Recent Advances in the Mitsunobu Reaction

In memoriam to Professor Mitsunobu (1934–2003) one of Japans' eminent scientists

This letter gives a brief overview of the most significant type of transformations under Mitsubonu protocol illustrated through recent works.

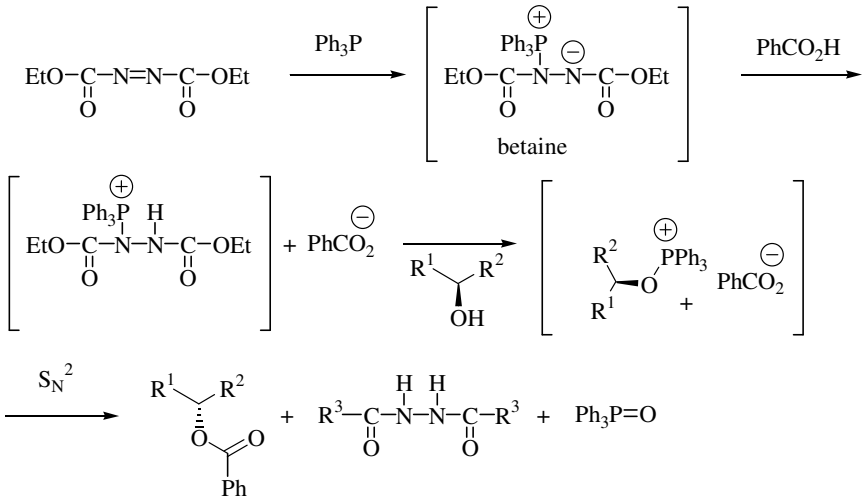
In 1967, Oyo Mitsunobu described the preparation of esters from alcohols and carboxylic acids with an equimolar amounts of diethyl azodicarboxylate (DEAD) and triphenylphosphine (more than 90% of reported Mitsunobu reaction in the literature have been run with these two reagents), with inversion of the configuration for asymmetric alcohols.[1] Since, this reaction has become quite popular for refunctionalization of alcohols and found numerous synthetic applications in organic chemistry.[2] The Mitsunobu protocol involves the reaction of an alcohol and an acidic pronucleophile (NuH) in the presence of phosphane and azodicarboxylate or azodicarboxamide to afford compounds containing newly formed C-O, C-S, C-N or C-C bond (see scheme 1).

Scheme 1

The Mitsunobu reaction is a highly stereoselective process occurring in mild conditions (essentially neutral at 0°C to room temperature), compatible with a large range of functional groups. Despite widespread use, removal of phosphine oxide and hydrazinecarboxylate generated in this reaction (see Scheme 2) can often be problematic. Many efforts have been directed to overcome such limitations, some useful methods have already been displayed including polymer supported reagents, acid labile phosphines and azodiesters.[3] Very recently triisopropyl phosphite has been introduced, to replace PPh_3, leading to the formation of phosphates more soluble in water than phosphine oxide.[4] Mechanism of this reaction continues to receive much attention, several mechanistic investigations have been recently published providing a better understanding of the different postulated pathways.[5]

The generally accepted mechanism for the inversion of the configuration for chiral secondary alcohols is outlined in scheme 2.

