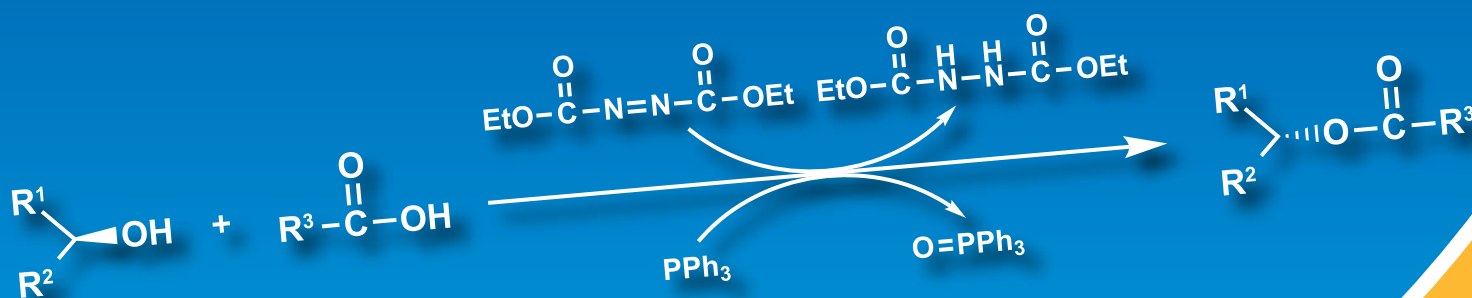


Mitsunobu Reaction



Azodicarboxylates & Amides

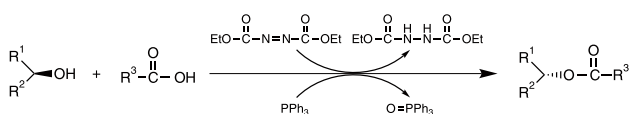
Phosphines

Tsunoda Reagent



Mitsunobu Reaction

In 1967 Mitsunobu reported the reaction of alcohols and carboxylic acids in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) to give the corresponding esters in high yield.¹⁾ This reaction involves the activation of an alcoholic hydroxyl group and the subsequent carbon-oxygen bond cleavage caused by an attacking carboxylate anion, to give an ester with complete Walden-inversion of the alcohol stereocenter. Furthermore, carboxylic acids are not the only nucleophiles which can be used in this reaction. Imides and thiols can also be used as the nucleophilic component. This reaction constitutes one of the most important organic reactions, and it is therefore called the "Mitsunobu reaction" after its developer.²⁾



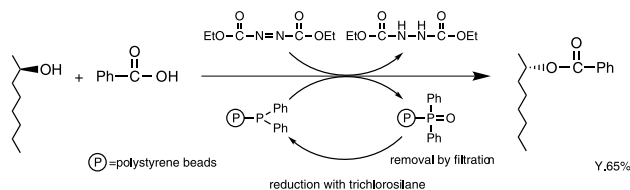
The Mitsunobu reaction has found widespread use in many fields because of its high reliability and extensive versatility. For example, searching SciFinder® for the keyword "Mitsunobu," from 1967 to today, one encounters about 4,500 related reports, indicating the high utility of this reaction.

However, the generation of phosphine oxide and hydrazinedicarboxylate as by-products often makes the isolation of pure product difficult. Furthermore, the pK_a of the usable acidic component must be below 13, but preferably below 11. Since the Mitsunobu reaction has its versatility, efforts have been made toward widening the utilization scope.

1. Removal of By-products

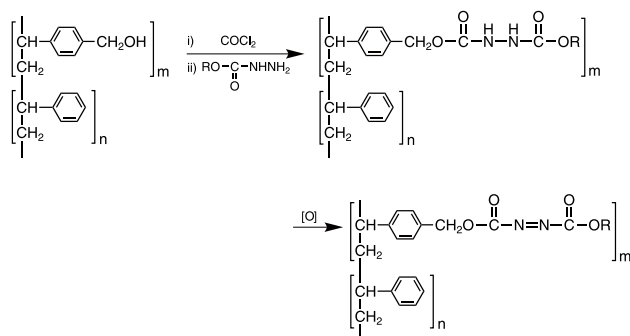
The Mitsunobu reaction is a condensation-dehydration reaction, with the loss of a water molecule from the alcohol and the carboxylic acid. This results from the strong affinity for oxygen by TPP, and for hydrogen by DEAD. This constitutes a simultaneous redox reaction, in which TPP is oxidized to an oxide while DEAD is reduced to a hydrazinedicarboxylate. Accordingly, one cannot avoid these by-products, phosphine oxide and hydrazinedicarboxylate, which are generated under the reaction conditions. Moreover, these by-products often hinder the desired product from being isolated in the pure state.

