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The Mitsunobu Reaction: Origin, Mechanism, Improvements, and Applications

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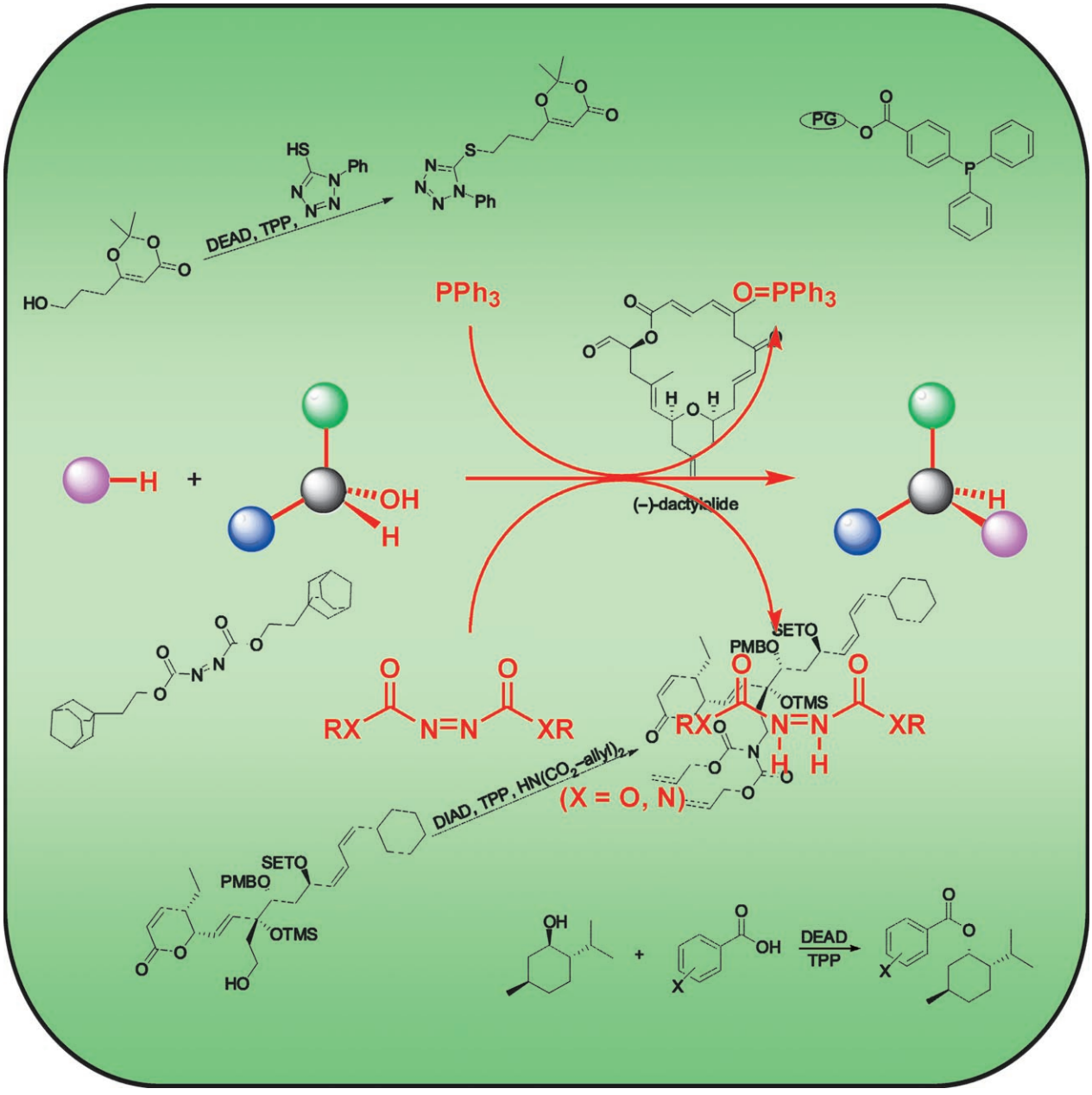
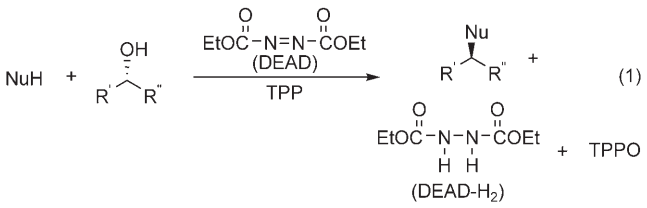


Abstract: The Mitsunobu reaction is a widely used and versatile method for the dehydrative oxidation–reduction condensation of an acid/pronucleophile usually with a primary or secondary alcohol that requires the combination of a reducing phosphine reagent together with an oxidizing azo reagent. The utility of this reaction stems from the fact that it is generally highly stereoselective and occurs with inversion of the stereochemical configuration of the alcohol starting material. Furthermore, as carboxylic acids, phenols, imides, sulfonamides, and other compounds can be used as the acid/pronucleophile, this reaction is useful for the preparation of a wide variety of functional groups. This Focus Review of the Mitsunobu reaction summarizes its origins, the current understanding of its mechanism, and recent improvements and applications.

Keywords: azo compounds · condensation · Mitsunobu reaction · oxidation–reduction · phosphines

1. Introduction

The Mitsunobu reaction is a versatile and widely used method for the dehydrative coupling of an alcohol with an acid/pronucleophile by using a combination of an oxidizing azo reagent, most commonly diethyl azodicarboxylate (DEAD), and a reducing phosphine reagent, usually triphenylphosphine (TPP), under mild and virtually neutral reaction conditions [Eq. (1)].[1–11] Carboxylic acids, phenols,



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diols, activated carbon acids, imides, and the like can all serve as the acid/pronucleophile reaction component. Thus, this reaction can be used to prepare esters, aryl ethers, cyclic ethers, carbon–carbon and carbon–nitrogen bonds, and so on. Besides the desired coupled product, a hydrazide such as diethyl hydrazinedicarboxylate (DEAD-H_2) from DEAD and a phosphine oxide such as triphenylphosphine oxide (TPPO) from TPP are also formed as by-products.

This Focus Review will concentrate on four aspects of the Mitsunobu reaction: 1) its early development by the late Professor Oyo Mitsunobu, 2) the current understanding of its mechanism, 3) the recent development of alternative reagents and improved experimental procedures, and 4) acid/pronucleophile choice and representative applications in the synthesis of complex organic molecules. Owing to the nature of Focus Reviews, this manuscript is not meant to be a comprehensive and definitive treatise on the Mitsunobu reaction, and several very thorough reviews have appeared over the years.[1–6] Specialized reviews have also been published concerning the use of modified reagents and techniques in the Mitsunobu reaction,[8,9] its use in amino acid and peptide chemistry,[10] and in macrolactonizations applied to the synthesis of natural products.[11] A review of the use of hindered secondary alcohol substrates has also appeared.[12]

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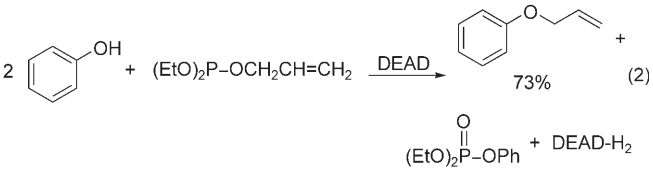
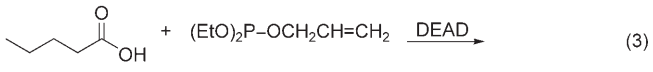
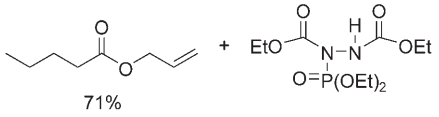
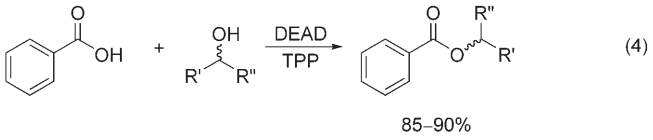
2. The Early Years: Oyo Mitsunobu

Professor Oyo Mitsunobu first described his eponymous reaction in its currently most recognizable form [Eq. (1)] in 1967.[13] However, this new reaction was undoubtedly inspired by Mitsunobu's previous observation, as a student with Prof. Teruaki Mukaiyama, of the synthesis of allyl phenyl ether from the reaction of phenol with allyl diethyl phosphite and DEAD [Eq. (2)],[14] as well as contemporary research by the Mukaiyama group into oxidation–reduction condensation reactions.[15] In the original publication, the first reaction reported was that of *n*-valeric acid with allyl diethyl phosphite and DEAD to produce allyl valerate and diethyl *N*-(diethyl)phosphoryl hydrazodicarboxylate [Eq. (3)]. This was followed by reactions of benzoic acid with alcohols in the presence of DEAD and TPP that resulted in the formation of the corresponding esters in excellent yields [Eq. (4)].

