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Unprecedented Base Effect On the Synthesis of Chiral Phosphinate Esters: A New Route to P-Chiral Phosphine Oxides of High Enantiomeric Purity

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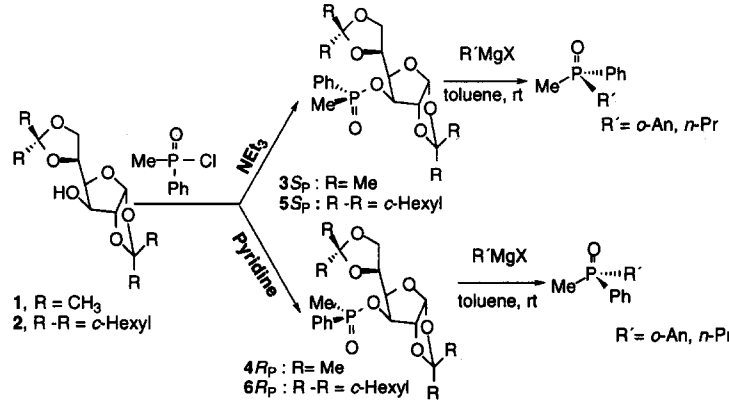
Abstract: The stereochemical outcome of the reaction of chiral secondary alcohols with a phosphinyl chloride was found to be highly dependent on the achiral base used. Thus, the reaction of the readily available sugar derived carbinols, **1** and **2**, with methylphenylphosphinyl chloride in the presence of *triethylamine* yields stereoselectively the corresponding *S*p-phosphinates **3***S*p and **5***S*p in 94 and 92% diastereomeric excess (de). Simply changing the base from triethylamine to *pyridine* affords *R*p-phosphinates **4***R*p and **6***R*p epimers to **3***S*p and **5***S*p at the phosphinyl phosphorus in 50 and 40% de respectively. These phosphinate esters were found to be good P-chiral transferring intermediates, they react with Grignard reagents under very mild conditions to give the corresponding phosphine oxides. Both enantiomers *S*p- and *R*p-*o*-anisylmethylphenylphosphine oxide (PAMPO) as well *S*p- and *R*p-methylphenylpropyl phosphine oxide were obained enantiomerically pure in high yields

P-chiral phosphine oxides are important precursors of P-chiral phosphines and diphosphines, important ligands in the transition metal catalysts for enantioselective reactions, particularly in hydrogenation processes.[1] Thus a general methodology for their synthesis in high enantiomeric purity is still highly desirable.[2] We report herein a new, cheap, and very simple method for the synthesis of either enantiomer of P chiral phoshine oxides in high enantiomeric purity and in a predictable manner.[3] This method makes use of a single readily available sugar derivative as inducer of chirality[4] to access either phosphine oxide enantiomer, due to an unprecedented useful base effect on the stereoselectivity of the parent phosphinate esters synthesis.[5]



Scheme 1

Our initial investigation was undertaken with diacetone-*D*-glucose (DAG),[6] **1** and methylphenylphosphinic chloride under various conditions, Scheme 1. The results are summarised in Table 1. The stereoselectivity of the reaction depends on the solvent, the temperature, but especially on the base used. Thus, the reaction of methylphenylphosphinic chloride with DAG in toluene, at 0°C, using 10 equiv. of *triethylamine* (entry 5) proceeds smoothly to give the corresponding phosphinate esters **3** and **4** *in nearly*

quantitative yield, in a 97 / 3 diastereomeric ratio. Moreover, phosphinate **3** is crystalline and a simple crystallization from hexane permits its isolation in enantiomerically pure form in 85 % yield, m.p. 102-104°C, $[\alpha]^{23}_D$ -54.5 (c. 0.8, acetone).

The diastereomeric ratio is easily determined by ^{1}HNMR analysis of the crude product due to the large difference in the chemical shift of the anomeric protons, H-2 and also in the proton H-4 of the sugar ring in the phosphinate esters **3** and **4**.[7a] We were delighted to find that when the same reaction is performed in the presence of 10 equiv. of *pyridine* instead of triethylamine as base, in THF, (entry 9) the two diastereisomers **3** and **4** are obtained in quantitative yield in a 30 / 70 diastereomeric ratio *in favour of* **4** *which is epimeric with* **3** *at the phosphinyl phosphorus.*

Table 1. Phosphinate esters synthesis from alcohol **1** or **2** and methylphenylphosphinyl chloride (PhMeP(O)Cl)[a,b]

Entry	Alcohol	Base	Equiv.	Solvent	T (°C)	Time (h)	Diast. Ratio (*Sp* : *Rp*)[c]
1	**1**	Et_3N	6	toluene	0	24	93 : 7
2	**1**	Et_3N	6	CH_2Cl_2	0	96	80 : 20
3	**1**	Et_3N	6	THF	0	96	87 : 13
4	**1**	Et_3N	6	toluene	-40	60	97 : 3
5	**1**	Et_3N	10	toluene	0	7	97 : 3
6	**2**	Et_3N	10	toluene	0	24	95 : 5
7	**1**	Py	3	toluene	0	72	40 : 60
8	**1**	Py	3	THF	0	96	37 : 63
9	**1**	Py	10	THF	0	24	25 : 75
10	**2**	Py	10	THF	0	24	30 : 70

[a]All the reactions were performed using 3 equiv. of the phosphinyl chloride, [b]Reactions were stopped when all the alcohol had reacted [c]Determined on ^{1}H NMR analysis of the crude.

