# The Mechanism of the Mitsunobu Reaction and its Application to $CO_2$ Fixation

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Difference in the mechanisms of the Mitsunobu reaction on using various types of phosphine is revealed from the reaction between $C^{18}O_2$ and ethanolamines forming 2-oxazolidones.

In the Mitsunobu reaction,[1-5] $Bu^n_3P$ (TBP) offers different results from those in $Ph_3P$ (TPP) system. For example, while the reaction between *N*-hydroxyphthalimide and 2,3,4,6-tetra-*O*-acetylglucofuranose with the diethyl azodicarboxylate(DEADC)–TPP system gives α- and β-glucofuranosides in the ratio of 1 : 7.1, the ratio is reversed to 5.5 : 1 when TBP is used instead of TPP.[1] To clarify the mechanistic differences between these systems, we have designed the reaction shown in eqn. (1). The present reaction system also presents a new

$$\text{Ethanolamine derivative} + CO_2 \xrightarrow{\text{Phosphine–DEADC}} \text{2-Oxazolidone derivative} \quad (1)$$

method of preparing useful 2-oxazolidone derivatives[6-8] from $CO_2$.

The reactivity was investigated with a typical experimental procedure as follows. Through an acetonitrile solution (5.0 ml) containing the ethanolamine derivative (0.04 mol $dm^{-3}$) (**1a–6a** in Scheme 1) and triethylamine (0.04 mol $dm^{-3}$) was bubbled $CO_2$ for 30 min at 25 °C. TPP (0.048 mol $dm^{-3}$) or TBP (0.048 mol $dm^{-3}$) and DEADC (0.048 mol $dm^{-3}$) were then added and the reaction mixture was stirred at 25 °C with continuous $CO_2$ bubbling. Yields of the corresponding 2-oxazolidone derivatives **1b–6b** were measured by HPLC (Table 1), which overall are high (>*ca.* 70%) except for a few reaction systems.

**Table 1** Yield of 2-oxazolidone derivatives after 1 h reaction[a]

| 2-Oxazolidone derivatives | Yield (%) | | | |
|---|---|---|---|---|
| | $Ph_3P$ | | $Bu^n_3P$ | |
| | 1.2 | 2.0 | 1.2 | 2.0 Equiv.[b] |
| **1b** | 72 | 95 | 53 | 89 |
| **2b** | 86 | 86 | 82 | 81 |
| **3b** | 85 | 90 | 68 | 87 |
| **4b** | 85 | 85 | 49 | 82 |
| **5b–1** and **5b–2**[c] | 78 | 95 | 97 | 98 |
| **6b** | 33 | 62 | 47 | 69 |

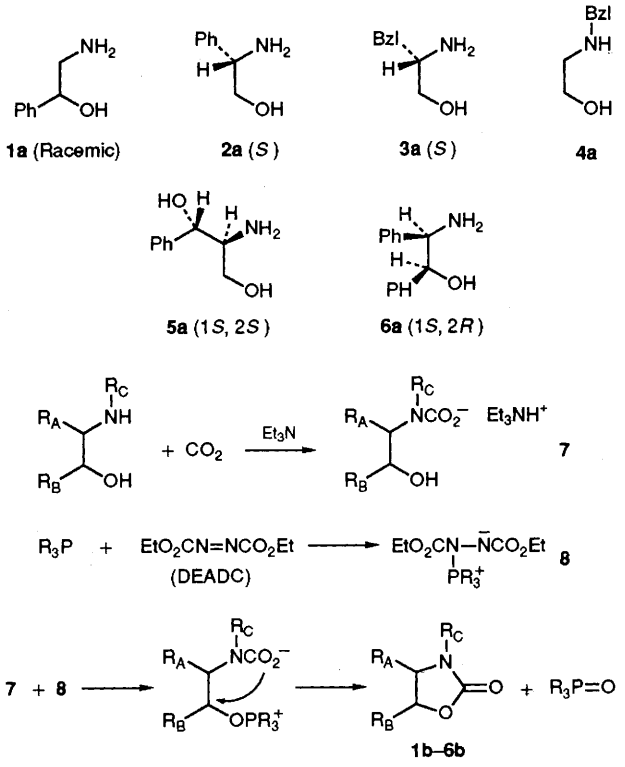
[a] Measured by HPLC. [b] Equivalent against ethanolamine; [DEADC]/[$Ph_3P$] = 1, [DEADC]/[$Bu^n_3P$] = 1. [c] Mixture of **5b–1** and **5b–2**, the structures of which are shown in Scheme 3.