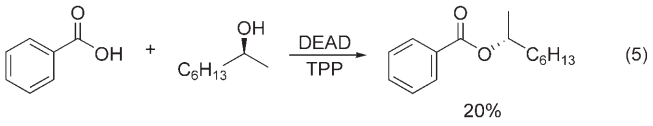








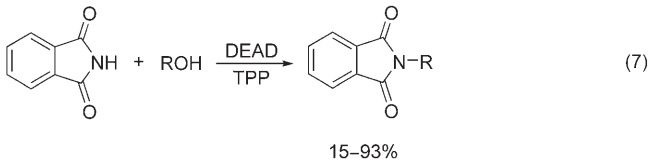
The current ubiquity of the Mitsunobu reaction in organic synthesis is due in large part to the fact that the coupling of the acid/pronucleophile and alcohol starting materials normally occurs with inversion of the stereochemical configuration of the carbinol center [Eq. (1)]. This stereochemical outcome was first observed by Mitsunobu and Eguchi in the reaction of enantiomerically enriched 2-octanol with benzoic acid [Eq. (5)].[16]

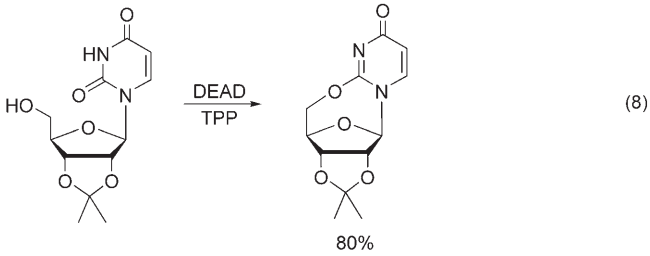


Other important reports by Mitsunobu with regard to the reaction named after him include: 1) the use of 4-nitrobenzoic acid (4-NBA) for reactions with sterically hindered alcohols [Eq. (6)],[17] 2) the use of phthalimide as the acid/pronucleophile coupling component for the synthesis of amines from alcohols [Eq. (7)],[18,19] 3) intramolecular versions (Equations (8) and (9)),[20,21] 4) selectivity for reaction at the primary alcohol center over the secondary in a diol [Eq. (10)],[22] and 5) the use of activated methylene groups as carbon acids (Equations (9) and (11)).[23]

Abstract in Chinese:

Mitsunobu 反應是一個被廣泛應用和多元化的有機合成方法。通過還原性有機膦試劑和氧化性偶氮試劑的聯合使用，有效應用於酸(親核試劑)和一級或二級醇的脫水氧化–還原縮合。經過手性中心的構形翻轉，可以高度的立體選擇性得到與起始原料(醇)構形相反的手性產物。此外，由於羧酸、苯酚、亞酰氨、磺酰胺等等可作為親核試劑，所以這反應可以用以制備不同的官能團分子。這篇關於 Mitsunobu 反應的綜述重點概括了它的發現、機理和近期的改善及在有機合成中的應用。





Tracy Yuen Sze But *received her BSc in chemistry from the Univ. of Hong Kong in 2004. She has the distinction of being the first student to volunteer to work in the group of Prof. Patrick H. Toy when she began her undergraduate studies. She is currently a senior PhD student in his group, and her research is centered on the development of organocatalytic versions of the Mitsunobu reaction.*

Patrick H. Toy *received his BS in chemistry from the Ohio State Univ. in 1990. He began his PhD at the Univ. of Minnesota under the direction of the late Prof. Paul G. Gassman and Prof. Hung-Wen (Ben) Liu, and completed it in 1998 with Prof. Martin Newcomb at Wayne State Univ. After two years' postdoctoral research with Prof. Kim D. Janda at the Scripps Research Institute, he worked at Wyeth in Pearl River, NY. In October 2001 he became Assistant Prof. at the Univ. of Hong Kong and was recently promoted to Associate Prof. His research interests include the use of polymers in organic synthesis and organocatalysis.*

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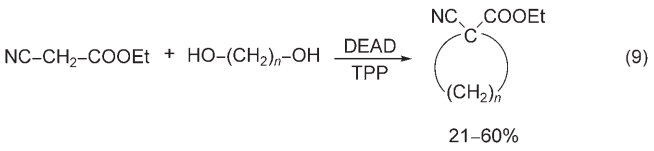

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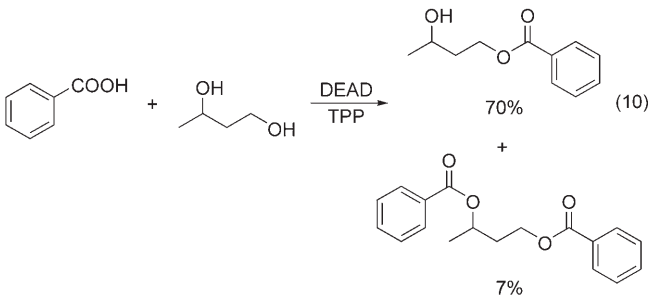

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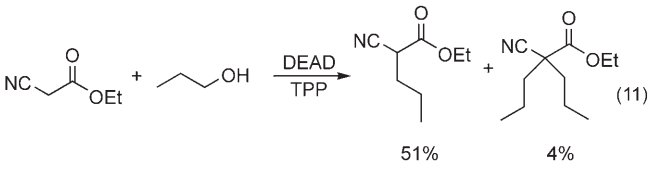

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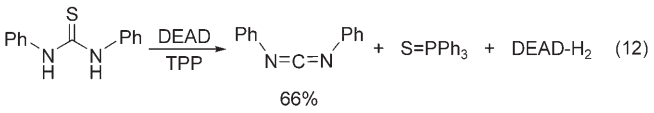
Furthermore, Mitsunobu also used the reagent combination of DEAD and TPP to convert thioureas into carbodiimides [Eq. (12)],[24,25] thioamides into ketenimines [Eq. (13)],[26] and thiols into disulfides [Eq. (14)].[27] The details of the mechanism of this last reaction were not reported; however, the function of TPP there was found to be only catalytic, as it was indeed necessary but was unchanged at the end of the reaction.



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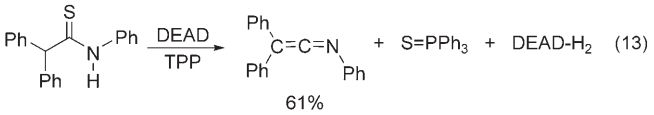

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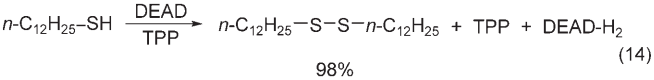

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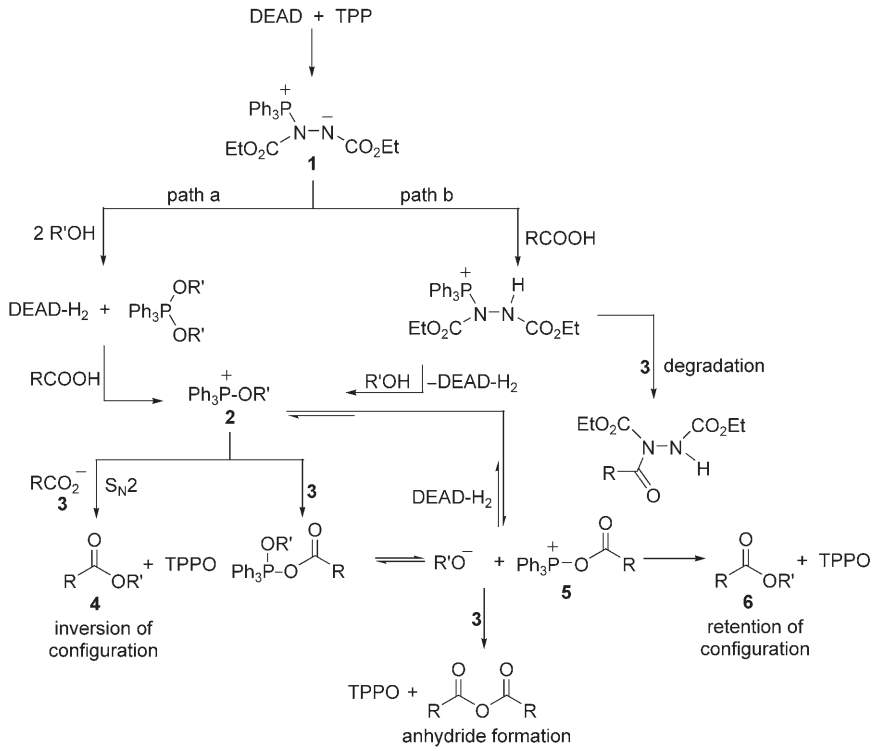
3. The Mechanism

Owing to the importance and widespread use of the Mitsunobu reaction, the details of its mechanism have been widely studied by a variety of methods.[28–49] The current generally accepted mechanism with DEAD and TPP as representative reagents that can account for all the experimentally observed outcomes is outlined in Scheme 1.[49] The first step in the Mitsunobu reaction is nucleophilic addition of TPP to DEAD to form the Morrison–Brunn–Huisgen betaine (**1**).[50–52] This reactive intermediate can then either react with two molecules of the alcohol to produce eventually DEAD-H_2, alkoxyphosponium species **2**, and carboxylate/nucleophile **3** (path a), or it can deprotonate the acid/pronucleophile to form eventually, again, DEAD-H_2, **2**, and **3** (path b). Nucleophilic displacement of TPPO from **2** by **3** completes the reaction to form the coupled product **4** that has inverted stereochemistry relative to the alcohol starting material. It was shown that **2** is in equilibrium with the corresponding acyloxyphosphonium species **5**,[29,32,37] and this species can, in rare cases, lead to coupled product **6**, which retains the original alcohol stereochemistry, and anhydride formation. The position of this equilibrium is possibly mediated by DEAD-H_2 and is dependent upon the pK_a of the acid/pronucleophile, with **2** favored by more-acidic compounds.[42,43] Furthermore, it was proposed[42] and supported by experimental evidence[46–48] that, in some cases, **5** can be formed first and then converted into **2**. This may explain why, when some very sterically hindered secondary alcohols are used as reaction substrates, they can favor the formation of **6**, as conversion of **5** into **2** can be sensitive to steric constraints.[53–55] Regardless of the details and complexity of this mechanism, formation of **2** is greatly favored to a large extent in most applications of the Mitsunobu reaction, and inversion of stereochemistry is reliably observed. The cases in which **5** is favored and retention of configuration is observed are very rare. Most recently, density functional investigations into the Mitsunobu reaction with PH_3 and dimethyl azodicarboxylate as the reducing and oxidizing reagents, respectively, indicate that the mechanism may actually be even more complex, with multiple additional competing equilibria.[49] This particular manuscript is highly recommended reading material as it contains the most up-to-date and detailed discussion regarding the mechanistic details of the Mitsunobu reaction as well as an excellent summary of the various factors that influence the numerous equilibria involved, and accounts for many of the reported anomalous results.