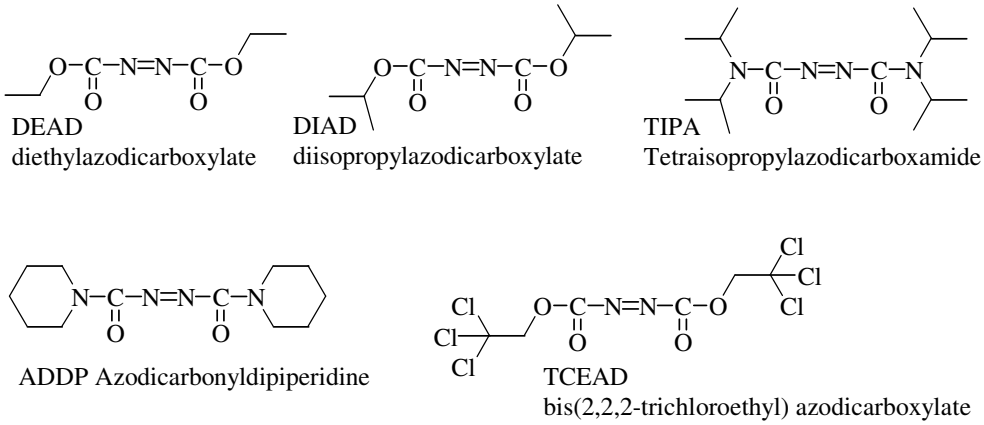
Scheme 2



[1] (a) O. Mitsunobu, M.Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380-2382. (b) O. Mitsunobu, O. Eguchi, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427-3430.
[2] For comprehensive reviews, see: (a) O. Mitsunobu, *Synthesis* **1981**, 1-28 (this review has been cited more than two thousand time). (b) D. L. Hughes, *Org. Prep. Proced. Int.* **1996**, *28*, 127-164.
[3] For an excellent overview of recent progress in this field, see: R. Dembinski, *Eur. J. Org. Chem.* **2004**, 2763-2772 and references therein.
[4] E. A. Véliz, P. A. Beal, *Tetrahedron Lett.* **2006**, *47*, 3153-3156.
[5] For mechanistic discussion, see: (a) S. Schenk, J. Weston, E, Anders, *J. Amer. Chem. Soc.* **2005**, *127*, 12566-12576. (b) K. C. K. Swamy, K. P. Kumar, N. N. B. Kumar *J. Org. Chem.* **2006**, *71*, 1002-1008. (c) D. L. Hughes, R. A. Reamer, J. J. Bergan, E. J. J. Grabowski, *J. Amer. Chem. Soc.* **1988**, *110*, 6487-6491, and cited literature.

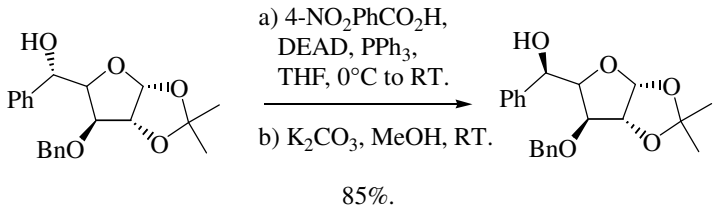
New efficient azo-types reagents have been also developed in particular by replacement of OEt group in DEAD[6] by electron-donating and bulky groups such as NR_2 groups (see figure 1). It is postulated that efficiency of the azo-amide compounds is due to enhanced basicity of the betaine (see Scheme 2) expanding versatility of the reaction with less acidic HA.

Figure 1



The Mitsunobu reaction is certainly the most efficient tool for the inversion of configuration in secondary chiral alcohols and this reaction has been widely used in synthesis as illustrated in Scheme 3.

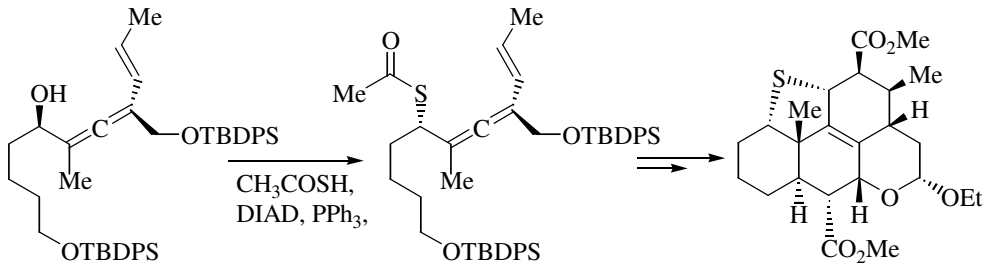
Scheme 3



In 1994, Dodge pointed out that the pKa value of the carboxylic acid partner appeared to be crucial for the yield: 4-nitrobenzoic acid or chloroacetic acid with lower pKa values (3.41 and 2.86, respectively) are more efficient compared to benzoic acid (pKa 4.19).[7] With carboxylic acids with lower pKa, esterification with retention of configuration is observed.
Mitsunobu reaction with thioacetic acid on an allenic alcohol has been used in a concise synthesis of an advanced pentacyclic intermediate of quassinoids (Scheme 4).[8]

