, the Andersen procedure is still the method of choice for the preparation of optically active sulfoxides.[2,3] However, the procedure, which is based upon the reaction of organometallic reagents with a menthyl arylsulfinate, is practically restricted to the synthesis of diaryl or aryl alkyl sulfoxides. Menthyl alkanesulfinates, which are necessary for the synthesis of dialkyl sulfoxides, cannot be prepared with the enantiomerically pure sulfur center. Due to these drawbacks, in the past decades a variety of approaches have been introduced. Modified Andersen procedures in which the leaving group is derived from a chiral auxiliary different from menthol have been used.[4−7]

In principle, the enantioselective oxidation of sulfides to sulfoxides represents an attractive and straightforward route. Besides biocatalyzed oxidations,[8] useful chemical oxidating agents have been also reported.[9−12] Kagan,[9] Modena, and Di Furia[10] have utilized a modified Sharpless alkyl hydroperoxide/diethyl tartrate/Ti(IV) system with or without added water. Uemura[11] has adopted a catalytic procedure based upon the use of hydroperoxides in the presence of binaphthol/Ti(IV) complexes and water. Despite these efforts, the preparation of enantiomerically pure dialkyl sulfoxides still remains an uphill task.

In recent work,[13−15] we have introduced the use of carbanionic leaving groups in the reaction of sulfinyl or phosphinyl derivatives with organometallic reagents. Focusing the attention on the sulfur series, we found that halovinyl[13,14] and dialkyl methylphosphonate[15] moieties bound to the sulfur atom behave as leaving groups in the reaction with organometallic reagents (eq 1).



We report now the successful enantioselective oxidation of commercially available diethyl (methylthio)methylphosphonate, **1**, diethyl (ethylthio)methylphosphonate, **2**, and diethyl (phenylthio)methylphosphonate, **3**, with hydroperoxides at room temperature in the presence of catalytic amounts of the complex formed in situ from Ti(O-*i*-Pr)$_4$, (+)-1,1′-bi-2-naphthol (BINOL) and water, with ee values in the range 91−>98%. The reaction produced the corresponding diethyl (methylsulfinyl)methylphosphonate, **4**,[16] diethyl (ethylsulfinyl)methylphosphonate, **5**,[17] and diethyl (phenylsulfinyl)methylphosphonate, **6**,[18] in ee values up to >98% (Table 1). The ee values of the products **4**−**6** were determined by ^{1}H NMR techniques (500 MHz), by using (*S*)-BINOL as a chiral solvating agent.[19]

The suggested mechanism for the enantioselective oxidation of sulfides in the presence of titanium/BINOL complexes is based on a combination of an enantioselective oxidation followed by a kinetic resolution of the formed sulfoxide.[11] When the (methylthio)methylphosphonate **1** was reacted with a strong excess of oxidant, a high amount of the undesired sulfone was obtained (entry 1). The addition of a smaller amount of oxidant caused a decrease in the produced sulfone (entries 2−6), whereas the enantiomeric purity of the formed sulfoxide remained unchanged. This result suggests that the oxidation promoted by the catalyst in our case is a genuine fully enantioselective process, without a significant contribution from kinetic resolution. The use of *tert*-butyl hydroperoxide (entries 1, 2, 4−8) or cumene hydroperoxide (entry 3) showed no significant difference. Water was found to have a beneficial, although not fully understood, effect, even in the large excess required in our reactions. Sulfides **2** and **3** were oxidized according to the optimized reaction conditions, obtaining sulfoxides **5** and **6** (entries 7 and 8). The configuration of sulfinylmethylphosphonates was inferred from the configuration of the sulfoxides produced in the reaction with organometallic reagents, which is known to occur with inversion of configuration.[15]

The sulfinylmethylphosphonates **4**-**6** were converted into sulfoxides having the same ee values by reaction with primary, secondary, tertiary, vinyl, and aryl Grignard reagents to give

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10.1021/ja982836w CCC: $18.00
Published on Web 05/04/1999

Table 1. Enantioselective Hydroperoxide Oxidation of Thiomethylphosphonates **1**−**3** Mediated by a Chiral Titanium/BINOL Catalyst

1-3 **4-6**

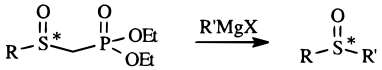
ox*= TBHP or CHP, Ti(O-*i*-Pr)$_4$/BINOL/H_2O

Ratios: Ti(O-*i*-Pr)$_4$:BINOL: water: substrate 1:2:20:40

entry	R	reagent	BINOL config.	oxidant	substr./oxid. ratio	products ratio[a]	product[b]	yield (%)[c]	ee (%)[d]	$[\alpha]_D$[e]
1	Me	**1**	(*R*)	TBHP	1:2	0:60:40	(*S*)−(**4**)	39	>98	
2	Me	**1**	(*R*)	TBHP	1:1.2	0:80:20	(*S*)−(**4**)	68	>98	
3	Me	**1**	(*R*)	CHP	1:1.2	0:82:18	(*S*)−(**4**)	*f*	>98	
4	Me	**1**	(*R*)	TBHP	1:1.1	2:91:7	(*S*)−(**4**)	85	>98	−55.9
5	Me	**1**	(*R*)	TBHP	1:1	9:85:6	(*S*)−(**4**)	*f*	> 98	
6	Me	**1**	(*S*)	TBHP	1:1.1	2:91:7	(*R*)−(**4**)	86	>98	+55.4
7	Et	**2**	(*R*)	TBHP	1:1.2	9:84:7	(*S*)−(**5**)	83	91	−74.9
8	Ph	**3**	(*R*)	TBHP	1:1.1	27:73:0	(*S*)−(**6**)	52	94	+98.1

[a] Ratios between (unreacted sulfide)/sulfoxide/sulfone. [b] Configurations were attributed assuming that the subsequent reaction with Grignard reagents (see text and Table 2) was enantiospecific with inversion of configuration. [c] Isolated yields. [d] Determined by NMR techniques, upon addition of (*S*)−BINOL as a CSA. [e] *c* = 1, $CHCl_3$. [f] Not determined.