4. New Reagents and Procedures

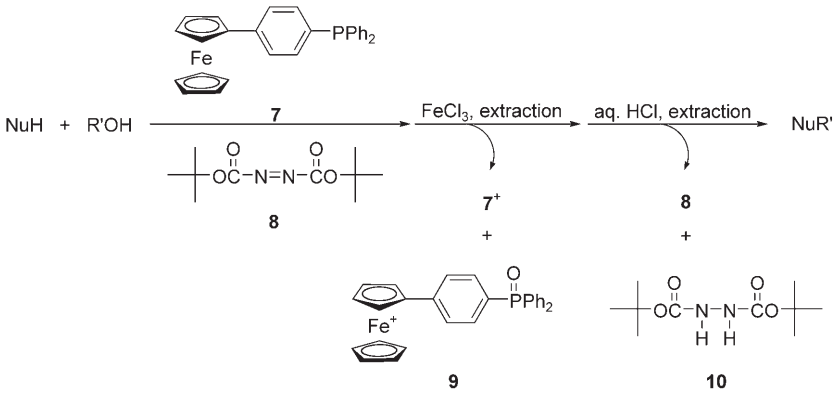
One major drawback of the Mitsunobu reaction is that, besides the two reactants, it requires the use of stoichiometric quantities of two other reagents that each produces a by-product. Thus, even in reactions that are relatively efficient and afford a high yield of the desired product, this product can be difficult to isolate from the reaction mixture, which can contain excess/unreacted reagents and starting materials in addition to the two by-products. Therefore, much research has been directed towards developing alternatives to DEAD and TPP that facilitate purification of the desired



Scheme 1. Current understanding of the mechanism of the Mitsunobu reaction as presented in reference [49].

product. These efforts were recently reviewed,[8,9] and we highlight herein work that has been subsequently reported.

The ferrocenyl-tagged triphenylphosphine reagent **7** has been used together with di-*tert*-butyl azodicarboxylate (**8**) in Mitsunobu reactions that do not require chromatographic purification of the desired product (Scheme 2).[56] The ferrocenyl group serves as a redox-switchable phase tag as it can be readily oxidized by $FeCl_3$ to a cation that is insoluble in nonpolar solvents. After the Mitsunobu reaction with **7**, $FeCl_3$ was added, and the cationic tagged phosphine species (**7**$^+$ and **9**) thus formed were extracted with water. This was followed by treatment with HCl to decompose any residual reagent **8** and its reduced by-product **10**. Such sequential treatments allowed for direct isolation of the desired product in essentially quantitative yield with high purity (generally $>90\%$). Furthermore, it was reported that reagent **7** could be regenerated by sequential reduction of **9** with $Na_2S_2O_3$ and $HSiCl_3$.



Scheme 2. Mitsunobu reaction with ferrocenyl-tagged phosphine reagent **7**.

Another alternative to the azo reagent DEAD was recently described.[57] Di-4-chlorobenzyl azodicarboxylate (**11**) was easily prepared in three steps by: 1) mixing 4-chlorobenzyl alcohol with 1,1′-carbonyldiimidazole, 2) reacting the resulting carbamate **12** with hydrazine to form **13**, and 3) oxidation of the hydrazide **13** with *N*-bromosuccinimide (NBS) (Scheme 3). Comparison of **11** to DEAD in a wide range of Mitsunobu reactions showed them to be equally efficient reagents. The reported advantages of **11** over DEAD are that it is a stable solid at room temperature and the retention of its by-product **13** on silica gel is distinctly different from that of DEAD-H_2. Furthermore, **13** can be mostly removed from the desired reaction product simply by precipitation with CH_2Cl_2.

Curran and co-workers reported a series of tagged azo reagents, including a pair of reagents tagged with cyclodextrin-binding adamantyl groups: bis(1-adamantylmethyl) azodicarboxylate (**14**) and bis(2-(1-adamantyl)ethyl) azodicarboxylate (**15**) (Scheme 4).[58] These reagents and their corresponding reduced products were found to have significantly longer retention times on cyclodextrin-bonded silica gel than typical Mitsunobu reaction products. Thus, they and their by-products can be easily separated from the desired coupled product.

Two second-generation fluorous azo reagents, **16** and **17**, were also reported (Scheme 5).[59] First-generation reagent **18** was found to be not very good for use in Mitsunobu reactions that involve sterically hindered alcohols and/or less acidic acids/pronucleophiles. It was found that the additional methylene groups separating the fluorous tails and the azo groups of **16** and **17** allowed them to be much more useful in such Mitsunobu reactions. For example, the coupling re-

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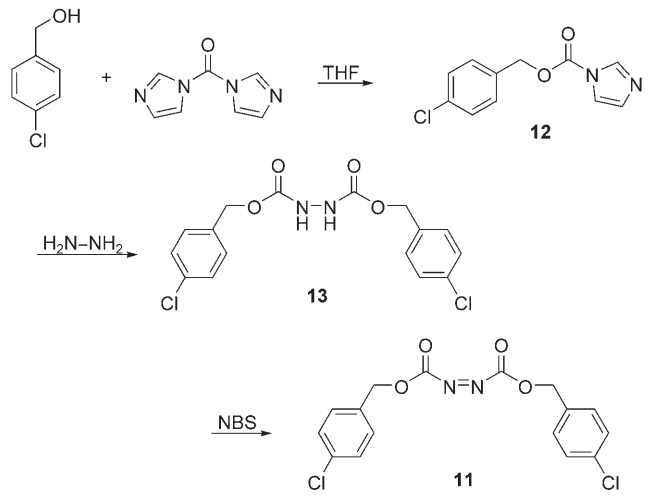
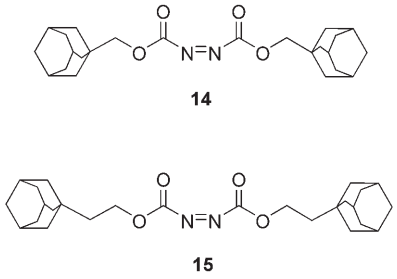
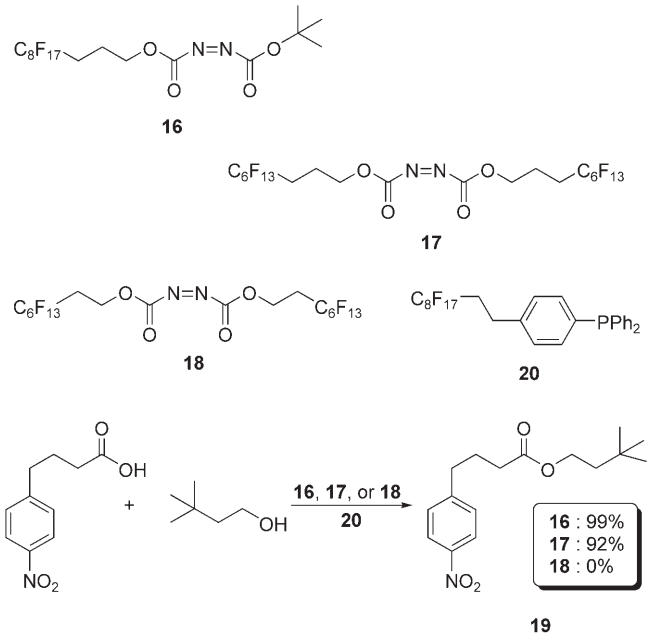


Scheme 3. Synthesis of DEAD analogue **11**.



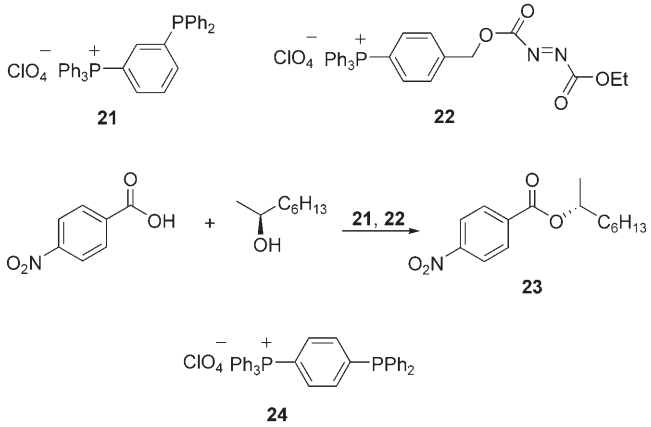
Scheme 4. Azo reagents tagged with cyclodextrin-binding groups.



