Kinetic resolution of alcohols in an asymmetric Mitsunobu reaction using chiral nonracemic 1,3,2-dioxaphosphepanes

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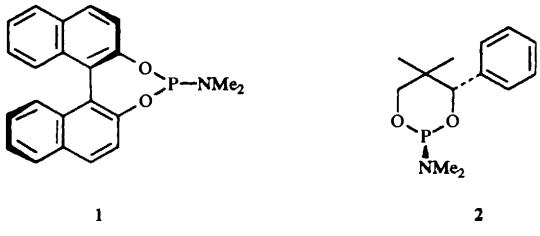
Non-racemic chiral trivalent phosphorus derivatives **1** and **2** when employed under Mitsunobu reaction conditions, induce esterification between racemic alcohols and acids with moderate enantiospecificity (up to 39%). At the expense of high conversion, the alcohols can be obtained in high ee (> 99%).

Alkyl (or aryl) phosphites and phosphines readily form phosphonium salts on reaction with heteroatom–heteroatom bonds like S–S and O–O; with N=N bonds, addition to form a zwitterionic structure occurs. Mitsunobu[1,2] demonstrated that the zwitterionic adducts of triphenylphosphine (TPP) and diethyl or diisopropyl azodicarboxylate (DEAD and DIAD) activate primary and secondary hydroxy groups to S_N2 substitution by various nucleophiles. The substitution is powered by a redox reaction in which phosphorus is oxidized and the azo group is reduced to the hydrazo compound[2] (Scheme 1).

$$Ph_3P + Pr^iO_2C{-}N{=}N{-}CO_2Pr^i + ROH + HNu \longrightarrow Ph_3P{=}O + Pr^iO_2C{-}NH{-}NH{-}CO_2Pr^i + R{-}Nu$$

Scheme 1

As far as we are aware *chiral recognition* is an unexplored aspect of the Mitsunobu reaction. An opportunity to examine this phenomenon is provided by trivalent phosphorus derivatives **1** and **2**,† which are both readily available and shelf-stable[3] but highly reactive as nucleophiles (Scheme 2).



1

2

Scheme 2

We find that (*a*) **1** with dialkyl azodicarboxylates undergoes quantitative cycloaddition rather than formation of a zwitterion, (*b*) that this cycloadduct mediates a redox-powered esterification of alcohols by carboxylic acids, (*c*) that labelling experiments (^{18}O) are consistent with a Mitsunobu type reaction,‡ and (*d*) that the enantiospecificity[5] between the enantiomers of some racemic alcohols (*kinetic resolution*) is modest. Compound **2** also mediates Mitsunobu reactions but mechanistic investigations have so far been confined to **1**.

On reaction with DIAD in benzene at room temperature **1** provides the cycloadduct **3**§ (Scheme 3). The pentavalent co-ordination about phosphorus in **3** and the indicated stereochemistry are concluded from the ^1H, ^{13}C and ^{31}P NMR studies (^{31}P NMR δ −36.72 ppm).[6,7] A salient point is the axial/equatorial attachment of the five-membered ring forcing the NMe_2 group to be equatorial; the pseudorotation needed for elimination of this group is blocked.[8]

Adduct **3** does not react with 1-phenylethanol over a period of hours. However, on addition of 1 equivalent of benzoic acid at ambient temperature, enantiomerically enriched ester (*S*)-**4** was formed (*vide supra*) as well as phosphorus oxide **5** and the hydrazo derivative (not shown) of DIAD ($DIADH_2$), both in nearly quantitative yield (Scheme 3). The latter compound was prepared independently from **1** by oxidation with H_2O_2; spontaneous oxidation of **1** by oxygen does not occur.¶ The unchanged alcohol was also enriched in the *S* enantiometer, which is only possible if an S_N2 inversion has occurred during esterification, consistent with a Mitsunobu-type process. Analogous results were obtained using **1** and DIAD instead of pre-formed **3**.