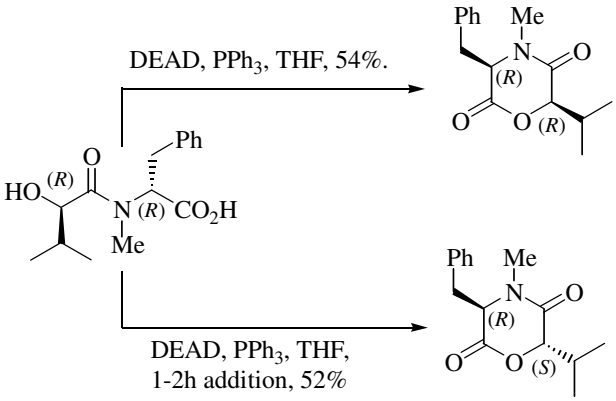
[6] It should be noted that azo and/or hydrazine dicarboxylates, especially DEAD, are susceptible to explosion when subjected to heat. DEAD is currently available as a 40% toluene solution or supported on polymers.
[7] J. A. Dodge, J. I. Trujillo, M. Presnell, *J. Org. Chem.* **1994**, *59*, 234-236.
[8] A. Dion, P. Dubé, C. Spino, *Org. Lett.* **2005**, *7*, 5601-5604.

Scheme 4



Quite recently, few examples of Mitsunobu reaction with retention of configuration appeared in the literature, most commonly with hindered substrates. In the synthesis of chiral morpholine-2,5-diones, Hughes and Sleebs found that, in some cases, hindered hydroxyacid substrates underwent Mitsunobu cyclization with either retention or inversion of configuration depending only on the rate addition of the substrate to the reaction mixture (see Scheme 5).[9] De Brabander[10] and McNulty[11] have reported that retention of configuration with sterically hindered chiral alcohols could be attributed to the formation of an acyloxyphosphonium salt intermediate instead of an alkoxyphosphonium salt in standard Mitsunobu reaction.

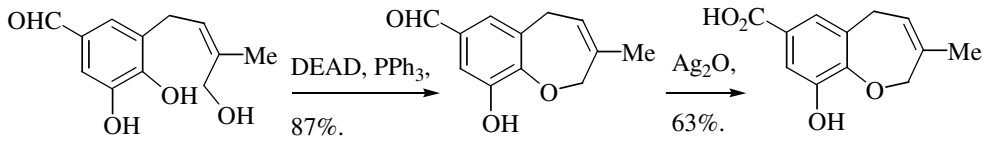
Scheme 5



Another important application of the Mitsunobu reaction is the aryl-alkyl ether linkage formation, the phenol moiety serving as a nucleophile (pKa< 12). As illustrated in Scheme 6, the synthesis of the naturally occurring 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carboxylic acid has been achieved under classical Mitsunobu cyclization.[12]

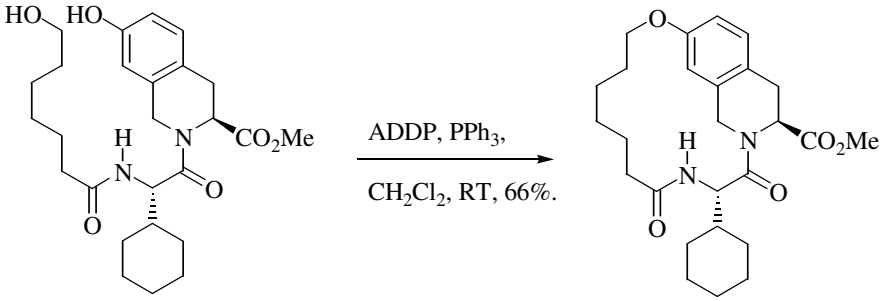
[9] A. B. Hughes, M. M. Sleebs, *J. Org. Chem.* **2005**, *70*, 3079-3088 and references cited herein.
[10] X. Liao, Y. Wu, J. K. De Brabander, *Angew. Chem. Int. Ed.* **2003**, *42*, 1648-1652.
[11] J. McNulty, A. Capretta, V. Laritchev, J. Dyck, A. J. Robertson, *Angew. Chem. Int. Ed.* **2003**, *42*, 4051-4054.
[12] S. Yamaguchi, N. Tsuchia, M. Miyazawa, Y. Hirai, *J. Org. Chem.* **2005**, *70*, 7505-7511.

Scheme 6



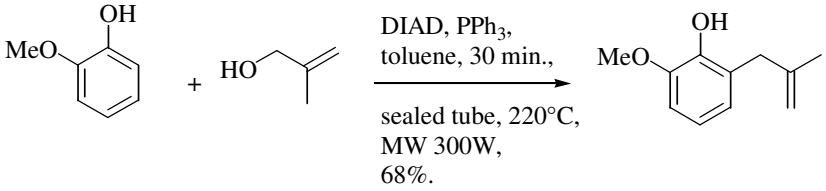
In this context, the macrocyclization of the phenol alcohol outlined in Scheme 7 has been successfully accomplished under Mitsunobu protocol leading to the left-hand part of a macrocylic inhibitor of hepatitis C virus NS3 protease.[13]