Scheme 5. Mitsunobu reactions with fluorous reagents.

action of 4-(4-nitrophenyl)butyric acid with 3,3-dimethylbutanol in the presence of **16**, **17**, or **18** afforded the desired product **19** in 99, 92, and 0% yield, respectively, when fluorous phosphine reagent **20** was used as the reducing reagent. It was suggested that **16** is the reagent of choice when product purification is to be achieved by medium-pressure fluorous chromatography, and that **20** should be used when fluorous solid-phase extraction is used. Most recently, a complementary methodology for liquid–liquid extraction was reported for the purification of products of fluorous Mitsunobu reactions with such tagged reagents.[60]

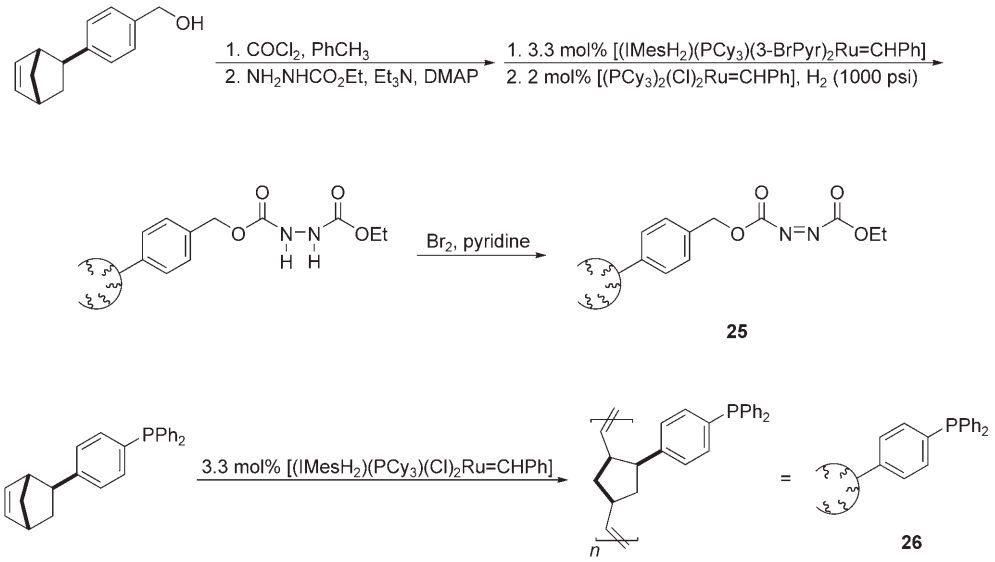
In another example of the simultaneous use of tagged reagents in Mitsunobu reactions, phosphonium salts were used to control reagent solubility and thereby facilitate product isolation.[61] Tetraarylphosphonium perchlorate and hexafluorophosphate salts are rather insoluble in diethyl ether, and this property allows them to be efficiently precipitated from reaction mixtures in more-polar solvents such as dichloromethane by the addition of these solvents. To demonstrate the utility of such salts in facilitating product purification, reagents **21** and **22** were prepared and used simultaneously in Mitsunobu reactions (Scheme 6). At the end of the



Scheme 6. Phosphonium ion tagged reagents.

reactions, diethyl ether was added to precipitate all of the phosphonium salt species. Subsequent filtration and concentration afforded the pure product. This reaction system is particularly efficient as only 1.5 equivalents of both **21** and **22** were necessary to achieve a high yield of **23**. Interestingly, isomeric reagent **24** was reported to be substantially less reactive in these reactions than **21**.

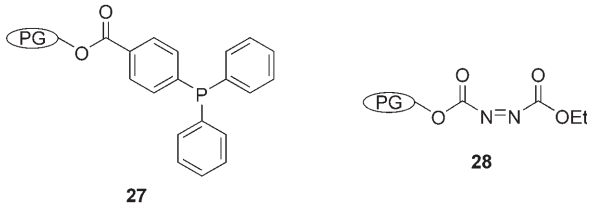
The simultaneous use of two polymer-supported analogues of DEAD and TPP in Mitsunobu reactions has been reported.[62] Reagents **25** and **26**, derived from ring-opening metathesis polymerization (ROMP), were prepared from the corresponding norbornene monomers (Scheme 7). These could be used together in Mitsunobu reactions to form the required betaine reactive species owing to their solubility in THF, and could be removed from the reaction mixture based on their insolubility in EtOAc. For example, the reaction between 4-NBA and 3-phenylpropanol produced the desired ester in high yield when 2 equivalents of both **25** and **26** were used. At the end of the reaction, excess **25** and **26** and the polymer-bound by-products were removed by



Scheme 7. Synthesis of ROMP-derived polymer-supported reagents. Cy = cyclohexyl, DMAP = 4-dimethylaminopyridine, Mes = mesityl, Pyr = pyridyl.

precipitation and filtration. Notably, although many examples of the use of insoluble polymer-supported phosphines or azo reagents in Mitsunobu reactions have been previously reported, their heterogeneous nature precludes the use of such reagents together. Such multipolymer Mitsunobu reactions are only possible when at least one of the polymer-supported reagents is present as part of the homogeneous reaction mixture.

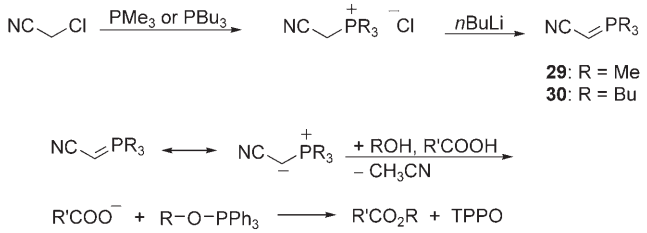
In a similar manner, soluble and highly loaded polyglycerol-supported reagents **27** and **28** were reported to be used simultaneously in Mitsunobu reactions (Scheme 8).[63] The



Scheme 8. Polyglycerol (PG)-supported reagents.

polyglycerol support material was prepared by the anionic polymerization of glycidol and has a dendritic structure. In the reported Mitsunobu reactions with these reagents, all polymeric reagents and by-products were removed by a simple precipitation/filtration procedure to afford chromatography-free products of high purity.

Tsunoda and co-workers recently published the details of the preparation and handling of their previously reported reagents cyanomethylenetrimethylphosphorane (**29**)[64] and cyanomethylenetributylphosphorane (**30**),[65] which can effect Mitsunobu reactions on their own (Scheme 9). Reagents **29** and **30** were synthesized in two steps from chloroacetonitrile and the appropriate trialkylphosphine, and are useful for performing Mitsunobu reactions in which the



Scheme 9. Synthesis and use of ylides **29** and **30**.

acid/pronucleophile starting material has $pK_a > 13$. Furthermore, **29** and **30** are reportedly the only reagents that can be effectively applied in the Mitsunobu reaction of *N*-unsubstituted sulfonamides such as *p*-toluenesulfonamide. Reagents **29** and **30** are very sensitive to both air and moisture; thus, they should be stored and used with great care.

In work related to the Mitsunobu reaction, Mukaiyama et al. continued their research into oxidation–reduction condensation reactions and recently reported the use of substituted quinone **31** as the oxidant in such reactions (Scheme 10).[66] In these reactions, an alkoxydiphenylphosphine generated in situ reacts with a carboxylic acid in the presence of **31** to afford an ester with inverted alcohol stereochemistry under neutral conditions. This substitution reaction proceeds even when a tertiary alcohol is used. Furthermore, when an alcohol is used in place of the carboxylic acid, an ether is formed.[67]

Recently, focus has shifted away from the development of alternative reagents for the facilitation of the purification of Mitsunobu reaction products towards the identification of new reaction procedures and workup protocols that achieve the same result. This is probably due to the fact that most of the alternative reagents reported in the literature are not commercially available and require multistep synthetic sequences for their preparation. In this regard, it was reported

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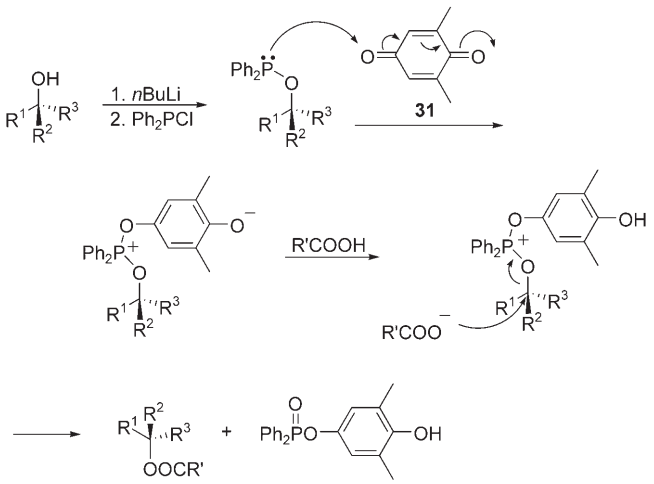
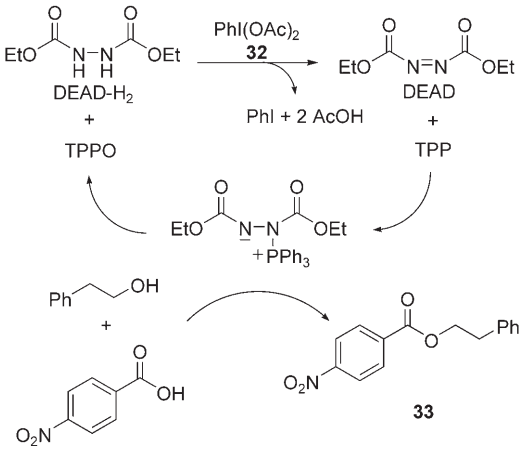


Scheme 10. Oxidation–reduction condensation reactions with **31**.

that pure Mitsunobu reaction products can be obtained by, first, washing of the crude reaction mixture with a solution of hydrogen peroxide of 15% by weight, followed by addition of aqueous sodium sulfite (to reduce any residual peroxides), and then filtration through silica gel.[68] The oxidative washing converts any residual phosphine into the corresponding oxide, which is highly polar. With this protocol, pure product was obtained in 96% yield from the reaction of *N*-hydroxyphthalimide with prenyl alcohol on the 20-g scale.