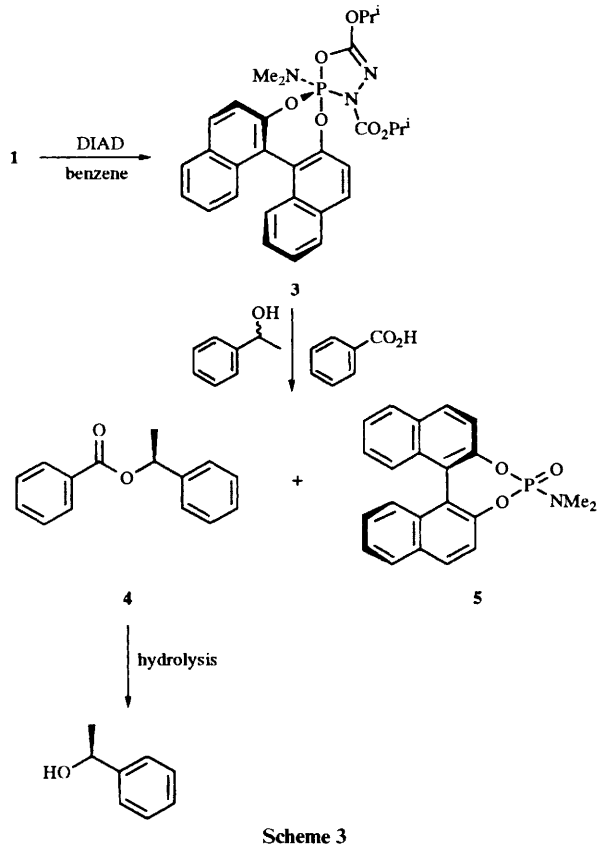
Nonpolar solvents (benzene and toluene) were found to improve both yield and enantiomeric excess compared to more polar solvents (diethyl ether or THF). The most convenient reaction temperature is ambient, although reaction occurs readily in the range from −50 to 110 °C. The use of 2 equivalents of both acid and alcohol was judged to be optimal. The less than quantitative yield of ester (see Table 1) was found

† Compound **2** is a single diastereoisomer that, on the basis of NOESY NMR analysis, is believed to be axially substituted as illustrated; the phosphorus atom in **1** is chirotopic but nonstereogenic owing to the C_2 axis.

‡ On using 50% ^{18}O labelled benzoic acid, **4** was formed in 50% yield with 50% labelling (50% theoretically), whereas **5** was formed quantitatively with 8% labelling (12.5% theoretically) as determined by means of HRMS (± 5%). These results clearly indicate that carboxylate rather than benzoyl is the attacking species in both ester and anhydride formation.[4]

§ Data for **3** (*J* values in Hz): mp 152 °C; $[\alpha]_D^{20}$ 428 (*c* 0.01, benzene); δ_H(300 MHz, C_6D_6) 0.54 (d, *J* 6.3, 3 H), 0.73 (d, *J* 6.2, 3 H), 0.97 (d, *J* 6.2, 3 H), 1.02 (d, *J* 6.2, 3 H), 2.22 (d, *J* 11.35, 6 H), 4.52 (m, 1 H), 5.05 (m, 1 H), 6.62 (m, 2 H), 6.81 (m, 2 H), 7.32 (m, 4 H), 7.42 (dd, 1 H), 7.51 (dd, 2 H) and 8.56 (dd, 1 H); δ_C(75.43 MHz, C_6D_6) 21.39 (CH_3), 21.48 (CH_3), 21.87 (CH_3), 22.39 (CH_3), 40.74 (d, *J* 4.88, CH_3), 68.71 (CH), 72.82 (CH), 124.55 (CH), 124.57 (CH), 124.81 (CH), 125.29 (CH), 126.13 (CH), 126.19 (CH), 127.64 (CH), 127.77 (CH), 128.50 (CH), 128.55 (CH), 128.66 (CH), 130.03 (CH), 131.14 (d, C), 132.01 (C), 132.35 (C), 132.38 (C), 132.71 (C), 132.74 (C), 150.88 (C), 151.28 (d, C), 151.41 (d, C) and 153.78 (d, C); δ_P(121.42 MHz, C_6D_6) −36.72.

