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# Enantioselective reaction of secondary alcohols with phthalimide in the presence of a chiral tri-coordinate phosphorus reagent in Mitsunobu reaction

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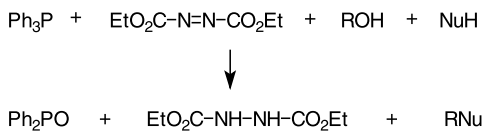
**Abstract**—The enantioselective reaction of racemic secondary alcohols with phthalimide has been carried out in the presence of a chiral cyclic phosphoramidite (+)-**1**/DEAD under Mitsunobu reaction conditions. Phthalimide reacted preferentially with the (−)-enantiomer of the alcohol to give a substituted imide (+)-**2**, while the unreacted enantiomeric alcohol, (+)-**3** was obtained in enantiomerically enriched form. Compound (+)-**2** was further treated with hydrazine hydrate to form the product amine, (+)-**4**.


## 1. Introduction

The Mitsunobu reaction is an intermolecular or intramolecular substitution reaction between alcohols and nucleophilic reagents mediated by diethyl azodicarboxylate (DEAD) and tri-coordinate phosphorus compounds, such as $Ph_3P$, $(Me_2N)_3P$ etc. The substitution is powered by a redox process in which phosphorus is oxidized and the azo group is reduced. By the use of this procedure, alcohols can be successfully converted into their corresponding esters, halides, ethers and amines (Scheme 1). Therefore, the Mitsunobu reaction has been widely used in organic synthesis, especially in the synthesis and transformations of various natural products.[1]

To the best of our knowledge, chiral recognition and enantioselectivity are almost unexplored aspects of the Mitsunobu reaction. In 1995, the first and only description of chiral recognition of racemic secondary alcohols using Mitsunobu reaction conditions was reported. Hulst and co-workers[2] found that enantioselectivity was seen when a chiral cyclic phosphoramidite/diisopropyl azodicarboxylate (DIAD) system was used instead of $Ph_3P$/DEAD in the reaction between a carboxylic acid and alcohols. Under these conditions, the carboxylic acid reacted preferentially with one enantiomer of the racemic alcohol, while the other enantiomer was left. Thus, kinetic resolution of the racemic alcohols occurred.




**Scheme 1.**

## 2. Results and disussion

Recently, we have accomplished the enantioselective reaction of racemic secondary alcohols with phthalimide using the chiral cyclic phosphoramidite **1** derived from (+)-(*R*)-1,1′-binaphthalene-2,2′-diol and DEAD as the activating reagent system under Mitsunobu reaction conditions (Scheme 2). Phthalimide reacted preferentially with the (−)-enantiomer of the racemic secondary alcohols to form the product (+)-**2** with inversion of configuration, and the enantiomerically enriched enantiomer, (+)-**3** remained unreacted. According to the mechanism of the Mitsunobu reaction, we believed the reaction of the alcohol with the imide anion took place on the α-carbon of the asymmetrically activated secondary alcohols via an $S_N2$ process, therefore, the

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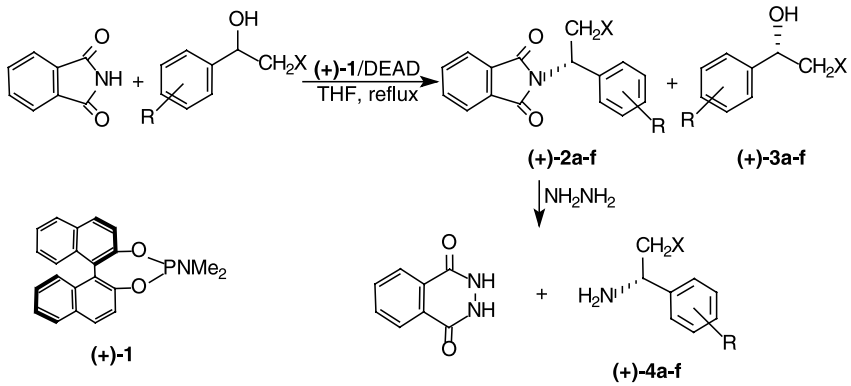



a. R=H, X=H; b. R=H, X=Me; c. R=H, X=Cl; d. R=2,4-$Cl_2$, X=H;
e. R=2,3,4-$Cl_3$, X=H; f. R=4-$NO_2$, X=H.

**Scheme 2.**

optically active products (+)-**2** formed with inversion of configuration. Compound (+)-**2** reacted further with hydrazine hydrate to form the products (+)-**4** with retention of configuration. This can be supported by the following experimental fact, (−)-(*R*)-2-octylamine was obtained when (+)-(*S*)-octan-2-ol was reacted with phthalimide under Mitsunobu conditions and the resulting phthalimide was cleaved with hydrazine hydrate.[3]

All the experimental data of the prepared compounds **2**, **3**, **4** is summarized in Tables 1 and 2.