The first version of the Mitsunobu reaction that is catalytic in the oxidant (DEAD) has been reported.[69] This reaction system utilizes iodosobenzene diacetate (**32**) as the stoichiometric oxidant, which reduces the role of DEAD to that of a catalyst (Scheme 11). In this way, product purification is facilitated by the reduction of the required quantity of a reagent that produces a by-product that is difficult to remove. For example, the reaction of 4-NBA and 2-phenylethanol with 0.1 equivalents of DEAD and 2 equivalents of both TPP and **32** provided the desired product **33** in 90% yield.

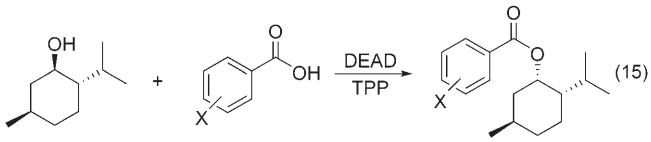


Scheme 11. Catalytic cycle of a Mitsunobu reaction system catalytic in DEAD.

To date, no version of the Mitsunobu reaction that is catalytic in either TPP or a surrogate for the reducing phosphine reagent has been reported, and the development of such a reaction system remains one of the key challenges in this field.

5. Acid/Pronucleophile Choice

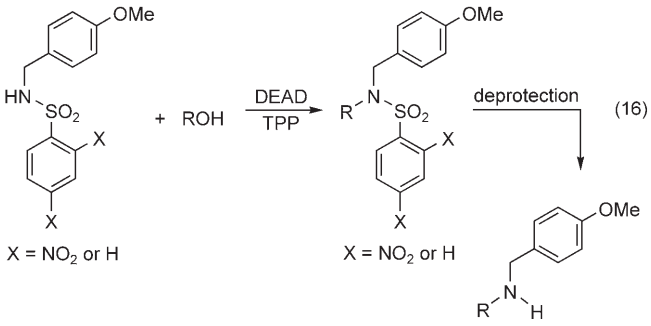
When stereochemical inversion of a carbinol center, especially of a sterically hindered one, is the aim of the Mitsunobu reaction, 4-NBA is generally the acid of choice, and the reports by Martin and Dodge[70] and Dodge et al.[71] are most often cited for its use. However, these were not the first reports of the advantages of 4-NBA over benzoic acid. As previously mentioned, Mitsunobu et al. were the first to do so in reactions of 4-NBA with sterically hindered alcohols,[17] and this was followed up by others.[72] Perhaps the most thorough examination of acid choice in Mitsunobu reactions that involve the stereochemical inversion of sterically hindered alcohols was reported by Dodge et al.[73] In this study, they treated a variety of substituted benzoic acids with menthol in several solvents and compared the product yields [Eq. (15)]. They found that there was a correlation



between the pK_a of the carboxylic acid used and the product yield, and that the use of 4-NBA in either benzene or THF was optimal. If a crystalline product with inverted stereochemistry is desired, 3,5-dinitrobenzoic acid is often used.[74,75] Interestingly, the use of 3,5-dinitrobenzoic acid was not examined in the study by Dodge et al.,[73] even though its use had been reported long before their study was undertaken. It was also reported that chloroacetic acid is useful in the transformation of sterically congested alcohols.[76]

As mentioned at the beginning of this Focus Review, a great variety of functional groups other than carboxylic acids can serve as the acid/pronucleophile reaction component in Mitsunobu reactions. As many of these have been summarized in previous reviews, included herein are a few examples that were reported relatively recently. Additionally, several other acid/pronucleophile groups are discussed later in the context of the synthesis of complex molecules.

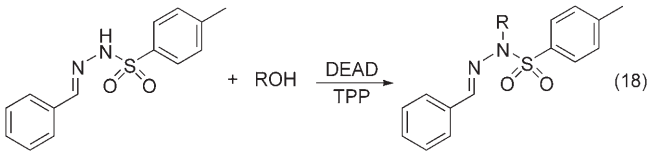
Fukuyama et al. reported the use of 2- and 4-nitrobenzenesulfonamides[77] and 2,4-dinitrobenzenesulfonamides[78] as pronucleophiles in what are often referred to as Fukuyama–Mitsunobu reactions, which eventually lead to the synthesis of secondary amines [Eq. (16)]. These sulfonamides were used as pronucleophiles as the sulfonamide portion is readily removed via the corresponding Meisenheimer complexes by treatment with thiolates.



(16)

For the synthesis of aminooxy acids from appropriately protected hydroxy acids by using the Mitsunobu reaction, *N*-hydroxyphthalimide is the pronucleophile of choice (Equation (17); Bn = benzyl, DIAD = diisopropyl azodicarboxylate).[79,80] Tosyl and *tert*-butoxycarbonyl (Boc) hydrazones are also suitable acid/pronucleophile components in Mitsunobu reactions, with the latter requiring electron-withdrawing substituents on the aryl ring (Equations (18) and (19); EWG = electron-withdrawing group).[81]

(17)



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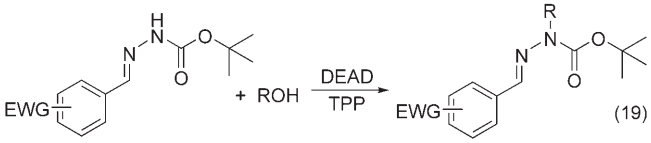
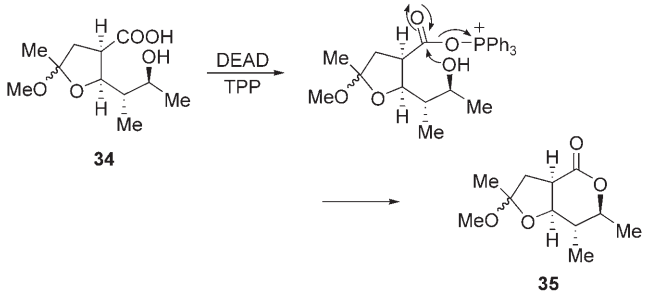


(19)

6. Representative Recent Synthetic Applications

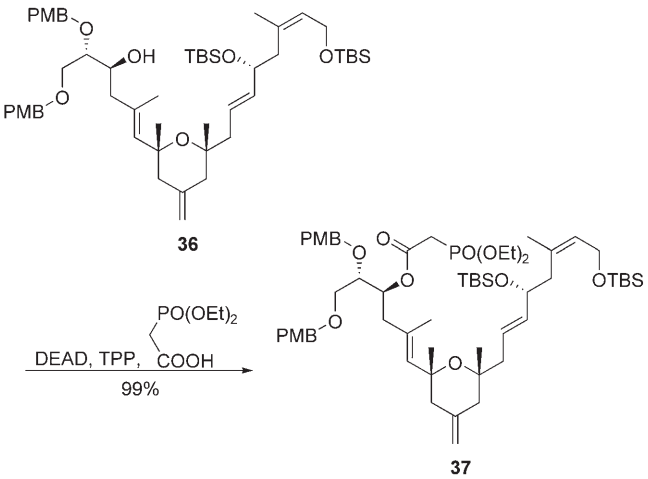
We conclude this Focus Review by presenting some recent examples of the application of the Mitsunobu reaction to the synthesis of complex molecules, both natural and non-natural, that showcase how it is currently being applied in modern organic synthesis. Several examples in which unexpected observations were made are highlighted here to show that, even with a reaction as well-known and widely practiced as the Mitsunobu reaction, surprises do sometimes, even if only rarely, occur.

As mentioned previously, one of the key features of the Mitsunobu reaction is that it normally proceeds with inversion of the stereochemical configuration of the carbinol center. However, Ahn and DeShong reported that with some sterically hindered alcohols, such as **34**, intramolecular lactonization with the Mitsunobu reaction afforded mainly products with retention of configuration, such as **35** (Scheme 12).[53] As discussed previously, the Mitsunobu reaction proceeds through an equilibrium between an alkoxyphosphonium salt and an acyloxyphosphonium salt (**2** and **5** in Scheme 1). It was proposed that if the hydroxy group is not sterically hindered, the alkoxyphosphonium salt is favored, and nucleophilic displacement of TPPO by the carboxylate group results in inversion of configuration. On the other hand, if the hydroxy group is sterically hindered, the acyloxyphosphonium salt is favored, and acyl transfer results in retention of configuration.[46]



Scheme 12. Retention of configuration in an intramolecular Mitsunobu reaction.

(+)-Dactylolide and (+)-zampanolide are macrolides that inhibit tumor cell growth, and in their unified total syntheses of these natural products, Smith et al. reported an example of an intemolecular Mitsunobu reaction that also proceeded with retention of configuration (Scheme 13).[54] Attempts to invert the stereochemistry of hindered secondary alcohol **36** while esterifying it with diethylphosphonoacetic acid afforded only the ester product **37** with unchanged stereochemis-



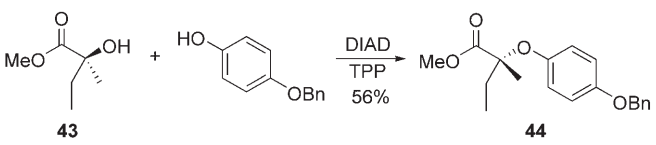
Scheme 13. Retention of configuration in an intermolecular Mitsunobu reaction. PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.

try. It was postulated that this could be due to either the failure of **1** to activate the alcohol and form an alkoxyphosphonium intermediate owing to steric inaccessibility, or to formation of an oxonium intermediate followed by ring opening by the carboxylate. However, the latter possibility was discounted owing to the level of regioselectivity necessary to account for the observed product.