Table 2. Enantiospecific Reactions of (Alkylsulfinyl)- or (Arylsulfinyl)Methylphosphonates **4**−**6** with Grignard Reagents



4-6 **7-16**

entry	R	substrate	R′	yield(%)[a]	product	$[\alpha]_D$	ee (%)
1	Me	(−)-**4**	*n*-octyl	54	(*R*)-**7**	−83.6 (*c* = 1, acetone)[b]	>98[c]
2	Me	(−)-**4**	*n*-decyl	46, 86[d]	**8**[e]	−52.7 (*c* = 1, $CHCl_3$)	>98[c]
3	Me	(−)-**4**	*n*-octadecyl	49	**9**[e]	−37.7 (*c* = 1, $CHCl_3$)	>98[c]
4	Me	(−)-**4**	cyclohexyl	50, 61[d]	**10**[e]	−69.5 (*c* = 1, acetone)[f]	>96[c,g]
5	Me	(−)-**4**	*t*-butyl	15, 71[d]	(*R*)-**11**	−8.1 (*c* = 1, $CHCl_3$)[h]	>98[c]
6	Me	(−)-**4**	(*E*)−2-stiryl	43[i]	(*R*)-**12**	−171.4 (*c* = 0.16, acetone)[j]	>98[c]
7	Et	(−)-**5**	*n*-octyl	40	**13**[e]	−23.8 (*c* = 1, $CHCl_3$)	*k*
8	Et	(−)-**5**	*p*-tolyl	36	(*R*)-**14**	+170 (*c* = 1, acetone)[l]	91[m]
9	Ph	(+)-**6**	methyl	60	(*S*)-**15**	−127.3 (*c* = 1, acetone)[n]	94[m]
10	Ph	(+)-**6**	*p*-tolyl	42	(*R*)-**16**	+19.4 (*c* = 1, acetone)[o]	94[m]

[a] Isolated yield. [b] Lit.[4] $[\alpha]_D = -79.7$. [c] Measured by NMR upon addition of (*R*)-(−)-3,5-dinitro-*N*-(1-phenylethyl)benzamide. [d] This yield refers to reactions performed following the CH_3I procedure (see text). [e] Configuration of this product was not known, but it should be (*R*), provided that the reaction with Grignard reagents was enantiospecific with inversion of configuration also in this case. [f] Lit.[9b] $[\alpha]_D = -44.3$ for an ee value of 54%. [g] A more accurate determination was made difficult by the overlapping of CH_3 and CH signals. The reported limit was obtained with the aid of a decoupling experiment. [h] Lit.[4] $[\alpha]_D = -7.3$. [i] The yield refers to a mixture of (*E*)- and (*Z*)-isomers in a 85:15 ratio corresponding to the original ratio of the halide used for the Grignard reagent. [j] Lit.[12b] $[\alpha]^{25}_D = +157$ for an ee value of 90% and for (*S*)-configuration. [k] It seems reasonable to assume that the ee value should correspond to the value of the substrate (91%). [l] Lit.[2b] $[\alpha]_D = +187.5$. [m] Measured by HPLC (Chiralcel OD). [n] Lit.[4] $[\alpha]_D = +120$ for an ee value of 90% and for (*R*) configuration. [o] Lit.[2b] $[\alpha]_D = +21.1$.

sulfoxides **7**−**16** (Table 2) in a very simple procedure. The organometallic compound (1.5 equiv) was added to the substrate at 0 °C, and then the reaction was left at room temperature for 1 h. The ee values of these products were determined by ^{1}H NMR techniques (addition of (*R*)−(−)-3,5-dinitro-*N*-(1-phenylethyl)-benzamide as a chiral solvating agent)[4] or by HPLC (Chiralcel OD).

The isolated yields of the sulfoxides **7**−**16** were not particularly high, due to the competing metalation of the starting material by the organometallic compound.[15] However, this drawback was overcome since the unreacted sulfinylmethylphosphonates could be recovered unchanged and reused.[15]

Furthermore, we have also evaluated the possibility of recovering in situ the metalated species by methylation of the carbanion, as reported for other sulfinylmethylphosphonates.[20] Therefore, in a few cases (entries 2, 4, and 5), after performing the first reaction with 1.1 equiv of Grignard reagent, methyl iodide (1.1 equiv) was added to the reaction mixture. After standing for 2 h at room temperature, the mixture was cooled to 0 °C and reacted with 1.1 equiv of fresh Grignard reagent. An improvement of the isolated yields was observed (particularly in entries 2 and 5). The ee values were found to be the same for the products obtained with the two procedures.

In conclusion, we are confident that particularly diethyl (methylsulfinyl)methylphosphonate, **4**, will represent in the future for the synthesis of methyl sulfoxides what *p*-tolyl menthyl sulfinate has represented so far for the synthesis of aryl sulfoxides. However, although a special interest attaches to the dialkyl sulfoxides for the reasons given above, it is worth noting that our process can also be considered a valid alternative to more classical procedures in the production of aryl sulfoxides.

Acknowledgment. This work was financially supported in part by the Ministero dell′Università e della Ricerca Scientifica e Tecnologica, Rome (National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni") and by the University of Bari.

Supporting Information Available: Experimental procedures and relevant spectral data for compounds **4**−**16** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA982836W

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