**Table 1.** Data of compounds **2**, **3**, **4** prepared

| No | **2** | | | | **3** | | | | **4** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mp (°C) | $[\alpha]_D^{20}$ ($CH_2Cl_2$)[a] | Yield[b] (%) | Config. | $[\alpha]_D^{20}$ (MeOH)[a] | Recovery[b] (%) | E.e.[c] (%) | Config. | $[\alpha]_D^{20}$ (EtOH)[a] | Yield[b] (%) | E.e.[c] (%) | Config. |
| a | Oil | +16.0 | 45 | *R* | +9.2 | 51 | 30 | *R*[4] | +8.0 | 59 | 26 | *R*[9] |
| b | Oil | +14.5 | 43 | *R* | +10.5 | 52 | 28 | *R*[5] | +9.6 | 62 | 38 | *R*[9] |
| c | 108 | +11.2 | 46 | *R* | +9.9 | 40 | 23 | *R*[6] | +9.1 | 55 | 32 | *R*[e] |
| d | 107 | +7.8 | 40 | *R* | +4.5 | 45 | 13 | *R*[7] | +8.8 | 60 | 36 | *R*[10] |
| e | 155 | +8.2 | 36 | Nd[d] | +5.6 | 46 | 17 | nd[d] | +10.5 | 58 | 45 | nd[d] |
| f | 102 | +8.9 | 38 | *R* | +7.0 | 39 | 19 | *R*[8] | +9.3 | 65 | 31 | *R*[11] |

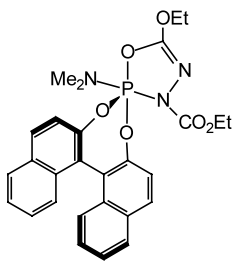
[a] $c=1$.
[b] Isolated yield or recovery.
[c] Determined by HPLC with chiral column (chiralcel OD or OJ).
[d] Not determined.
[e] Determined according to the absolute configuration of **3c**.

**Table 2.** $^1$H NMR and elemental analysis data of compounds **2** prepared

| Compd. | $^1$H NMR ($CDCl_3$, $\delta$) | C (%) (Calcd/found) | H (%) (Calcd/found) | N (%) (Calcd/found) |
|---|---|---|---|---|
| **2a** | 1.90 (d, $^3J_{H-H}=7.71$ Hz, 3H), 5.50 (q, $^3J_{H-H}=7.71$ Hz, 1H), 7.24–7.95 (m, 9H) | 76.49/76.40 | 5.18/5.15 | 5.58/5.46 |
| **2b** | 0.95 (t, $^3J_{H-H}=7.76$ Hz, 3H), 2.50 (m, 2H), 5.20 (t, $^3J_{H-H}=7.29$ Hz, 1H), 7.31–7.67 (m, 9H) | 76.95/76.83 | 5.70/5.65 | 5.28/4.99 |
| **2c** | 4.12 (dd, $^3J_{H-H}=9.52$ Hz, $^2J_{H-H}=16.13$ Hz, 1H), 4.80 (t, $^3J_{H-H}=9.52$ Hz, 1H), 5.50 (dd, $^3J_{H-H}=9.52$ Hz, $^2J_{H-H}=16.13$ Hz, 1H), 7.31–7.72 (m, 9H) | 67.25/67.31 | 4.24/4.31 | 4.90/4.69 |
| **2d** | 1.80 (d, $^3J_{H-H}=7.17$ Hz, 3H), 5.79 (q, $^3J_{H-H}=7.17$ Hz, 1H), 7.24–7.76 (m, 7H) | 60.02/59.95 | 4.38/4.25 | 3.46/3.45 |
| **2e** | 1.80 (d, $^3J_{H-H}=7.23$ Hz, 3H), 5.77 (q, $^3J_{H-H}=7.23$ Hz, 1H), 7.26–7.88 (m, 6H) | 54.19/53.98 | 2.85/2.65 | 3.95/3.77 |
| **2f** | 1.94 (d, $^3J_{H-H}=7.15$ Hz, 3H), 5.65 (q, $^3J_{H-H}=7.15$ Hz, 1H), 7.70–8.14 (m, 8H) | 64.85/64.60 | 4.09/4.00 | 9.46/9.30 |

As shown in Table 1, when phthalimide was reacted with one equivalent of secondary alcohol in the presence of (+)-**1**/DEAD, the corresponding product **2** and remaining alcohol **3** can both be obtained in good chemical yield, but the enantiomeric excess values of the remaining alcohols were low. The enantioselectivity was also influenced by the nature of the secondary alcohols employed. The e.e. values seen for unsubstituted 1-phenylethanols (**3a**–**c**) were slightly higher than those for compounds substituted with electron withdrawing groups (**3d**–**f**). Compounds **2** reacted further with hydrazine hydrate to afford optically active amines **4** in moderate chemical yield, and e.e. values varied from low to moderate. Various solvent and temperature conditions were investigated with the aim of increasing the enantioselectivity. The most favorable conditions were found on completing the reaction in refluxing THF. Because of the low solubility of the reactants and some of the products, nonpolar or less polar solvents were unfavorable for these substitution reactions. When the reaction temperature decreased to room temperature or below, the reaction was very slow or no reaction occurred, and the yield of by-product increased markedly.