Amos and co-workers³⁾ have employed a polystyryl-diphenylphosphine, which is equivalent to TPP anchored to a polystyrene resin, in the Mitsunobu reaction. In this system, the phosphine is in excess and, at the end of the reaction, the remaining phosphine and the resulting oxide are anchored to the polystyrene resin, and can be easily removed by filtration. The resulting oxide can be recycled by reduction with trichlorosilane to give the phosphine, which is reused again. The chiral alcohol, 2-octanol, reacts with benzoic acid with complete Walden-inversion, to give the corresponding ester. Thus, demonstrating that the characteristics of the Mitsunobu reaction is preserved, while the removal of the reaction by-products is made easier.

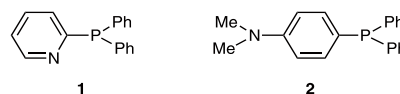


This methodology can also be applied to combinatorial chemistry. For example, Tunoori and co-workers⁴⁾ have configured a library of the aryl alkyl ethers from phenols and alcohols by means of liquid phase synthesis using polystyryldiphenylphosphine.

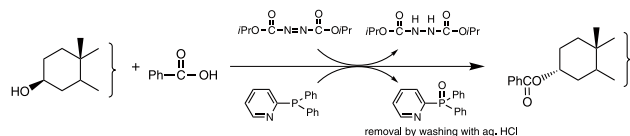
Similarly, an attempt to anchor dialkyl azodicarboxylate to a resin has also been reported. Arnold and co-workers⁵⁾ first reacted hydroxymethylpolystyrene with phosgene, and then with a carbazilic ester, followed by oxidation to give the resin bound azodicarboxylate. This resin affords good results in combination with TPP.



A method to remove the unreacted phosphine and the by-product, phosphine oxide, has also been considered. A basic functional group was introduced into TPP and upon completion of the reaction, it was washed by acid. Diphenyl(2-pyridyl)phosphine (**1**) and (4-dimethylaminophenyl)diphenylphosphine (**2**) were developed to contain a basic amine functional group attached to the phosphine group.



Camp and co-workers⁶⁾ have reported that in the Mitsunobu reaction using **1**, 3 α -ester can be obtained in 80% yield from cholestane-3 β -ol and benzoic acid. In this instance, they have removed the by-product, phosphine oxide by washing the organic layer with 2M hydrochloric acid upon completion of the reaction. Furthermore, the reaction has been followed by ³¹P NMR which showed that the basic moiety has no effect on the reaction rate or the reaction mechanism.



Itzstein and co-workers⁷⁾ have employed (4-dimethylaminophenyl)diphenylphosphine **2** as a replacement for TPP. This phosphine has a basic dimethylamino group. For this reason, the accompanying oxide by-product can be removed by washing with dilute hydrochloric acid.

They have also observed the reaction via 31P NMR and reported the results of their investigation.

2. Application toward Weak Acids

The mechanism of the Mitsunobu reaction is considered to proceed as shown in Figure 1. A betaine **3** is formed from TPP and DEAD. This betaine reacts with an alcohol to yield an anion **4** and a phosphonium **5**. An anion **7** is generated by proton abstraction by the anion **4** from acid **6**. This anion **7** attacks the phosphonium **5** to give the desired inversion product **8**. If the acidity of the acid **6** is low and the pKa value is over 11, the proton abstraction by the anion **4** from the acid **6** is inhibited and the anion **4** attacks the phosphonium **5** to yield an undesired product **9**.

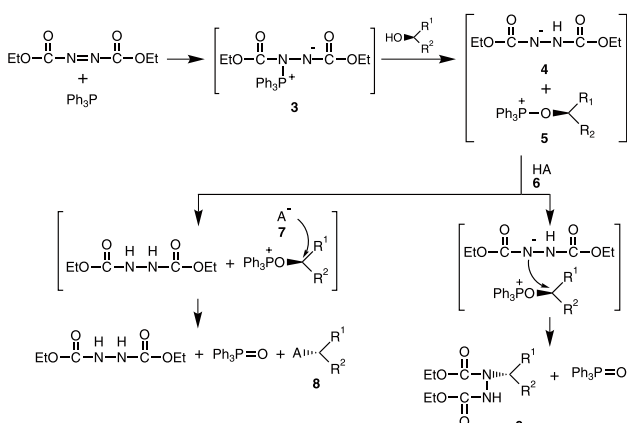
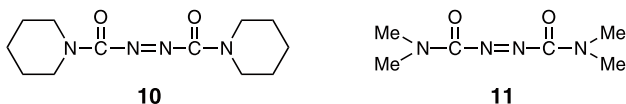
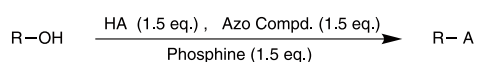