Scheme 7



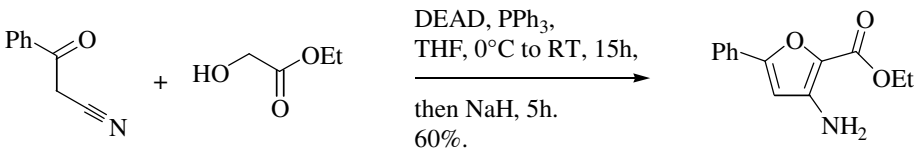
Only few examples of microwave-promoted Mitsunobu reaction have been published in the literature.[14] Moddy and Jacob[15] have demonstrated that a combined Mitsunobu reaction-Claisen rearrangement under microwave irradiation provides a useful single one-pot method for preparation of 2-allylphenols, as illustrated in Scheme 8.

Scheme 8



An efficient one-pot sequence to prepare 3-aminofuane-2-carboxylate esters from □-cyanoketone and ethyl glycolate under Mitsunobu conditions followed by treatment with NaH has been developed as exemplified in Scheme 9.[16] This method is limited to the preparation of 5-alkyl and 5-aryl, as well as 4,5-fused furans.

Scheme 9

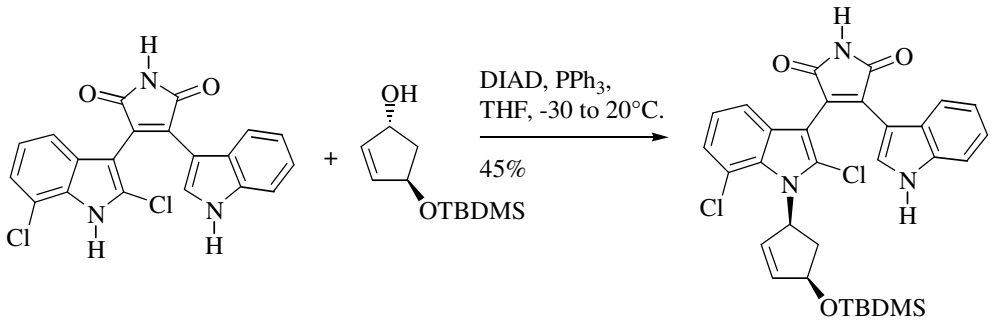


[13] K. X. Chen, F. G. Njoroge, J. Pichardo, A. Prongay, N. Butkiewicz, N. Yao, V. Madison, V. Girijavallabhan, *J. Med. Chem. Soc.* **2006**, *49*, 567-574.
[14] L. R. Lampariello, D. Piras, M. Rodriquez, M. Taddei, *J. Org. Chem.* **2003**, *68*, 7893-7895.
[15] A. M. Jacob, C. J. Moody, *Tetrahedron Lett.* **2005**, *46*, 8823-8825.
[16] A. M. Redman, J. Dumas, W. J. Scott, *Org. Lett.* **2000**, *2*, 2061-2063.

The Mitsunobu reaction can be applied to the formation of C-N bond providing a powerful tool for the preparation of nitrogen-containing molecules as highlighted in the following examples.

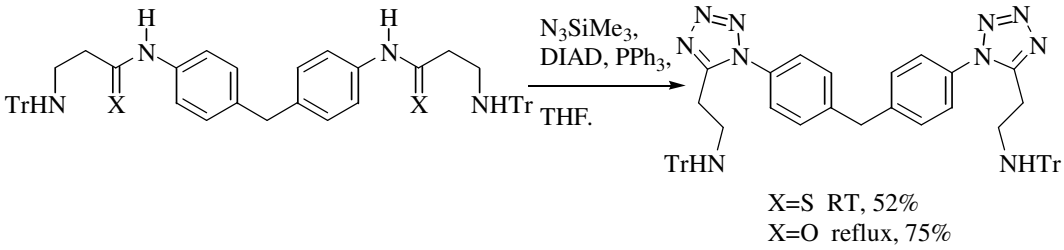
The tremendous potential of Mitsunobu reaction is outlined in Scheme 10. In the presence of three unprotected nitrogen atoms, the Mitsunobu alkylation occurred in a regiospecific fashion on the 2-chloro-substituted indole due to its acidity induced by chlorine.[17]