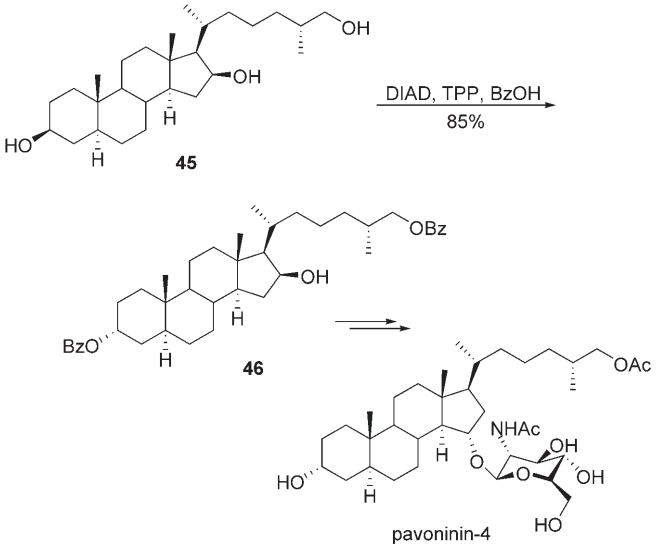
Another case of an intramolecular Mitsunobu reaction that afforded a product lactone with retained stereochemical configuration was reported by De Brabander and co-workers in their studies on the synthesis of peloruside A.[55] They found that two diastereomeric advanced intermediates, **38** and **39**, afforded the same lactone product **40** when they were treated under Mitsunobu reaction conditions either individually or as a mixture (Scheme 14). They speculated that geometrical and/or conformational constraints prevent the diastereomers from reacting in the same manner, and that **38** must form alkoxyphosphonium intermediate **41**, whereas **39** must form acyloxyphosphonium intermediate **42**, in order for the observed product to be formed.

In the final example presented herein of a Mitsunobu reaction that provided results that might not have been expected, Shi et al. reported the inversion of the configuration of ester-group-activated chiral tertiary alcohol **43** when it was treated with phenols in the presence of TPP and DIAD (Scheme 15).[82] Whereas Mitsunobu reactions between tertiary alcohols and phenols have previously been described in the literature, this was the first time an S_N2 displacement occurred cleanly to provide the product, aryl alkyl ether **44**. In these reactions, sensitivity to the steric environment of the chiral alcohol was observed.

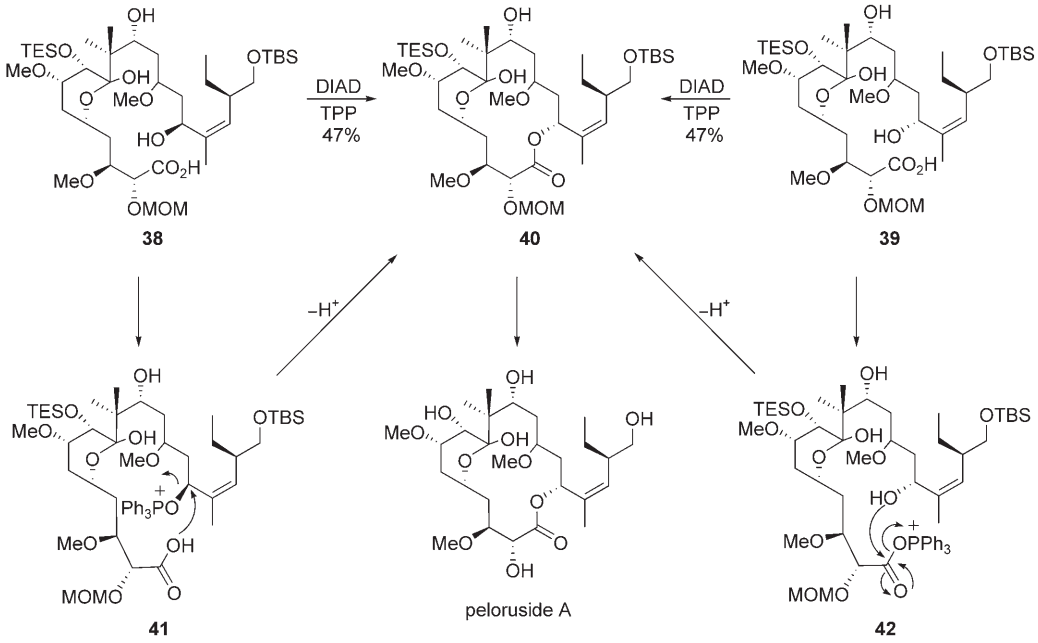
An example that shows the importance of the steric environment of the reacting alcohol in the Mitsunobu reaction is displayed in the synthesis of the shark repellent pavoninin-4 by Williams et al.[83] A key step in this synthesis is the conversion of steroidal triol **45** into dibenzoate **46** by using DIAD, TPP, and benzoic acid (Scheme 16). This reaction is selective and afforded the desired product in 85% yield



Scheme 15. Inversion of tertiary-alcohol stereochemistry.



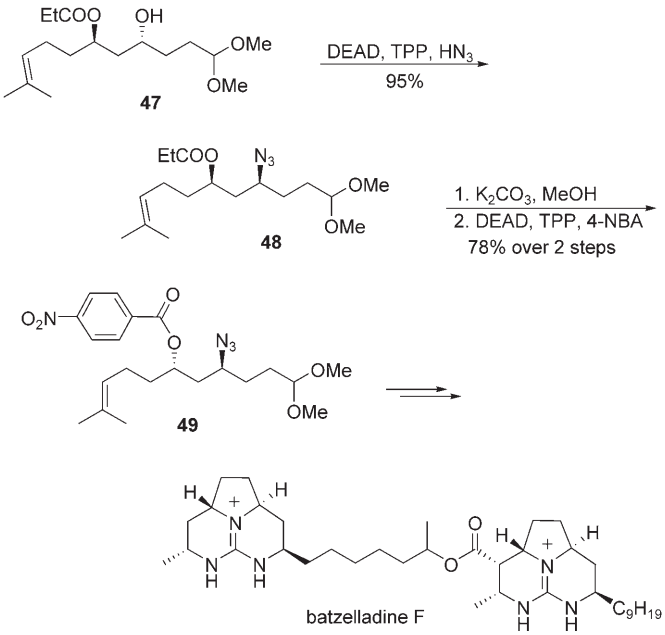
Scheme 16. Synthesis of pavoninin-4. Bz = benzoyl.



Scheme 14. Synthesis of peloruside A. MOM = methoxymethyl, TES = triethylsilyl.

with stereochemical inversion of the less sterically hindered secondary alcohol. The more sterically hindered secondary hydroxy group remained unchanged.

In their synthesis of the proposed structure of batzelladine F, Cohen and Overman used the Mitsunobu reaction in two steps that required inversion of stereochemistry (Scheme 17).[84] In the first reaction, monoprotected diol **47**



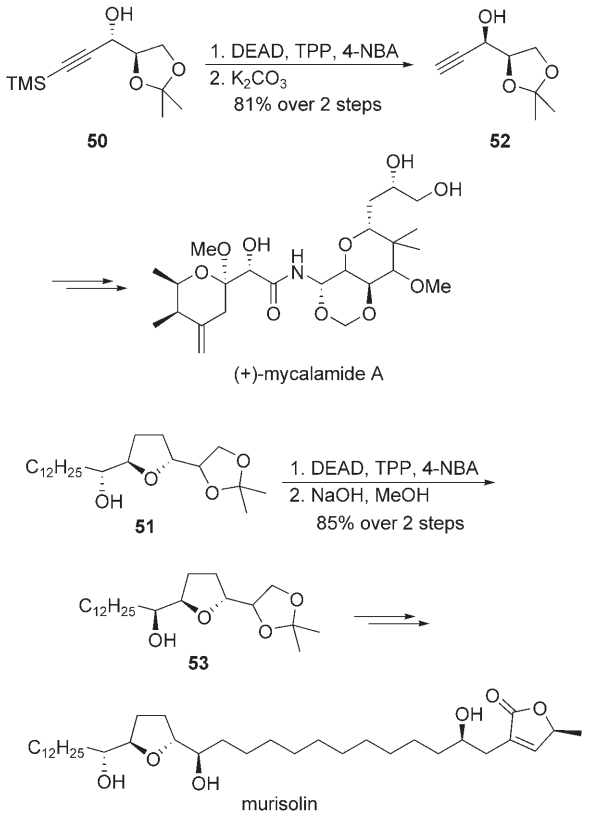
Scheme 17. Synthesis of the proposed structure of batzelladine F.

was treated with hydrazoic acid to install the azide group in **48**. This was followed by methanolysis of the azido ester thus formed and Mitsunobu reaction of the product alcohol with 4-NBA to afford aryl ester **49** with the desired 1,3-*anti* configuration.

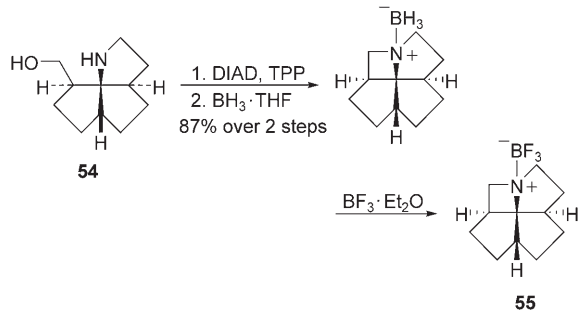
Other recent examples of the Mitsunobu reaction of a chiral secondary alcohol with 4-NBA for the sole purpose of inversion of configuration were reported in the syntheses of mycalamide A[85] and murisolin (Scheme 18).[86] In these syntheses, chiral secondary alcohols **50** and **51** were converted into their corresponding epimers **52** and **53** through a two-step esterification/hydrolysis sequence in 81 and 85% overall yield, respectively.