Fig. 1 Mechanism of Mitsunobu reaction

Tsunoda and co-workers⁸⁾ have carried out an additional investigation of DEAD and TPP in order to apply the Mitsunobu reaction to weak acids with high pKa value. This investigation constitutes a new system by converting the ethoxy terminal of DEAD to the amino group in order to increase the basicity of anion **4**. Sterically bulky groups were introduced on the amino group in order to inhibit the increased nucleophilic substitution activity as a result of the increased basicity. This system is able to easily abstract the proton from **6**. To achieve this, they utilized azo compounds such as 1,1'-(azodicarbonyl)dipiperidine (**10**) and *N,N,N',N'*-tetramethylazodicarboxamide (**11**) in combination with tri-*n*-butylphosphine (TBP).⁹⁾



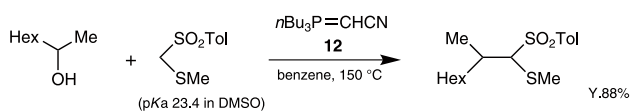
In the systems of **10**, **11**, and TBP, as shown in Table 1, the Mitsunobu reaction proceeds in high yields in spite of the amide having pKa value higher than 11. Accordingly, the method developed by Tsunoda and co-workers has attracted a great deal of attention as a method to moderate the limitations of pKa, and extend the scope of the Mitsunobu reaction.



HA	R-OH	DEAD-TPP	10-TBP	11-TBP
CF ₃ -C(=O)-NCH ₂ Ph (pKa 13.6)	PhCH ₂ OH	3	53	86
	CH ₂ =CH-CH ₂ -OH	—	56	78
Ts-N-Me (pKa 11.7)	PhCH ₂ OH	65	86	99
	CH ₂ =CH-CH ₂ -OH	51	99	96

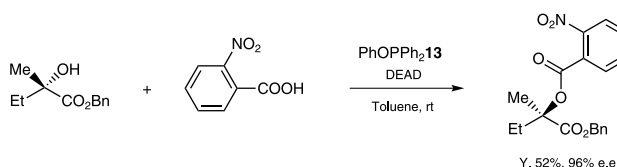
Table 1 Mitsunobu alkylation with some azo compounds (% Yield of RA)

They have also investigated the use of cyanomethylenetri-*n*-butylphosphorane (**12**) in the Mitsunobu reaction.¹⁰⁾ With **12**, acid components having high pKa values can be utilized and the **12** alone can achieve the functions of both DEAD and TPP.



3. Application toward Tertiary Alcohols

Moreover, the DEAD-TPP reaction system is generally not applicable to sterically-hindered tertiary alcohols. Mukaiyama and Kuroda *et al.* have reported the modified method using phenoxydiphenylphosphine (**13**), instead of TPP. In this system, condensation of tertiary alcohols and 2-nitrobenzoic acid affords the corresponding ester with inversion of the configuration as shown below.⁷⁾



The isolation of the desired product can be readily performed by employing a combination of DEAD anchored to a resin and phosphine **1,2** having a basic functional group, or that of TPP anchored to a resin and DEAD. The methods developed by Tsunoda and co-workers to use 1,1'-(azodicarbonyl)-dipiperidine (**10**)-TBP, *N,N,N',N'*-Tetramethylazodicarboxamide (**11**)-TBP or **12** moderate the limitation of pKa and extend the scope of the Mitsunobu reaction beyond the conventional DEAD-TPP system, thus further enhancing the usefulness of the Mitsunobu reaction. Cyanomethylenetri-*n*-butylphosphorane **12** is expected to be very useful in the synthesis of biologically active compounds.

