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Asymmetric Synthesis of Phosphine Oxides with the Arbuzov Reaction

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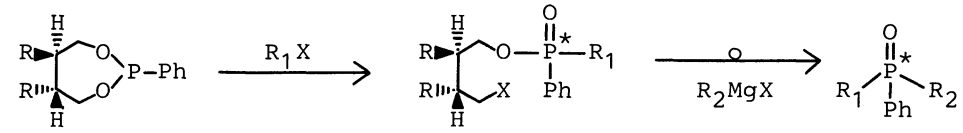
The Arbuzov reaction of (5S,6S)-dimethoxy-2-phenyl-1,3,2-dioxaphosphacycloheptane with various alkyl halides produced acyclic phosphinates in a moderate to high diastereomer excess. The same reaction of (1S,7S)-9,9-dimethyl-4-phenyl-3,5,8,10,4-tetraoxaphosphabicyclo[5.3.0]decane with the alkyl halides needed the more vigorous reaction conditions and gave phosphinates in a low diastereomer excess. These phosphinates were converted into optically active phosphine oxides.

As our continuing interest in the synthesis of compounds containing chiral hetero atom center,[1] we have reported a convenient method for the preparation of optically active phosphinates by the regioselective cleavage of diastereomerically pure phenylphosphorinanes with alkyl halides.[2] This paper describes the first example of an asymmetric synthesis of phosphinates with the Arbuzov reaction using C_2-symmetry compounds. The reaction of (5S,6S)-dimethoxy-2-phenyl-1,3,2-dioxaphosphacycloheptane (**1**) or (1S,7S)-9,9-dimethyl-4-phenyl-3,5,8,10,4-tetraoxaphosphabicyclo[5.3.0]decane (**2**) with various alkyl halides gave the diastereomeric phosphinates (**3**,**4**), which were converted into the optically active phosphine oxides (**5**) using the Grignard reagents as follows.



1 R=OMe **2** R=O,Me / R=O,Me **3** R=OMe **4** R=O,Me / R=O,Me **5**

Scheme 1.

Dichlorophenylphosphine was treated with (S,S)-2,3-dimethoxybutanediol[3] and (S,S)-2,3-O-isopropylidenethreitol[4] which had been derived from L-tartaric acid, in the presence of 4 equiv. pyridine in ether at 5-10 °C under an argon atmosphere to give the seven-membered cyclic phenylphosphonite **1**, bp 125 °C / 0.25 Torr, $[\alpha]_D$ +26.1°(c 22.3 MeOH), in 70% yield and the ten-membered bicyclic phenylphosphonite **2**, bp 150 °C / 0.25 Torr , $[\alpha]_D$ -7.6°(c 10.9 MeOH), in 65% yield, respectively. These phosphonites gave satisfactory NMR data.[5]

The Arbuzov reaction of **1** or **2** with various substituted benzyl halides was

carried out in the presence of 3-4 equiv. halides relative to the phosphonite under an argon atmosphere in a sealed glass tube. The products of diastereomeric phosphinates isolated by vacuum distillation or columm chromatography (silica gel; hexane-ethanol 90:10) gave satisfactory ^{1}H-NMR data.[5] The diastereomer ratios of resulting phosphinates were determined by the HPLC and/or ^{1}H-NMR analysis. The results are shown in Table 1.

Table 1. The Arbuzov Reactions of Phosphonite **1** or **2** with Various Benzyl Halides

Run	Phosphonite	p-$YC_6H_4CH_2X$ Y	X	Conditions[a] Temp/°C	Time/h	Conv. of phosphonite/%	**3** or **4** de/%[b]
1	**1**	Me	I	64	3	70	24
2	**1**	Me	I	rt	10	60	40
3	**1**	H	I	rt	10	50	45
4	**1**	Br	I	rt	10	46	50
5	**1**	CN	I	36	3	58	>99
6	**1**	NO_2	I	36	3	63	>99
7	**1**	NO_2	I	80	0.5	100	>99
8	**1**	Me	Br	80	10	91	28
9	**1**	H	Br	80	10	97	23
10	**1**	CN	Br	80	10	no reaction	
11	**1**	NO_2	Br	80	10	no reaction	
12	**2**	Me	I	rt	6	25	0
13	**2**	H	I	36	15	50	11
14	**2**	Br	I	36	6	31	5
15	**2**	CN	I	36	6	36	4
16	**2**	NO_2	I	36	6	43	9
17	**2**	Me	Br	80	6	23	11
18	**2**	H	Br	80	20	65	6
19	**2**	CN	Br	80	20	no reaction	

a)In benzene solution. b) Determined by HPLC analysis ; silica gel, eluent, hexane-2-propanol 92(97):8(3), and/or ^{1}H-NMR analysis.