In order to test the scope of the methodology and to get both phosphinate esters epimers at the phosphinyl phosphorus in enantiomerically pure form we performed the same reactions using as inducer of chirality the secondary alcohol **2** and the best conditions determined above. Phosphinate esters **5** and **6** were thus obtained in nearly quantitative yield in 95 / 5 diastereomeric ratio with triethylamine as base (entry 6).[7b] Interestingly, **5** and **6** are well resolved on TLC which permitted their purification by column chromatography. Thus, phosphinate **5** was obtained enantiomerically pure in 85% isolated yield, $[\alpha]^{23}_D$ -37.75 (c. 0.8, acetone). The use of pyridine as base induces the formation of **5** and **6** in 30 / 70 diastereomeric ratio respectively and in high yield (entry 10). Column chromatography purification allows the isolation in enantiomerically pure form of phosphinate **6** in 65% yield, m.p. 127-128°C, $[\alpha]^{23}_D$ -7.6 (c. 0.25, acetone). To the best of our knowledge this is the first time where it is demonstrated that the stereochemical outcome of the phosphinate esters synthesis is dependent not only on the chiral secondary alcohol but also on the achiral base used.[8] Conceptually, the stereochemical result of the base change from pyridine to triethylamine is even better than the change of the inducer of chirality from the readily available *D*-glucose derivatives **1** and **2** to the unnatural and expensive *L* enantiomers.

In order to determine the absolute configuration of phosphinate esters **3**, **4**, **5**, and **6** and to evaluate their ability as P-chiral transfer intermediates we transformed them to known phoshine oxides of synthetic interest

by the reaction with the corresponding Grignard reagents, scheme 1. The results are summarised in table 2. In all the cases studied the displacement step proceeds under very mild conditions (less than 2 hrs at room temperature), in contrast to the reactivity observed with the known menthyl phosphinates which proceeds under somewhat stringent conditions (usually at reflux in toluene for several hours).[9]

Table 2: Synthesis of phosphine oxides from diastereomerically pure phosphinate esters **4**, **5**, and **6**.

Entry	Phosphinate	R (in RMgX)	yield (%)[a]	$[\alpha]_D^{25}$,[b]	Config.
1	**3**	*o*-An[c]	95	-26	*S*
2	**3**	*n*-Pr	75	+18	*R*
3	**5**	*o*-An	85	-24	*S*
4	**5**	*n*-Pr	80	+17	*R*
5	**6**	*o*-An	91	+25	*R*[d]
6	**6**	*n*-Pr	70	-21	*S*

[a]All the reactions were conducted in toluene at r.t. for 2 to 3 hrs. [b]Taken in MeOH, at concentration of 0.75-1.20 g / 100mL. [c]Freshly prepared. [c]Lit[12] +25.9 (c 1.0, MeOH).

Condensation of **3** with freshly prepared *o*-anisylmagnesium bromide in toluene gives the synthetically important *S*-*o*-anisylmethylphenylphosphine oxide (*S*-PAMPO),[10] in 85 % yield (entry 1, Table 2), while condensation of *n*-propylmagnesium chloride yields enantiomerically pure. *R*-methylphenylpropyl phosphine oxide[11] in high yield (entry 2, Table 2). The same phosphine oxides *S*-PAMPO and *R*-methylphenylpropyl phosphine oxide are obtained enantiomerically pure (>95% ee) in 85% and 80 % yield, respectively, when the reactions are conducted on the phosphinate **5**. Phosphine oxide enantiomers, the industrially important *R*-PAMPO[12] (entry 5, Table 2) and *S*-methylphenylpropyl phosphine oxide (entry 6, Table 2), are obtained enantiomerically pure and in high yields when using the phosphinate **6** as starting material. By assuming that the condensation step occurs with complete inversion of configuration at the phosphorus atom, as rigorously established by Mislow for menthyl phosphinates, we can conclude that phosphinates **3** and **5** have an *S* absolute configuration at the phosphorus atom while phosphinates **4** and **6** have the *R* absolute configuration at the phosphorus atom. Thus in a predictable manner, the use of pyridine as base induces the formation of *R* phosphinate predominately, while the use of triethylamine yields mainly *S* phosphinate. The mechanism accounting for the observed change on the stereochemistry at the phosphorus atom when changing the base is not fully understood but we suppose that, as in the "DAG methodology" recently introduced by us for the synthesis of chiral sulfoxides,[13] this is a result of the stereochemistry of the sugar matrix, the base hindrance, and at a large extents to the ability of the phosphorus to undergo pseudorotation during the reaction.[14]

In conclusion, we have found that the stereochemistry of the formation of phosphinate esters is dependent on the nature of the base used. By this method both phosphinate esters, *R*P and *S*P, can be obtained in a predictable manner and in enantiomerically pure form. Addition of Grignard reagents to these phosphinates proceeds smoothly and gives the corresponding homochiral phosphine oxides. The application of this method to the synthesis of new chiral phosphines and diphosphines and their use as chiral ligands in transition metal catalysts for enantioselective reactions is underway in our laboratory and will be reported in due course.

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6. Cholesterol instead of menthol has also been used as inducer of chirality with some but limited success see Nudelman, A.; Cram, D. J. *J. Org. Chem.* **1971**, *36*, 335.
7. (a) A $\Delta\delta$ of 0.36 and 0.53ppm are observed in the case of H-2 and H-4 protons, respectively (**3** δ (ppm): H-1 = 5.95, H-2 = 5.05, H-4 = 4.40; **4** H-1 = 5.82, H-2 = 4.65, H-4 = 4.88), making the diastereomeric excess determination very easy. (b) Similarly a $\Delta\delta$ of 0.32 and 0.57ppm are also observed for H-2 and H-4 in phosphinate esters **5** and **6**.
8. It is generally assumed that the base to be used in the synthesis of phosphinate esters from a secondary alcohol is pyridine.
9. The reaction of Grignard reagents with mentylphosphinates was found to be very sensitive to the variation of the groups at phosphorus, oxygen, and magnesium, see ref 3b.
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