¶ Data for (−)-**5** obtained upon treatment of **1** with H_2O_2 in CH_2Cl_2. Mp > 250 °C, $[\alpha]_D^{20}$ −575.6 (*c* 0.03. $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 2.62 (d, *J* 9.52, 6 H), 7.25–7.52 (m, 8 H) and 7.92–8.03 (m, 4 H); δ_C(75.43 MHz, $CDCl_3$) 37.45 (CH_3), 120.84 (d, *J* 3.19, CH), 121.09 (d, *J* 3.21, CH), 125.01 (d, *J* 3.18, CH), 126.65 (d, *J* 9.58, CH), 126.82 (d, *J* 7.98, CH), 127.19 (CH), 128.43 (d, *J* 3.19, CH), 131.03 (d, *J* 19.16, CH), 131.52 (d, *J* 20.74, C), 132.30 (d, *J* 3.20, C), 146.77 (d, *J* 9.57, C) and 148.17 (C); δ_P(121.42 MHz, $CDCl_3$) 14.16.



Scheme 3

to be (mainly) the result of competitive formation of acid anhydride, the presence of which was independently determined by ^{1}H and ^{13}C NMR spectroscopy. It was shown, however, that benzoyl anhydride does not acylate the alcohol at a significant rate under these conditions. The somewhat more hindered and less nucleophilic *o*-nitrobenzoic acid gave the least anhydride.

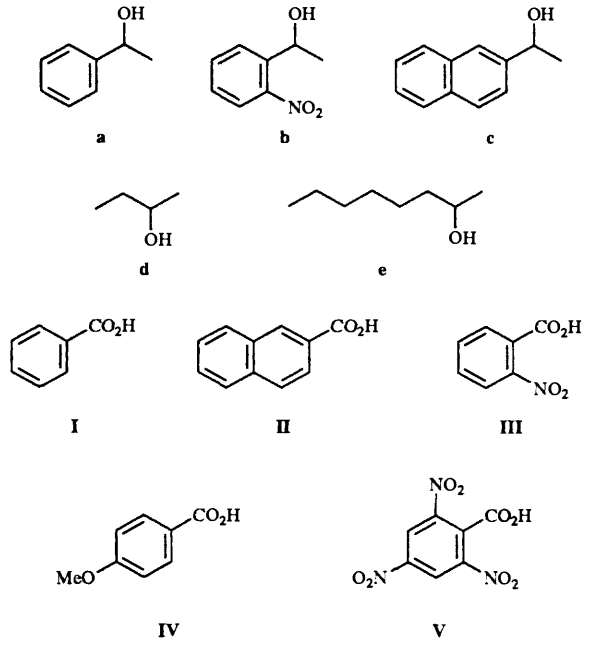
An extensive investigation was made of the reactions of **1** with racemic alcohols and acids as nucleophiles (Table 1). Various temperatures, concentrations and ratios of reagents were used in search for an optimum combination. Note in Table 2 that equal amounts of **1**, alcohol and acid were used to simplify interpretations. An important variable is the purity of **1**; freshly prepared material is best used to obtain maximum reaction rates and minimize anhydride formation (*vide supra*).

To the best of our knowledge, this is the first description of a kinetic resolution using Mitsunobu reaction conditions. The product esters have low to moderate ees whereas, at the expense of high conversions, the remaining alcohols have excellent ees. The stereospecificity,‖ however, is only moderate.

The high reactivity of **1** leads to conversions somewhat higher than the desired 50%; we hope to temper the reactivity with other phosphorus derivatives. The conclusions are clear: reagent **1** is capable of modest kinetic discrimination. However, by an, at this moment, undefined mechanism some racemization occurs during ester formation *via* the Mitsunobu reaction. Further mechanistic work revealing the basis of stereodifferentiation and the use of *meso*-diols is in process and will be reported in due course.[4]

‖ *E* Values are not calculated, since the conversion is determined by means of ^{1}H analysis of the crude reaction mixtures, with an estimated error of ± 5%; this error limit is too high for the accurate determination of *E*.