Scheme 10



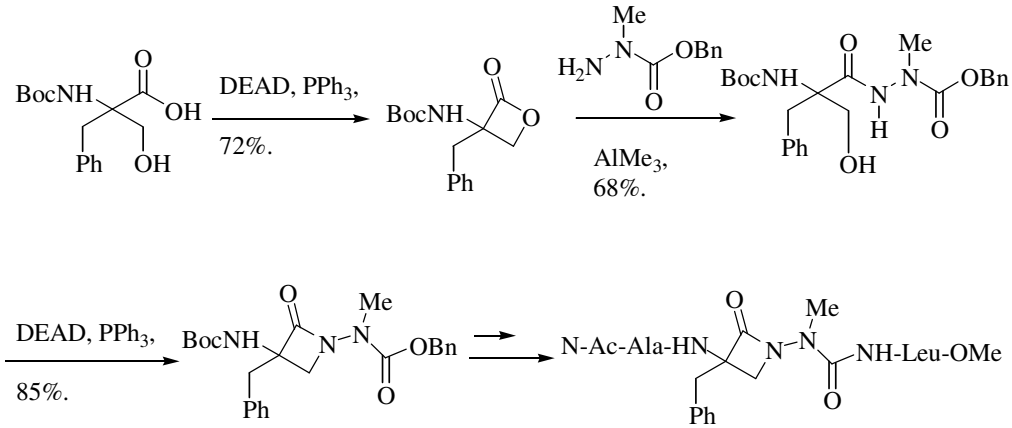
Another promising feature of the Mitsunobu reaction is found in the recent literature, wherein tetrazole derivatives are efficiently prepared from amides or thioamides upon treatment with azidotrimethylsilane as outlined in Scheme 11.

Scheme 11



An efficient preparation of azapeptidomimetic lactams using two Mitsunobu reactions has been performed as presented in Scheme 12.[18]

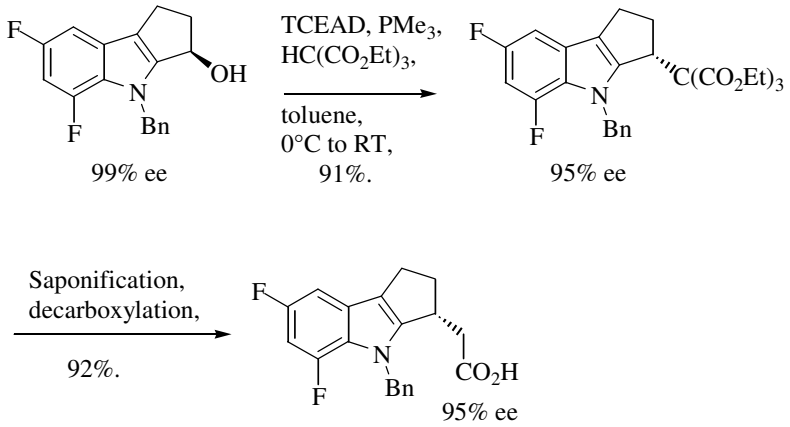
Scheme 12



[17] W. Fröhner, B. Monse, T. M. Braxmeier, L. Casiraghi, H. Sahagùn, P. Seneci, *Org. Lett.* **2005**, *7*, 4573-4576.
[18] R. L. Broadrup, B. Wang, W. P. Malachowski, *Tetrahedron* **2005**, *61*, 10277-10284.

The Mitsunobu reaction was also successfully applied to the formation of C-C bond. However, due to the requirement concerning the pKa value, the nucleophiles are restricted to active methylene compounds (*e.g.*, malonate esters) with a pKa<11-12 in most cases. The stereoselective formation of C-C bond on chiral substituted cyclopent[b]indanoles under Mitsunobu conditions, with commercially available trimethylmethanetricarboxylate as the carbon acid nucleophile, proceeds with a good to excellent degree of inversion as presented in Scheme 13.[19] It should come as not surprising that with electron-rich cycloalkyl[b]indanoles racemization is observed.

Scheme 13



Outlook

The development of new azo-type and phosphorane reagents will facilitate the isolation, and purification of a desired product, amenable to large-scale synthesis in safety fashion and extend the scope of the Mitsunobu-type reactions to various acidic pronucleophiles (NuH) with low pKa, in particular for C-C bond formation.

The author would like to warmly thank Dr. André Guingant for fruitful discussions and invaluable comments.

[19] M. C. Hillier, J.-F. Marcoux, D. Zhao, E. J. J. Grabowski, A. E. McKeown, R. D. Tillyer, *J. Org. Chem.* **2005**, *70*, 8385-8394.