Because of the inversion of configuration characteristic of the substitution reaction and the known absolute configuration of (+)-**3** and (+)-**4** (determined by comparison with literature values, except for **3e** and **4e**), we could assign the absolute configuration of compounds (+)-**2** except for **2e** (Table 1). We found that with DEAD **1** underwent cycloaddition to form the pentavalent coordinated phosphorus compound **5** ($^{31}$P NMR ($CDCl_3$), $\delta$ −30.85 ppm) rather than formation of a zwitterionic adduct, which was identical to Hulst's results. However, the mechanism of asymmetric induction in these kinetic resolutions is still unclear.




**5**

## 3. Conclusion

In conclusion, enantioselective reaction between a racemic secondary alcohol and phthalimide can be realized in the presence of a chiral tricoordinate phosphorus reagent under Mitsunobu conditions. Since this method can transform a racemic secondary alcohol into the corresponding optically active alcohol and amine, it is very useful in organic synthesis. Although only moderate enantioselectivity has been obtained at the present time, we believe that the enantioselectivity can be improved by screening chiral tricoordinate phosphorus reagents.

## 4. Experimental

$^1$H and $^{31}$P NMR were recorded in $CDCl_3$ as solvent on AC-P200 instruments using TMS as internal standard and 85% $H_3PO_4$ as external standard, respectively. Elemental analyses were conducted using an MF-3 automatic analyzer. Melting points were determined using a T-4 melting point apparatus. Optical rotation measurements were obtained on a Perkin–Elmer 241MC polarimeter. All melting point temperatures are uncorrected.

### 4.1. Preparation of compound 1

A mixture of (+)-(*R*)-binaphthol (2.35 g, 8.2 mmol), hexamethyl phosphorous triamide (3.08 g, 12.5 mmol) and anhydrous toluene (50 mL) was heated under reflux for 9 h under a nitrogen atmosphere. After cooling to room temperature, the solvent was removed under reduced pressure. The crude pale yellow product was purified through flash column chromatography (silica gel 200–300 μ), gradient elution with petroleum ether/ethyl acetate afforded product (+)-**1** (2.80 g, 88%); mp 190–191°C; $[\alpha]_D^{20}$ −565 (*c* 0.5, $CHCl_3$); $^{31}$P NMR: 148.7 ppm; $^1$H NMR ($CDCl_3$, $\delta$): 2.53 (d, $^4J_{P-H}=9.32$ Hz, 6H), 7.37–7.92 (m, 12H). Literature:[12] mp 190–191°C, $^{31}$P NMR: 148.72 ppm, $[\alpha]_D$ −579 (*c* 0.06, $CHCl_3$).

### 4.2. Typical procedure for the reaction of phthalimide and secondary alcohols

To a stirred solution of (+)-**1** (1.07 g, 3.0 mmol) and phthalimide (0.44 g, 3.0 mmol) in THF (10 mL) was added 1-phenylethanol (0.37 g, 3.0 mmol). DEAD (1.07 g, 3.0 mmol) was subsequently added dropwise under a nitrogen atmosphere. The mixture was then heated under reflux for 8 h. After removing the solvent under reduced pressure, ether (50 mL) was added to the residue with stirring. The precipitated solid was removed by filtration and the filtrate was evaporated under reduced pressure to yield a yellowish oil, which was purified by means of column chromatography (silica gel 200–300 μ), gradient elution with petroleum ether/ethyl acetate afforded product **2a** (0.34 g) and remaining secondary alcohol **3a** (0.19 g).

### 4.3. Typical procedure for the reaction of compound 2 with hydrazine hydrate

A mixture of compound **2** (0.4 g) 85% hydrazine hydrate and ethanol (10 mL) was heated under reflux for 2 h. Aqueous HCl (1N, 3 mL) was added and the mixture was subsequently heated under reflux for 0.5 h. After cooling to room temperature, the mixture was filtered to remove the precipitated solid. The filtrate was evaporated under reduced pressure. Aqueous NaOH (1N, 5 mL) was added to the residue and the mixture was then extracted with ether (3×25 mL). The combined ether solution was dried with magnesium sulfate, filtered and evaporated in vacuo, the crude product was purified on column chromatography (silica gel 200–300 μ), gradient elution with petroleum ether/ethyl acetate afforded compound **4a** (0.09 g).

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