Table 1 Efficiency and ees of the formation of **4** using benzoic acids as nucleophiles



Ligand	Solvent	Alcohol (equiv.)	Acid (equiv.)	Conversion (%)	Ester ee (%)
1	Et_2O	**a** (1)	**I** (2)	9	39
1	THF	**a** (1)	**I** (2)	11	20
1	CH_2Cl_2	**a** (1)	**I** (2)	13	0
1	Benzene	**a** (1)	**I** (2)	34	36
1	Benzene	**c** (1)	**I** (2)	21	17
1	Benzene	**c** (2)	**II** (1)	14	23
1	Benzene	**a** (2)	**I** (1)	46	39
1	Benzene	**a** (2)	**I** (2)	44	35
2	Benzene	**a** (2)	**I** (1)	43	25
2	Benzene	**a** (1)	**I** (1)	31	11
1	Benzene	**a** (1)	**III** (1)	73	26

Typical experimental conditions: phosphepane (2 mmol) with the given amounts of alcohol and acid in solvent (5 cm^3) at RT. See Experimental section for optimized conditions. [a] Conversions were determined by comparison of the **4**:**5** ratio by means of ^{1}H NMR (± 5%) using the crude reaction mixtures.

Experimental

Optimized procedure for the stereoselective esterification

Phosphepane **1** or **2** (2 mmol) and diisopropyl azodicarboxylate (2 mmol) were dissolved at 0 °C in solvent (5 cm^3) and subsequently refluxed for 30 min. The alcohol (4 mmol) was added and the mixture was stirred for 1 h at room temp. (RT). After this period, the acid (4 mmol) was slowly added at 0 °C to the mixture which was then stirred at RT for 12 h. The crude mixture was filtered and the residue washed with the appropriate solvent (3 × 5 cm^3). The combined filtrates were washed with 1% aqueous NaOH (25 cm^3) and brine (25 cm^3) and then evaporated under reduced pressure to yield a yellowish oil, which was purified by means of column chromatography (silica gel, CH_2Cl_2–hexane, 95:5), followed by a second purification by column chromatography (Al_2O_3, CH_2Cl_2–hexane 95:5). The resulting colourless oil was distilled *in vacuo* and analysed by means of ^{1}H NMR spectroscopy. The oil was taken up in THF (10 cm^3) to which a slight excess (1.2 equiv.) of a 4 mol dm^{-3} aqueous NaOH was added. Subsequently, the solution was brought to reflux for 12 h. After addition of CH_2Cl_2 (25 cm^3), and washing with 1 mol dm^{-3} aqueous NaOH (3 × 10 cm^3) and brine (2 × 10 cm^3) the CH_2Cl_2 layers were

Table 2 Efficiency of kinetic resolution for unreacted alcohol

Acid	Alcohol	Conversion	Alcohol ee	Reaction time (h)
I	**a**	75	55	5
I	**a**	92	>99	15
I	**b**	59	77	15
III	**a**	60	75	1
III	**a**	93	>99	10
III	**b**	60	76	10
III	**b**	95	89	15
IV	**a**	92	30	10
III	**d**	89	94	10
III	**e**	91	91	10
V	**a**	>99	0[a]	10

Typical experimental conditions: 2 mmol each of alcohol, acid and phosphepane in solvent (5 cm^3) at RT; see Experimental section. Conversions were determined by means of ^1H NMR (±5%) using the crude reaction mixtures. [a] The corresponding ether was obtained in quantitative yield.

dried (Na_2SO_4). The ee was determined either by means of chiral GC [Hewlett-Packard 5890A gas chromatograph equipped with a 50 m WCOT fused silica capillary GC column coated with CP cyclodextrin-β-2,3,6-M-19 (Chrompack No. 7501) and a Hewlett-Packard HP 3396 Series II integrator] or by means of a ^{31}P NMR method.[3]

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