In their synthesis of 1-azafenestranes, Denmark et al. used an intramolecular Mitsunobu reaction in which the amine group of **54** served as the pronucleophile for the formation of a strained azetidine ring of a *c*,*c*,*c*,*c*-[4,5,5,5]-1-azafenestrane (Scheme 19).[87] The tetracyclic product was purified as its borane adduct **55**, which was characterized by X-ray crystallographic analysis.

An intramolecular Mitsunobu macrolactonization was successfully employed in the total synthesis of (+)-tedanolide.[88] In this synthesis, deprotection of *seco*-acid allyl ester **56** by palladium catalysis was followed immediately by treatment with TPP and DEAD to afford desired macrolactone



Scheme 18. Synthesis of mycalamide A and murisolin.



Scheme 19. Synthesis of 1-azafenestrane **55**.

57 in 66% yield (Scheme 20). The authors noted that this methodology afforded a higher yield than other macrolactonization techniques such as the Keck–Boden protocol or Yamaguchi esterification.

In the Li and O'Doherty synthesis of milbemycin β_3, the Mitsunobu reaction was used to install the *p*-methoxyphenyl protecting group of important early intermediate **58** and for the macrolactonization step (Scheme 21).[89] The protection of 5-hexyn-1-ol as the corresponding *p*-methoxyphenyl ether was part of their synthesis of an alkynoate fragment that was rearranged to the corresponding *E*,*E* diene. In the penultimate step of the synthesis, TPP/DIAD-mediated macrolactonization of **59** afforded the macrocycle in 79% yield.

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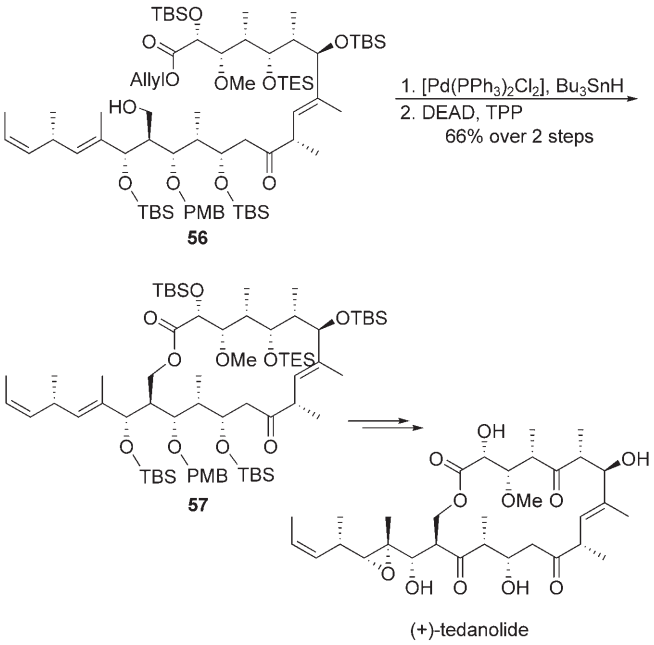
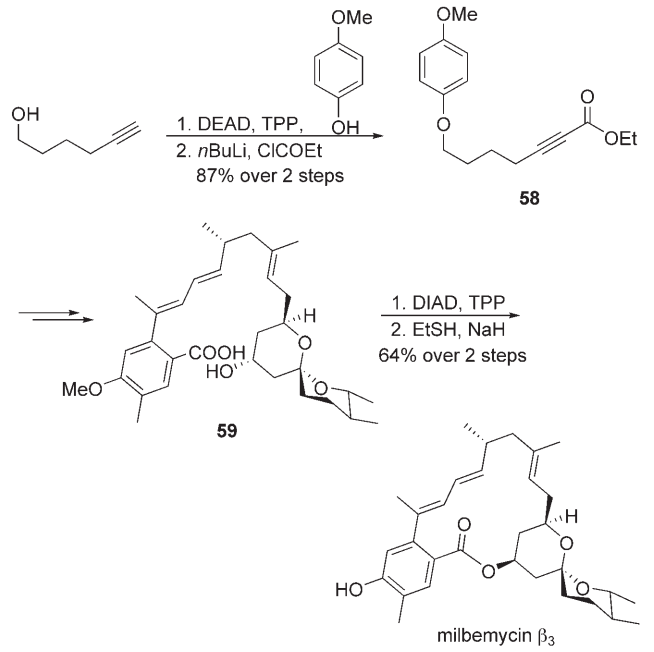
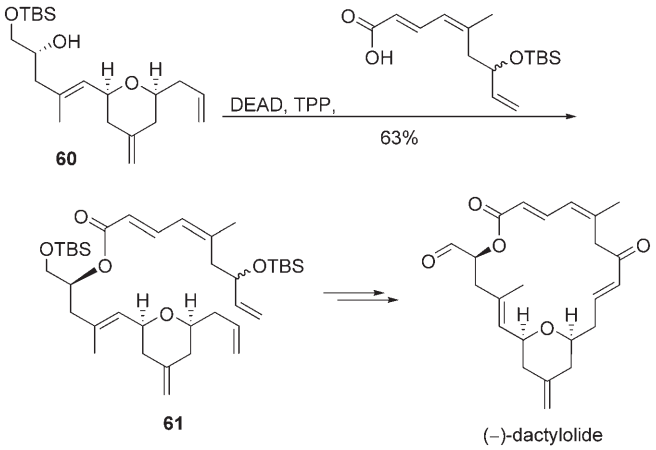


Scheme 20. Synthesis of (+)-tedanolide.



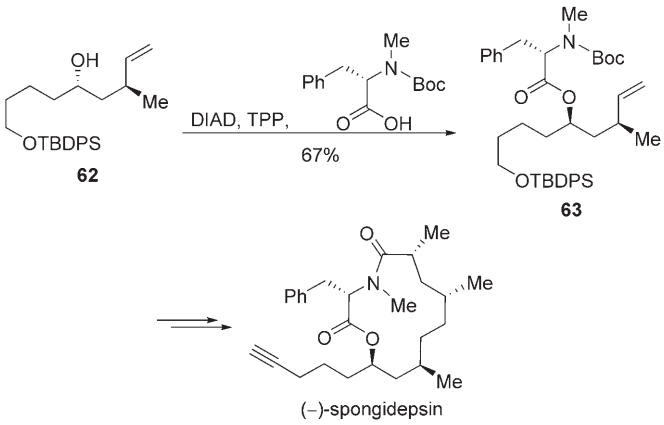
Scheme 21. Synthesis of milbemycin β_3.

The Mitsunobu reaction was used in a synthesis of dactylolide that was reported by McLeod and co-workers.[90] In the late stages of their synthesis of (−)-dactylolide, tetrahydropyran fragment **60**, which contains a secondary alcohol, was treated with a trienoic acid to form ester **61** with inversion of configuration (Scheme 22). This was followed by ring-closing metathesis to construct the macrocycle and a deprotection/oxidation sequence to afford the target compound. It is interesting to compare the successful esterification accompanied by inversion of configuration in this synthesis with the anomalous esterification previously discussed for the synthesis of dactylolide by Smith et al.[54]



Scheme 22. Synthesis of (−)-dactylolide.

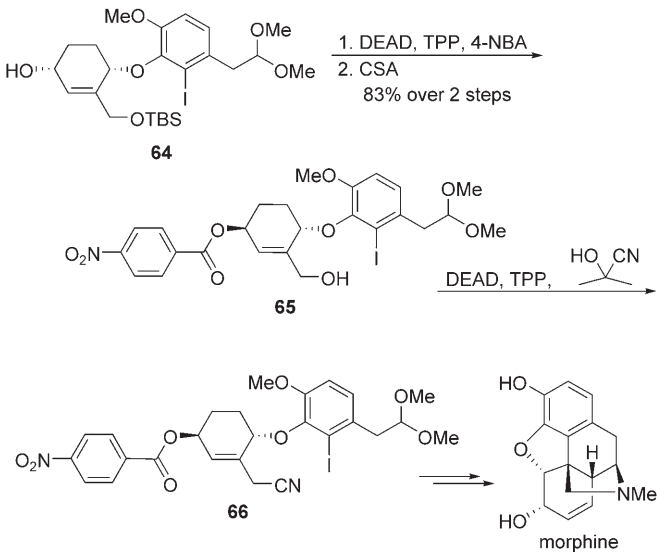
In the synthesis of (−)-spongidepsin by Cossy and co-workers, the Mitsunobu reaction was used to couple chiral secondary alcohol fragment **62** with *N*-Boc-protected (*S*)-*N*-methylphenylalanine, with inversion of configuration, to afford **63** (Scheme 23).[91] The authors reported that **63** was accompanied by "minor isomers" and that it could be purified by silica-gel chromatography.



Scheme 23. Synthesis of (−)-spongidepsin. TBDPS = *tert*-butyldiphenylsilyl.