According to the conventional Mitsunobu reaction,[1] the basic reaction scheme was first estimated to be as given in Scheme 1. In the presence of $Et_3N$, the amino group of the ethanolamine reacts with $CO_2$ forming carbamic acid salt. The hydroxy group is then activated through the reaction of **7** and **8**, followed by the cyclization forming 2-oxazolidones.

It is generally observed that the Mitsunobu reaction brings about an inversion of the configuration at the carbon atom attached to a hydroxy group.[1] In the case of **6a**, there is also a possibility that the configuration at C-1 of **6b** is inverted. The reaction product **6b**, however, turned out to retain its original configuration.† This suggests that the phosphines activate the $-CO_2H$ group rather than the secondary hydroxy group. Therefore, the reaction mechanism in Scheme 1 does not seem always to hold true in the present reaction.

The reaction pathways are expected to depend on the property of phosphine as well as the kind of hydroxy group (primary or secondary). Thus, in order to investigate the dependence of the reaction mechanism on phosphine, we undertook an experiment using $C^{18}O_2$ and substrate **3a**. The principle of the experiment is shown in Scheme 2. If path (A′) is taken, the resultant phosphine oxide should be an ordinary species containing $^{16}O$, while the reaction *via* path (B′) should offer $Ph_3P{=}^{18}O$ or $Bu^n_3P{=}^{18}O$. IR spectra clearly show that most of the $Ph_3P{=}O$ formed is an ordinary $^{16}O$ species, while $^{18}O$ is introduced into the $Bu^n_3P{=}O$ (P=O stretching band: 1157 $cm^{-1}$ for $Bu^n_3P{=}^{16}O$ and 1127 $cm^{-1}$ for $Bu^n_3P{=}^{18}O$).

† This was confirmed by the fact that CD, $^1H$ NMR and IR spectra, and m.p. agreed with those of the main product obtained from bis(*p*-nitrophenyl) carbonate (BNC) and **6a**; in the reaction between BNC and **6a**, the amino group of **6a** preferentially attacks the carbonyl carbon of BNC and thus the inversion of configuration cannot occur in principle.




**Scheme 1** Structures of ethanolamines and the basic reaction estimated on the basis of the conventional Mitsunobu reaction

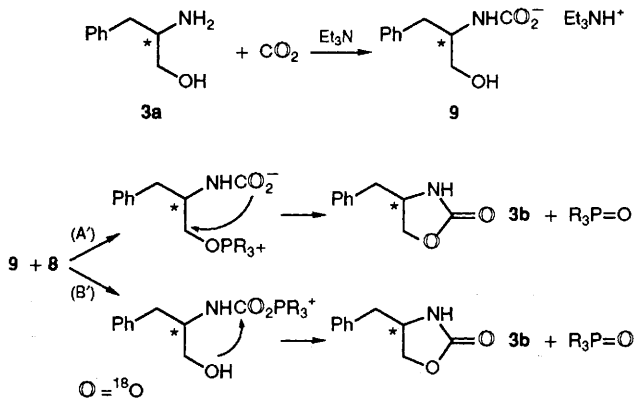
**Table 2** Dependency of ratios (**5b–1** : **5b–2**) on phosphines in the Mitsunobu reaction and the Mukaiyama reaction.

