Recent Advances in the Mitsunobu Reaction: Modified Reagents and the Quest for Chromatography-Free Separation

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Recent progress in synthetic approaches to the Mitsunobu reaction are reviewed. Efforts that have focused on the phase-switching modifications of phosphane, azodicarboxylate, and nucleophilic components are emphasized. An approach to product separation with fluorous compounds is reviewed in detail. Alternative reagents and recently introduced products are cited.

I. Introduction

The Mitsunobu protocol involves the reaction of an alcohol **1** and an acidic pronucleophile **2** (NuH) usually promoted by stoichiometric amounts of a phosphane **3** (commonly triphenyl or tributylphosphane, R′ = Ph or Bu) and an azodicarboxylate or azodicarboxamide **4** (Figure 1).[1] In addition to product **5**, which contains the newly formed C−O, C−N, C−S, C−X, or C−C bond, the phosphane oxide **6** and the hydrazinedicarboxylate or hydrazinedicarboxamide **7** are produced.

The Mitsunobu reaction has been widely used in organic synthesis, often for the inversion of configuration in secondly alcohols or the synthesis of aryl ethers. The reaction is popular due to its stereoselectivity, compatibility with a wide range of functional groups, and mild reaction conditions. However, isolation of the desired product from the spent and excess reagents consumes time and resources, and significantly lowers the yield of the process.

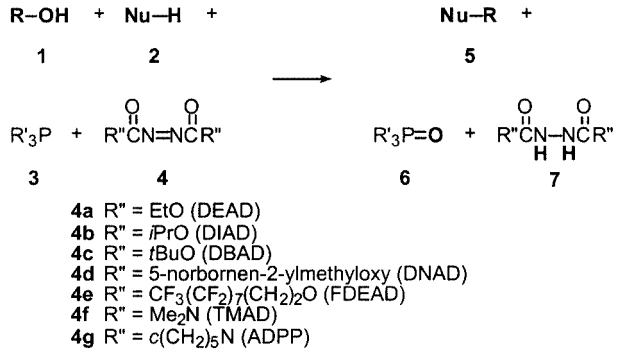

Figure 1. The Mitsunobu reaction

Significant progress has been made over the last few years since the comprehensive review by Hughes.[2,3] More specialized review articles have also been published.[4] The current microreview highlights selected recent advances, focusing on novel, separation-friendly reagents and methodologies that avoid column chromatography, with a particular emphasis on fluorous chemistry. In addition, references to a

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MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

selection of alternative reagents, pronucleophiles, mechanistic studies, and synthetic accomplishments are provided. A complementary concept article by Dandapani and Curran that has elegantly classified separation strategies is published concurrently.[4k]

II. Modifications of Classical Reagents

Many efforts have been directed toward modifying triphenylphosphane or azodicarboxylate reagents to facilitate the isolation and purification of a desired product. In addition to fluorous chemistry, three types of separation approaches are established: acidic or basic aqueous workup, post-reaction sequestration (solution or solid-phase reaction), and polymer assisted phase-switching or solid-phase immobilization.

Recently, new or improved methodologies involving the use of chemically tagged reagents have been developed to enhance their chemoselective removal from reaction mixtures.

1. Modified Phosphanes

Traditionally, the separation of the product from phosphane oxide was problematic. For acidic workup, amino-modified phosphanes have been employed in the Mitsunobu reaction.[5] Kiankarimi et al. refined an acidic aqueous procedure by combining diphenyl-2-pyridylphosphane (**3a**, Figure 2) and di-*tert*-butyl azodicarboxylate (DBAD, **4c**).[6] Treatment of the reaction mixture with 4 M HCl in dioxane followed by an acidic aqueous wash was used to remove by-products from the reaction mixture and gave crude products in 30−69% yields.

Flynn et al. have used *tert*-butyl-masked, carboxy-tagged alkyldiphenylphosphane (**3b**, Figure 2) with DBAD **4c**.[7] Unmasking of **3b** with trifluoroacetic acid and subsequent sequestration with an ion-exchange basic resin allows for product purification. Yoakim et al. have demonstrated that 2-(trimethylsilyl)ethyl 4-(diphenylphosphanyl)benzoate (**3c**, Figure 2) combined with diisopropyl azodicarboxylate (DIAD, **4b**) are also efficient reagents that facilitate product isolation.[8] The corresponding phosphane oxide is removed after fluoride (Bu_4NF) cleavage of the ester and washing with aqueous base. Phosphane **3c** has been used in a 100 g synthesis without the need for chromatographic purification, although flash chromatography may be necessary in some cases. When 2-(trimethylsilyl)ethyl 3-(diphenylphosphanyl)propanoate is used as the phosphane reagent, a poor yield is observed. Acidic workup has limitations for products containing acid-labile groups.