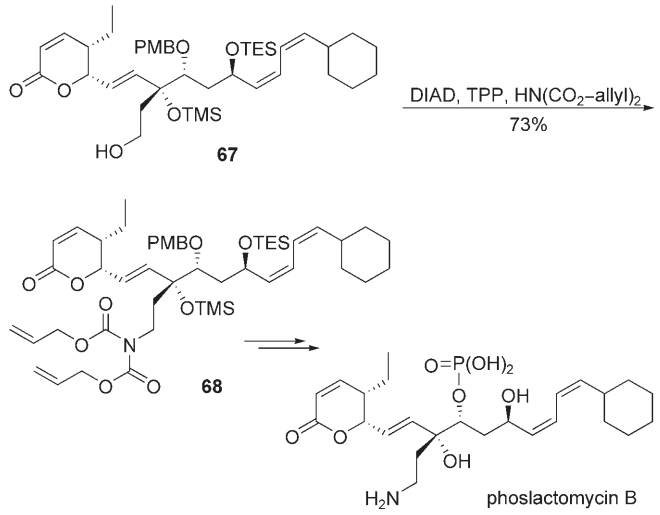
Fukuyama and co-workers showed the synthetic versatility of the Mitsunobu reaction in their synthesis of (±)-morphine (Scheme 24).[92] First, it was used to invert the stereochemistry of the hydroxy group in **64**. Subsequent removal of the TBS protecting group afforded **65**, which was subjected to a second Mitsunobu reaction to convert the exposed hydroxy group into the homologated nitrile group in **66** by reaction with acetone cyanohydrin, DEAD, and TPP.

In the synthesis of phoslactomycin B by Kobayashi and co-workers, the Mitsunobu reaction was used to convert the hydroxy group of advanced intermediate **67** into the corre-



Scheme 24. Synthesis of morphine. CSA = camphor-10-sulfonic acid.

sponding amine (Scheme 25).[93] In this case, diallyl imidodicarbonate was chosen as the nitrogen-containing pronucleophile to afford **68**, so that final global deprotection could be

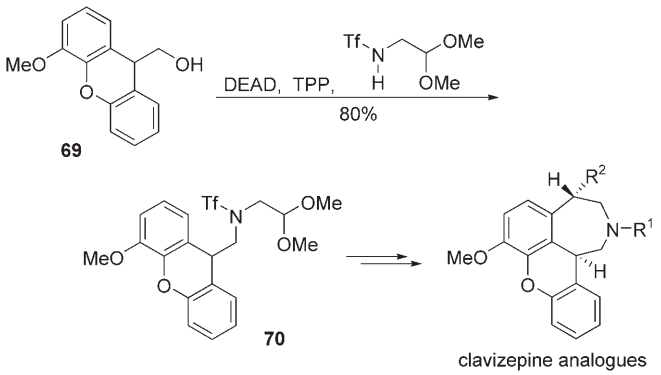


Scheme 25. Synthesis of phoslactomycin B. TMS = trimethylsilyl.

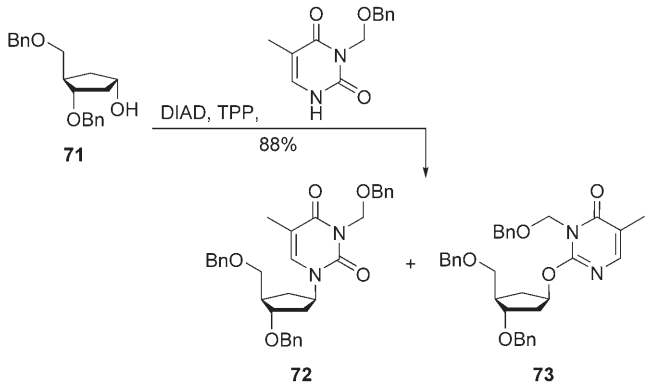
achieved by palladium-catalyzed deallylation in the presence of tributyltin hydride.

In their synthesis of clavizepine analogues, Dominguez and co-workers used an *N*-trifluoromethanesulfonamide pronucleophile to introduce an amine group (Scheme 26).[94] Hydroxymethylxanthene **69** was coupled with *N*-(dimethoxyethyl)trifluoromethanesulfonamide under standard Mitsunobu reaction conditions to give desired nitrogenated product **70** in high yield.

In their convergent synthesis of carbocyclic nucleoside analogues, Ludek and Meier used the Mitsunobu reaction to add a thymine derivative to chiral substituted cyclopentanol **71** (Scheme 27).[95] This route to such medicinally important



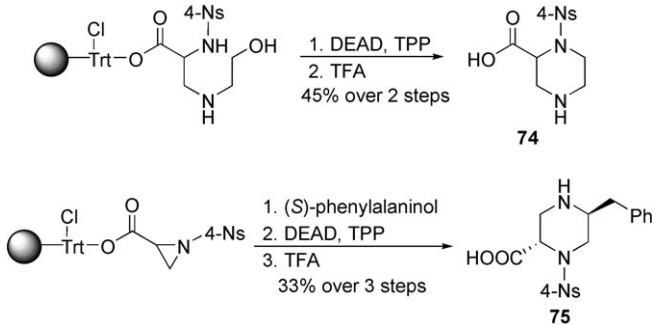
Scheme 26. Synthesis of clavizepine analogues. Tf = trifluoromethanesulfonyl.



Scheme 27. Synthesis of carbocyclic nucleoside analogues.

compounds is much shorter than the linear strategy normally used for their construction. Furthermore, the effect of the protecting group at N3 of the pronucleophile on the ratio of N1 versus O2 alkylation (**72** versus **73**) was studied, and good selectivity for either reaction was found depending on the structure of the N3 protecting group.

An intramolecular Fukuyama–Mitsunobu reaction was reported in the solid-phase synthesis of resin-bound *N*-nitrobenzenesulfonyl-activated piperazine-2-carboxylic acid derivatives such as **74** by Olsen et al. (Scheme 28).[96] By using this methodology, a variety of enantiopure piperazinecar-



Scheme 28. Solid-phase intramolecular Fukuyama–Mitsunobu cyclization reactions. Ns = nitrobenzenesulfonyl, TFA = trifluoroacetic acid, Trt = trityl.

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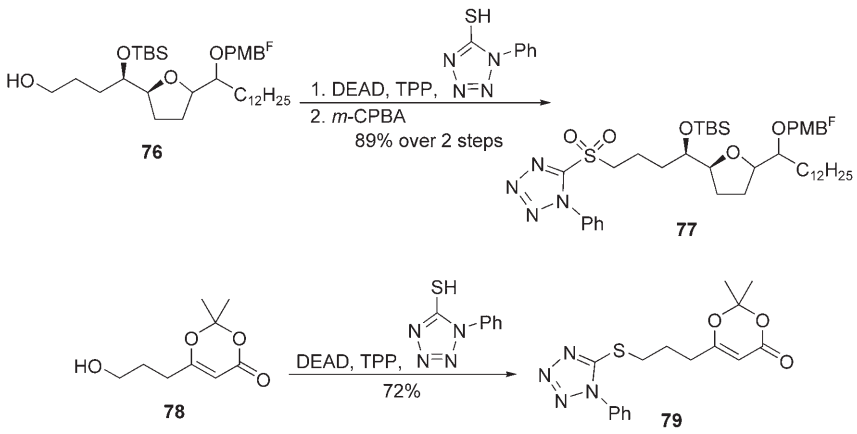
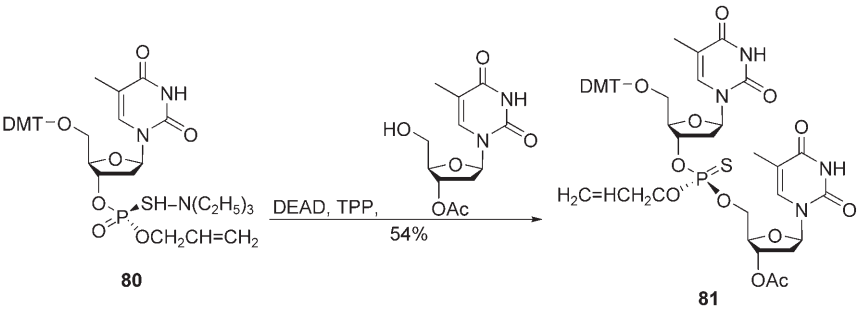


Scheme 29. Introduction of 1-phenyl-1*H*-tetrazole-5-sulfide groups. *m*-CPBA = *m*-chloroperbenzoic acid, PMB^F = a fluorous tagged benzyl ether.

boxylic acid derivatives, such as **75**, were synthesized in good yield.

The Kocienski–Julia coupling reaction is an important method for the formation of carbon–carbon double bonds and requires the introduction of a 1-phenyl-1*H*-tetrazole-5-sulfide group. In this context, many examples have appeared in the recent literature in which the Mitsunobu reaction is used to couple an alcohol with 1-phenyl-1*H*-tetrazole-5-thiol (Scheme 29). Subsequent oxidation of the resulting sulphide moiety completes the installation of the necessary *N*-phenylsulfonyltetrazole group. This methodology was used in the synthesis by Curran et al. of a library of murisolin isomers by using fluorous phase-separation technology (**76**→**77**)[97] and in a synthesis of cylindramide by Laschat and co-workers (**78**→**79**).[98]

The final example in this Focus Review demonstrates how nucleoside phosphorothioate diesters, such as **80**, can be converted into their corresponding dithymidine phosphorothioates, such as **81**, by using the Mitsunobu reaction (Scheme 30).[99]



Scheme 30. Synthesis of thymidine phosphorothioates. DMT = 4,4′-dimethoxytrityl.

7. Summary and Outlook

Since it was first reported in 1967, the Mitsunobu reaction has been extensively applied in a wide range of organic-synthesis contexts and in the process has become one of the most well-known reactions in organic chemistry. However, despite its long history and common use, research into new variations and the study of its mechanism continue to this day. It is expected that in the future, such research will increase our understanding of this workhorse reaction, and that improved versions and unprecedented applications will appear and thus broaden its utility.

Acknowledgements

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