| Phosphine | Partner reagent | |
|---|---|---|
| | DEADC | PySSPy[a] |
| $Ph_3P$ | 83 : 17 | 13 : 87 |
| $(4\text{-Me-}C_6H_4)_3P$ | 78 : 22 | 18 : 82 |
| $(2\text{-Me-}C_6H_4)_3P$ | 23 : 77 | 24 : 76 |
| $Pr^nPh_2P$ | 34 : 66 | N.D.[b] |
| $(Bzl)_3P$ | 30 : 70 | 23 : 77 |
| $Bu^n_3P$ | 16 : 84 | 13 : 87 |
| $Bu^t_3P$ | 11 : 89 | 20 : 80 |

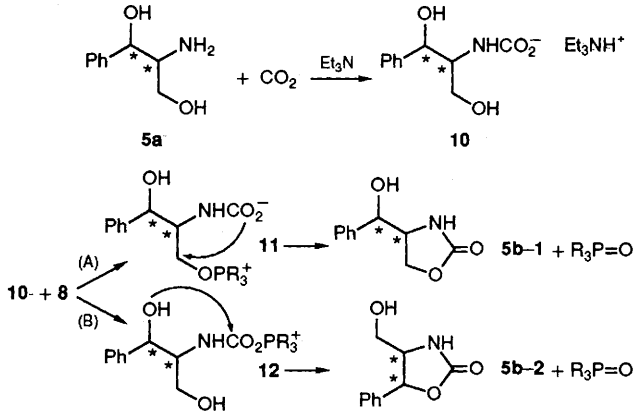
[a] Di-2-pyridyl disulfide. [b] Not determined.

These results suggest that in the TPP system the reaction proceeds mainly *via* path (A') and in the TBP system *via* path (B'). The reason why the primary hydroxy group is more easily activated in the TPP system is not obvious at present. We may have to take into account the hardness and softness of the reaction centre of the intermediate **8** in Scheme 1.

In the case of **5a**, the corresponding 2-oxazolidone derivatives should be composed of two isomers (**5b–1** and **5b–2** in Scheme 3) in principle. Table 2 summarizes the correlation between the ratios **5b–1** : **5b–2** and the types of phosphine. The difference in bulkiness of TPP and TBP cannot account for the difference in the distribution of products, since $Bu^t_3P$ with its bulky substituents gives the same main product **5b–2** as TBP. On the other hand, the product ratios seem to be closely correlated with the electronic properties (electron-withdrawing or -donating ability) of the substituent groups bound to phosphine atoms. Namely, a phosphine with high electron density tends to give **5b–2**, since the main product changes from **5b–2** to **5b–1** as the electron density decreases from $(2\text{-Me-}C_6H_4)_3P$ to $(4\text{-Me-}C_6H_4)_3P$. Interestingly, in the Mukaiyama reaction, **5b–2** remains the main product in all phosphines used, perhaps owing to some difference in electronic properties between DEADC and di-2-pyridyl disulfide (PySSPy). Reaction between **5a** and bis(*p*-nitrophenyl) carbonate also yields primarily type **5b–2**. Considering the reaction scheme presented for **3a**, the most possible reaction mechanism for **5a** must be that shown in Scheme 3. In path (A), there are two possible ways of forming a phosphonium group by either a primary or a secondary hydroxy group. Lower steric hindrance causes the primary hydroxy group to react more easily than the secondary one,[9] and thus compound **11** would form predominantly. In path (B), there are also two possibilities of nucleophilic attack by the hydroxy groups, where easier attack by the secondary hydroxy group rather than the primary one appears reasonable,‡ although **5b–1** may be formed partly from compound **12**.




**Scheme 2** Principle of the experiment using **3a** and $C^{18}O_2$




**Scheme 3** Estimated reaction mechanism of **5a**

We have proposed an efficient chemical method of $CO_2$ fixation applying the Mitsunobu reaction; using this reaction we were able to determine the fundamental difference in the mechanism between the TPP and TBP systems.

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‡ Heat of formation of model intermediates calculated by MNDO method supports this conclusion.