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ASYMMETRIC CATALYSIS IN CARBON-PHOSPHORUS BOND FORMATION

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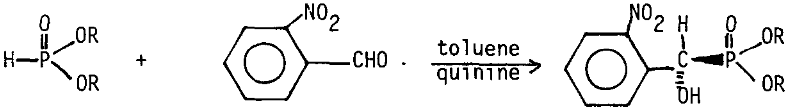
Summary: o-Nitrobenzaldehyde reacts smoothly with dialkylphosphonates in the presence of catalytic quantities of cinchona alkaloids (e.g. quinine) to produce the α-hydroxy phosphonate esters in excellent chemical yields, with excellent enantiomeric enrichment.

Chiral organophosphorous compounds are becoming increasingly important.[1] Since dialkyl phosphonates (1) are excellent nucleophiles it occurred to us that their well-established ability to condense with carbonyl compounds under base catalyzed[2] and thermal[3] conditions might be subject to catalysis by chiral amines.

This proved to be the case. Thus when o-nitrobenzaldehyde[4] (3.45 g, 23 nM; m.p. 43-44°)[5] in 75 ml dry toluene was treated with freshly distilled dimethyl phosphonate (1 R-CH_3) (2.54 g; 23 nM) and 60 mg (0.18 nM) quinine was added, the initial rotation (α = -0.174, 1 dm tube) changed steadily reaching a value of α = -7.5 after 12 hrs.



1 2 3

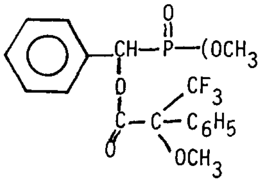
$[\alpha]^{21}_{578} = -417$ (for enant. pure 3; R=CH_3)

Although crystallization of racemic 3 (m.p. 110-111°C) occurs during the reaction, a non-fractionating work-up furnishes a quantitative yield of optically active 3, [α]= -113 (c = 1, $CHCl_3$).[5] The ee of this material is 28% as determined using Mosher's reagent.[7]

Recrystallization of (-)3 to constant rotation $[\alpha]^{RT}_{578}$ = -417 (c = 1, $CHCl_3$), m.p. 108.1-109.4°C proceeds smoothly (toluene, then acetone). The use of quinidine furnishes (+)3 in virtually the same enantiomeric yield.[8,9] When O-acetylquinine was used as basic catalyst optically inactive product in a very slow reaction was formed. The infrared spectrum of a 1:1 mixture of dimethyl phosphonate and quinine in CH_2Cl_2 showed a distinct band at 3400 cm^{-1} assigned[10] to the $-\overset{|}{\underset{|}{N}}{}^{+}-H$ bond, possibly indicating a tight phosphonate-quinine complex.

Preliminary experiments using the di-isopropyl, di-n-butyl- and di-t-butyl-phosphonates and o-nitrobenzaldehyde showed that the corresponding α-hydroxy esters 3 (R-iPr, n-Bu and t-Bu) are formed as optically active products. The ee's increase (to nearly 100% for R=t-Bu) with increasing bulk of the phosphonate ester, while the reaction rate decreases (to about 1/6 of that for the dimethylphosphonate). Hydrolysis of enantiomerically pure 3 ($[\alpha]^{21}_{578}$ = -417°, R = R^1 = CH_3) to the monoacid (3, R = CH_3, R^1 = H, $[\alpha]^{21}_{578}$ = -484° (c = 1, MeOH))[8] using NaI in acetone[11] and to the diacid, 3, R = R^1 = H, $[\alpha]^{21}_{578}$ = -497° (c = 1, MeOH)[8] using 18% aqueous HCl[4] proceeded smoothly and thus opens a facile route to the interesting and useful[11] chiral acids.

The ^{31}P as well as the ^{19}F NMR spectra of the Mosher[7] derivative of ± 3 (i.e. 4) showed beautifully separated sharp singlets for the two diastereomers.



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In fact, in the case of R = $CH(CH_3)_2$ the ^{31}P spectrum was better resolved than the ^{19}F spectrum. Thus enantiomerically pure ester 3 is a potential reagent for the determination of the enantiomeric purity of chiral acids.[13]

Although preliminary data show termolecular kinetics, the formation of a tight phosphonate-quinine complex does not rule out Michaelis-Menten behavior.

References

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2. E.K. Fields, U.S.P. 2, 579, 810 (1951); V.S. Abramov, Chem. Abstr. 1952, 46, 6140.
3. M.S. Kharash, R.A. Mosher and I.S. Bengelsdorf, J.Org.Chem., 1960, 25, 1000.
4. Although other aromatic aldehydes also undergo the reaction, the reaction with o- and p-nitrobenzaldehyde went at a convenient rate. Consequently, 2 was used in most studies thus far.
5. The o-nitrobenzaldehyde must be carefully purified before use, since the photochemical rearrangement[6] produces o-nitrosobenzoic acid. The latter may neutralize the amine catalyst.
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8. All new compounds gave satisfactory spectroscopic and analytical data.
9. Rapid (and expected)[6] photo rearrangement takes place when 3 is irradiated furnishing the achiral α-keto-2-nitrosoester.
10. B. Dmuchovsky, B.D. Vineyard and F.B. Zienty, J.Am.Chem.Soc., 1964, 86, 2874.
11. J. Jacques, M. Le Clerq and M.J. Brienne, Tetrahedron, 1981, 37, 1727; M. Le Clerq and J. Jacques, Nouv. J. Chim., 1979, 3, 629.
12. Alkylation of the mono- or diacid with diazomethane furnished diester 3 (R,R^1 = CH_3) with the same rotation as starting material.
13. See A.B. Shortt, L.J. Durham and H.S. Mosher, J.Org.Chem., 1983, 48, 3125 for an instructive paper on the difficulties with using ^{31}P NMR spectra for quantitative purposes. We find that the ester derived from 3-mercapto-2-methylpropionic acid (and other simple acids) give beautifully resolved ^{31}P spectra (S. Noorda).

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