In general, even though the reaction of **1** or **2** with the benzyl iodides bearing electron withdrawing substituents proceeded smoothly under mild reaction conditions, the reaction with benzyl bromides needed more vigorous reaction conditions. The reactivity of **1** was superior to that of **2**. The high diastereo-selectivity (>99%de) was attained in the reaction of **1** with p-nitro or p-cyano benzyl iodide. The rise of the reaction temperature caused the decrease in the diastereo-selectivity of p-methylbenzylphosphinate (runs 1,2), but did not in the reaction of phosphonite **1** with p-nitrobenzyl iodide (runs 6,7). The reaction of **2** with varicus benzyl iodides and benzyl bromides did not make much differences in the diastereo-selectivity.

To elucidate the stereochemistry at phosphorus in the Arbuzov reaction, the resulting phosphinates were converted with the Grignard reagents into the phosphine oxides **5** whose absolute configurations[6] are known. The representative procedure of phosphine oxides is : the Arbuzov reaction of **1** (10 mmol) with benzyl iodide

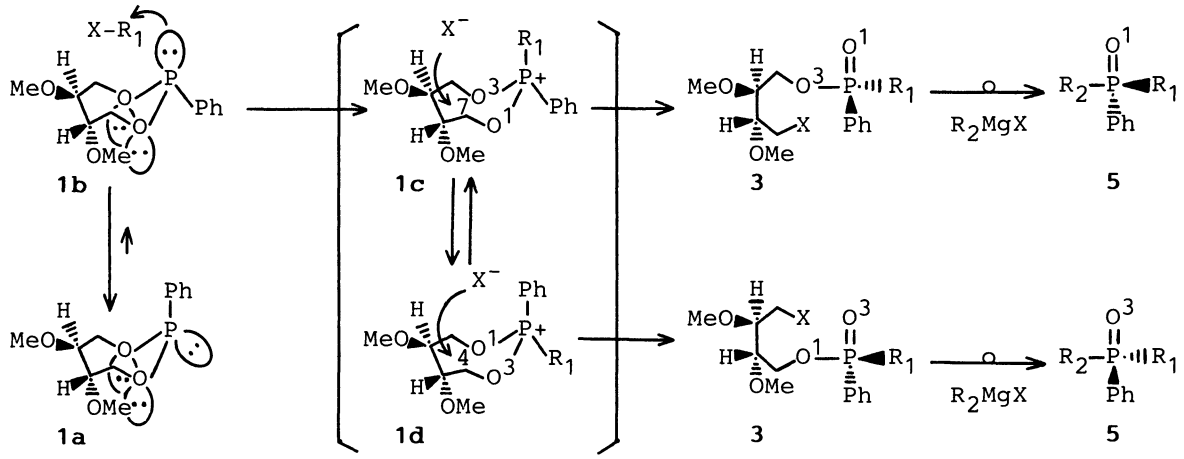
(30 mmol) was carried out in benzene (150 ml) with stirring for 10 h at room temperature under an argon atmosphere. The resulting benzylphenylphosphinate was subsequently reacted with methylmagnesium iodide (5 equiv.) for 15 h at 70 °C to give the optically active (R)-benzylmethylphenylphosphine oxide ($[\alpha]_D$ +23.0°, 45%ee), which was isolated by vacuum distillation. Various optically active phosphine oxides were prepared in a similar manner. The optically active phosphine oxides **5** derived from **2** had the absolute configurations opposite to those of the corresponding **5** derived from **1**. The reaction conditions and results are shown in Table 2.

Table 2. The Optically Active Phosphine Oxides **5** Derived from the Phosphonite **1,2**

					Phosphine oxides **5**			
Run	Phosphonite	R_1X	Temp/°C	R_2	Yield[a]/%	$[\alpha]_D$/deg[b]	ee/%	Config.[c]
1	**1**	MeI	36	Pr	70	-5.5	26[d]	S
2	**1**	$PhCH_2I$	rt	Me	80	23.0	45[c]	R
3	**1**	$PhCH_2Br$	80	Me	85	11.6	23[c]	R
4	**1**	$CH_2=CHCH_2Br$	80	Me	40	3.8	18[c]	R
5	**2**	MeI	36	Pr	40	0.5	2.4[d]	R
6	**2**	$PhCH_2I$	36	Me	45	-5.4	10[c]	S
7	**2**	$CH_2=CHCH_2Br$	80	Me	15	-2.5	12[c]	S

a) Isolated yield. b) c 8.3, 8.0, 25.1, 11.8, 6.5, 19.0, 18.2 g/dl(MeOH).
c) Optical yields were calculated from the maximum rotations of phosphine oxides.[6] d) based on +21.2°(MeOH).[7]

The results in Tables 1 and 2 lead to the probable reaction mechanism shown in Scheme 2. Since the Grignard reaction proceeds with inversion[2,6] at phosphorus , the Arbuzov reaction is the determinant step of the absolute configuration and the enantiomer excess of resulting phosphine oxides.