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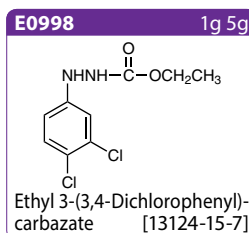
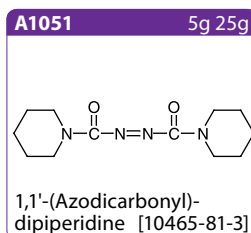
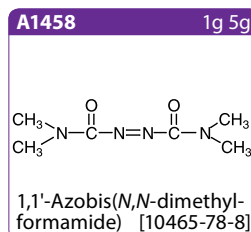
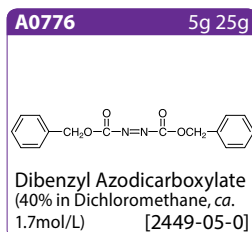
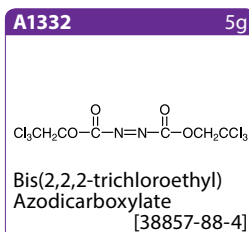
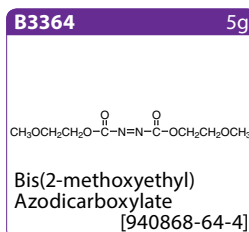
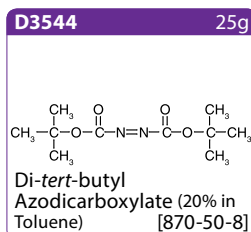
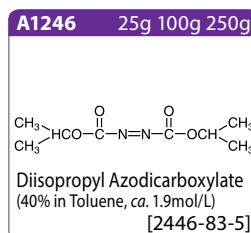
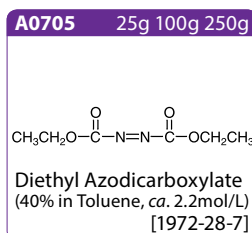
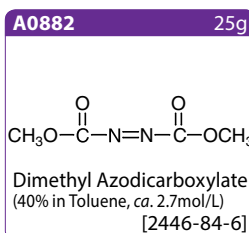
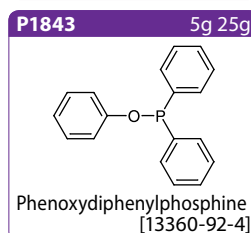
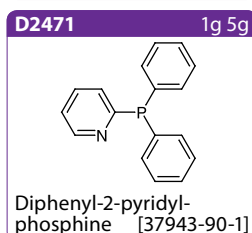
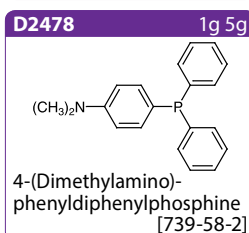
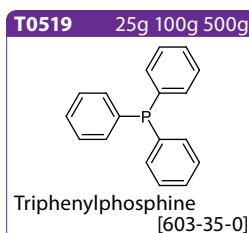
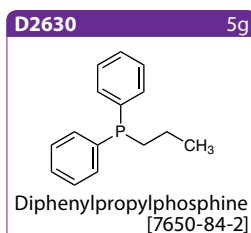
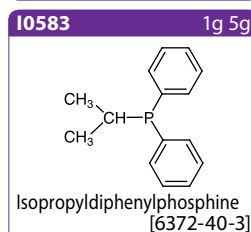
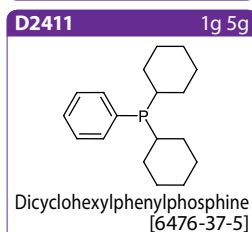
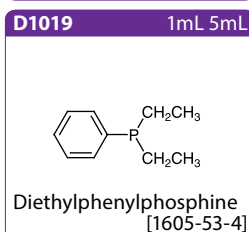
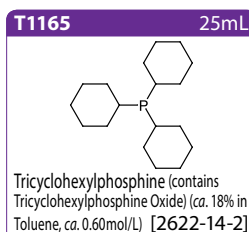
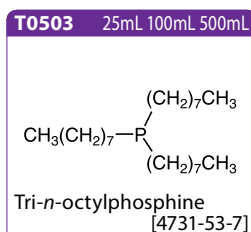
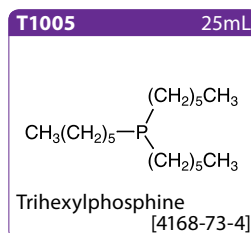
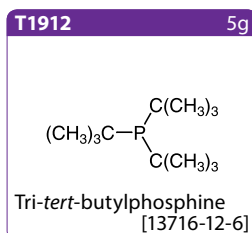
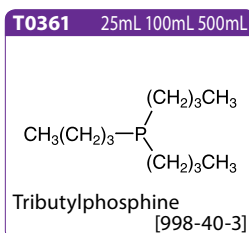
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Cautions

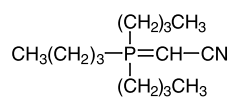
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Org. Synth. **1995**, 72, 273. *Org. Synth. Coll. Vol. 3*, 375, **1955**; *Org. Synth. Coll. Vol. 4*, 411, **1963**.

Azodicarboxylates & Amides**Phosphines**

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