2,2′-Spirobi(1,3,2-benzodioxaphosphole): an Inexpensive and Effective Reagent for Peptide Synthesis

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The readily accessible spirocyclic oxyphosphorane, 2,2′-spirobi(1,3,2-benzodioxaphosphole) (**1**), is a convenient and effective reagent for peptide coupling, racemisation as measured by the Izumiya test being strikingly suppressed to <0.1% in the presence of *N*-hydroxysuccinimide.

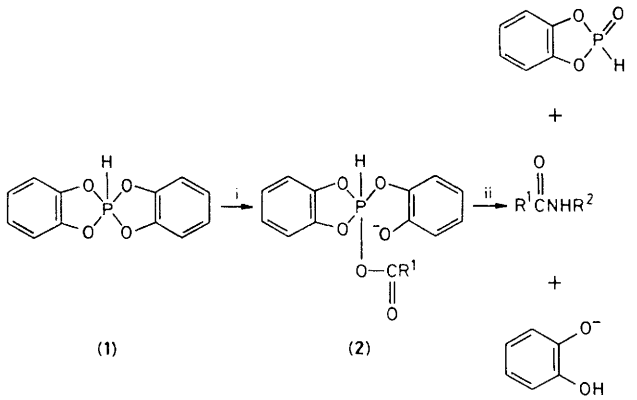
Although much attention has been focused on the preparation[1] and dynamic stereochemistry[2] of penta-co-ordinate oxyphosphoranes, little interest has so far been paid to their use in general organic synthesis, and synthetic applications are somewhat rare.[3] We now show for the first time that this class of compounds, exemplified by the spirocyclic oxyphosphorane (**1**), can readily induce the formation of peptide bonds under conditions where no racemisation takes place.

Table 1. Yields and extent of racemisation in the Izumiya test using (**1**) as coupling reagent.

Base (solvent)[a]	Additional component	Reaction conditions[b] temp./°C, time/h	Yield[c]/ %	Racemisation[d]/%
Et_3N(THF)		60,24	56	20.3
		100,24	58	23.1
NMM(DMF)		40,96	60	11.3
NMM(THF)		40,96	61	11.0
	HOSu	40,96	60	4.1
DAMP(THF)		40,96	64	3.2
	HOSu	40,96	66	2.1
	HOSu	25,24	60	<0.1
	HOSu	25,96	65	<0.1

[a] THF = tetrahydrofuran, DMF = dimethylformamide, NMM = *N*-methylmorpholine. [b] To a stirred solution of 0.5 mmol Z-Gly-L-Ala-OH and 1 mmol (**1**) in 5 ml dry THF or DMF was added a mixture of H-L-Leu-OBzl *p*-toluenesulphonate and base (0.5 mmol each in 5 ml solvent). After coupling, the solvent was removed *in vacuo* and the residue extracted into EtOAc. The extract was washed with 3% $NaHCO_3$ solution and then 1 M HCl, dried over anhydrous Na_2SO_4, and evaporated to dryness *in vacuo*. Hydrogenolysis of the residue in 90% HOAc (10 ml) over palladium black (200 mg) gave, after filtration and removal of solvent, Gly-Ala-Leu(D,L plus L,L) as an oil. [c] Yields of isolated product after recrystallisation from MeOH–H_2O. [d] Separation of the diastereomeric mixture of Gly-Ala-Leu was achieved using a Beckman 120C automatic amino acid analyser (R. P. Ambler).

The reagent (**1**), easily prepared[4] from catechol and phosphorus trichloride, is a stable, crystalline compound (m.p. 90—91 °C from ether) unless exposed to atmospheric moisture for a long time. Its usefulness in fragment couplings is demonstrated here by the extremely sensitive Izumiya test[5] involving condensation of Z-Gly-L-Ala-OH with H-L-Leu-OBzl. The procedure employed was straightforward† and had the practical advantage that isolation of the pure peptide was made easy by virtue of the phosphorane by-products being soluble in base. Table 1 records the yields of Gly-Ala-Leu(D,L plus L,L) obtained under a variety of reaction conditions, and also the extent of racemisation,[6] which is defined as {100[D,L/(D,L + L,L)]}. The results show that (**1**) compares favourably with established reagents including dicyclohexylcarbodi-imide[5,7] and, significantly, produces only 3.2%



Scheme 1. *Reactants*: i, $R^1CO_2^-$; ii, R^2NH_2 or by a series of steps.

† For details see footnote in Table 1.

racemisation when used in conjunction with diethylaminomethylpolystyrene (DAMP) (200—400 mesh) as base. This is strikingly suppressed to $<0.1\%$ by the addition of *N*-hydroxysuccinimide (HOSu) which, in coupling reactions,[8] rapidly furnishes an activated ester of the carboxyl component not prone to racemisation.

Although the mechanism of action of (**1**) is not certain, the known high reactivity of penta-co-ordinate phosphoranes towards nucleophiles suggests the intermediate formation of (**2**). Whether this reacts directly with the amino component to give the observed products or by a series of intermediate steps (*e.g.*, *via* symmetrical anhydrides) remains to be established (Scheme 1).

Preliminary observations show that (**1**) is merely one of several readily available oxyphosphoranes capable of forming peptide bonds and further work is now underway to evaluate fully the potential of this new class of coupling reagents in peptide synthesis.

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