Scheme 2.

Based on the analogy with the results of conformation analysis of phosphorinanes[8] and Gorenstein's results,[9] the most stable conformation should be the chair form with phenyl axial (**1a**) because the lone pairs on the ring oxygens tend to be synclinal to the phosphorus lone pair (the Ground-State Stereoelectronic Effect).[9] However, at the nucleophilic attack stage of phosphorus lone pair,

the nucleophilicity is much enhanced by the antiperiplanar lone pairs on oxygens (the Transition-State Stereoelectronic Effect).[9] So that, the nucleophilic attack of phosphorus lone pair onto alkyl halide proceeds from the axial position (**1b**) after the interconversion (**1a** → **1b**) to give the phosphonium ion intermediate (**1c**). The phosphonium ion (**1c**) possessing an electron withdrawing substituent such as p-nitro or p-cyano group is so unstable that the ion undergoes S_N2 reaction at less hindered carbon 7 (**1c**) by the halide anion as soon as it is formed and gives the diastereomerically pure phosphinate **3** (runs 5,6,7 in Table 1). When the phosphonium ion, however, has enough long life to allow the thermodynamic equilibrium between **1c** and **1d**, it causes the decrease in the diastereomer excess of the resulting phosphinates **3** (e.g. runs 1,2,3,8,9 in Table 1, runs 1,2,3,4 in Table 2). On the other hand, the reactivity of **2** with alkyl halides is much lower than that of **1** because the phosphonite **2** can not be expected the enhanced nucleophilicity of the phosphorus lone pair by the stereoelectlonic effect due to the very rigid bicyclic system.[9] We have, however, at present no satisfactory explanation for the reason why the phosphine oxide **5** derived from **2** has the opposite configuration to that of corresponding **5** derived from **1**.

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5) Phosphonite **1**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.46, 3.48 (s,s, 6H,2OMe), 3.26-3.98 (m, 4H,2-CH_2-), 4.00-4.23 (m, 2H,2CH≡), 7.40-7.89 (m, 5H, Ph). Phosphonite **2**: ^{1}H-NMR (270 MHz,$CDCl_3$) δ 1.43 (S, 6H,2Me), 3.70-4.36 (m, 6H,2CH≡, 2-CH_2-), 7.53-7.85 (m,5H, Ph). Benzylphenylphosphinate **3** (R=OMe,X=Br,R_1=CH_2Ph): NMR(400 MHz, $CDCl_3$) δ 3.36, 3.37, 3.40, 3.42 (s,s,s,s, 6H,2OMe), 3.86-3.92, 4.11-4.16 (m,m,2H 2CH≡), 3.26-3.41 (m,4H,2-CH_2-), 3.43-3.72 (m, 2H,P-CH_2-), 7.14-7.66 (m,10H,2Ph). p-Nitrobenzylphenylphosphinate **3** (R=OMe, X=I, R_1=$CH_2C_6H_4NO_2$): NMR(400 MHz,$CDCl_3$) δ 3.39, 3.43 (s,s,6H,2OMe), 3.90-3.96, 4.11-4.17 (m,m,2H,2CH≡), 3.20-3.76 (m,6H, 3-CH_2-), 7.27-8.13 (m,9H,C_6H_4,Ph). p-Cyanobenzylphenylphosphinate **3** (R=OMe,X=I, R_1=$CH_2C_6H_4CN$): NMR(270 MHz,$CDCl_3$) δ 3.38, 3.42 (s,s,6H,2OMe), 3.87-3.96, 4.09-4.18 (m,m,2H,2CH≡), 3.22-3.43 (m,6H,3-CH_2-), 7.23-7.68 (m,9H,Ph,C_6H_4). Benzylphenylphosphinate **4** (R=acetal,X=Br,R_1=CH_2Ph): NMR(400 MHz,$CDCl_3$) δ 1.17, 1.19, 1.39, 1.40 (s,s,s,s,6H,2Me), 3.30-4.17(m,8H,2CH≡,3-CH_2-), 7.07-7.85 (m,10H,2Ph).
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