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**Preliminary communication**

# ONE-POT SYNTHESIS OF CHIRAL PHOSPHONOUS ESTERS, CONVERSION INTO ASYMMETRIC PHOSPHINES

W. CHODKIEWICZ

*C.N.R.S. Laboratoire de Recherches de Chimie Organique — E.N.S.C.P., 11, rue Pierre et Marie Curie, 75005 Paris (France)*

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## Summary

Bulky phenols react with phosphonous chloroesters of cinchonine, or cinchonidine, to yield, quantitatively, the corresponding phosphonous esters of high diastereomeric purity. The aryloxy group can be specifically replaced by reaction with aromatic Grignard reagents and the resulting phosphinous esters can be converted into phosphines retaining the high enantiomeric purity.

The chemistry of asymmetric phosphorus(III) in its various aspects, especially chiral ester synthesis, continues to attract much attention [1].

The direct synthesis of chiral phosphinous cinchonine esters has been reported previously and discussed in terms of the different reactivities of the two chloroesters I in equilibrium (*R* or *S* at phosphorus) towards organometallics [2,3].

$$PhPCl_2 \xrightarrow[-76°C]{\text{Cin OLi}} \underset{\text{(I)}}{PhP(Cl)OCin} \xrightarrow[-76°C]{\text{HOAr, B}} \underset{\text{(II)}}{Ph\overset{*}{P}(OAr)OCin} \xrightarrow{XMgAr'}$$

$$Ph(Ar')\overset{*}{P}OCin \xrightarrow{MeLi} \underset{\text{(IV)}}{Ph(Ar')\overset{*}{P}Me}$$

$$\text{(III)}$$

(CinOH = cinchonine, cinchonidine; B = $NEt_3$, MeLi)

Displacement of the chlorine atom from I can also be achieved with other nucleophiles, and reactions with phenols result in quantitative conversions to II. The asymmetric induction observed in the formation of II seems to depend on the steric requirements of the nucleophile, being less than 50% for

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phenol, approximately 90% for 2-t-butyl-4-methylphenol, and at least 95% for 2,6-dimethylphenol.

The reasonably stable phosphonous esters II are isolated as equimolecular complexes with cuprous salts (CuX: X = CN, SCN, I), from which they can be recovered by treatment with alkaline cyanide. The diastereomeric purity of these esters can be estimated from the $^1H$ NMR spectra of their $H_2O_2$ oxidation products, i.e. the corresponding phosphonic esters. Thus for II (Ar = 2,6-dimethylphenyl) the major product shows: $\delta(CH_3)$ 2.40 ppm, $\delta$(Ar) = 7.00 ppm whereas the minor* product (<5%) shows: $\delta(CH_3)$ 2.00 ppm, $\delta$(AR) 6.50 ppm. These values are very similar for both cinchonine and cinchonidine esters.

The major isomers II, and their cuprous complexes (X = SCN), are readily stereospecifically converted, into the corresponding phosphinous esters III by reaction with aromatic Grignard reagents (Ar'= *o*-tolyl, *o*-anisyl, mesityl). The products are identical with the predominant esters prepared by direct condensation from I [2,4]. $^1H$ NMR analysis of the crude reaction products reveals that the minor isomers II are less reactive, since these remain essentially unchanged during reaction at $t < 0°C$. Thus a routine purification [1] of esters III can be avoided.

The esters III [5] and their cuprous complexes [2] can be transformed stereospecifically by methyllithium into the phosphines IV which have the (*S*)-configuration in the cinchonine series and the (*R*)-configuration in the cinchonidine ones. The specific rotations found for the phosphine oxides obtained from phosphines IV by $H_2O_2$ oxidation are: +31.7° (Ar'= *o*-tolyl) and +24.9° (Ar'= *o*-anisyl) very close to their highest values, i.e. +31.8° [6] and +25.9° [7], respectively.

Extension of these reactions to other nucleophiles and determination of the stereochemistry of the products obtained are in progress in order to open a general route to the chiral phosphorus(III) derivatives.

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*The minor isomer II can be prepared as the major product by an inverse condensation, i.e. addition of 2,6-dimethylphenol then cinchonine or cinchonidine.