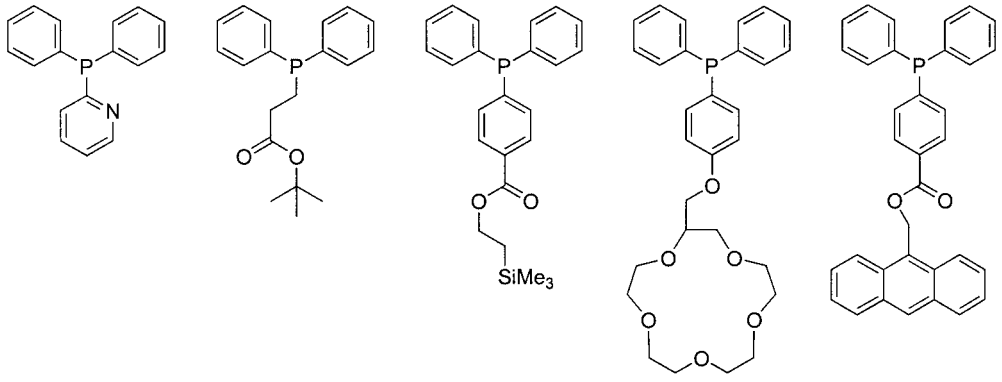

Figure 2. Modified phosphanes used in the Mitsunobu reaction

Routledge et al. have synthesized 15-crown-5-tagged triphenylphosphane (**3d**, Figure 2), which gives conversions similar to that of Ph_3P when used in the Mitsunobu reaction.[9] The 18-crown-6-tagged triphenylphosphane analogue has a lower reactivity. Purification of reactions, with the crown ether tagged reagent, is achieved by post-reaction sequestration onto an ammonium-functionalized solid phase.

A polymer-assisted, solution-phase Mitsunobu reaction using a combination of anthracene-tagged phosphane and polymer-supported azodicarboxylate was developed by Parlow et al.[10] The anthracene-modified phosphane (**3e**, Figure 2) gives similar yields to Ph_3P and allows for the removal of the phosphane/phosphane oxide by sequestration through a Diels−Alder reaction using a polymer-bound maleimide dienophile. The chemoselective removal of **3e** and its oxide through cyclization accommodates a broad range of functional groups. The polymer-supported azodicarboxylate also facilitates the removal of reaction by-products, excess alcohol and reagents. The desired products are isolated after filtration and concentration. This methodology is bona fide if the final product does not react with the polymer-bound dienophile.

1,2-Bis(diphenylphosphanyl)ethane has also proved to be a convenient alternative for Ph_3P. In this case, the desired products are separated from by-products by flash silica gel chromatography.[11]

In attempts to reduce reaction times when using neopentyl alcohol, several phosphanes and different solvents and temperatures have been examined, with limited success.[12] Electron-deficient phosphanes such as $(m\text{-}ClC_6H_4)_3P$, $(p\text{-}FC_6H_4)_3P$, and $(F_5C_6)_3P$ offer no improvement over Ph_3P. No detectable coupling product was obtained when Bu_3P was used. The rate of the coupling reaction is only moderately solvent-dependent with a slight preference for THF over the other solvents tested. Increased temperature (40−55 °C) enhances both the rate of reaction and side-product formation. For the reactions of sterically hindered alcohols with phenols, high concentrations of reactants combined with sonication reduces reaction times and increases yields.[13,14]

The use of alkylphosphanes can lower steric congestion, thus allowing sterically hindered substrates to react (see also part IV.4). For example, trimethylphosphane (Me_3P) has been reported to be the only phosphane reagent that allows alkylation of 2-nitrobenzenesulfoamides with a wide range of secondary alcohols, while Bu_3P is selective for primary alcohol groups.[15] Me_3P is usually more effective than Bu_3P or Ph_3P, as for example in the alkylation reaction of secondary benzylic alcohols.[16] The application of alkylphosphanes in the Mitsunobu reaction has recently been reviewed.[4a]

Phosphanes with one or two fluorous tags attached to the aromatic rings that were insulated by ethylene spacers (**3f** or **3g**, FTPP) have been used in the Mitsunobu reaction. Selection of the phosphanes, to ensure an appropriate fluorophilicity for the separation, is based on a correlation with HPLC retention times on a fluorous column.[17] On the basis of this method, the preferred phosphane for the fluorous process is $Ph_2PC_6H_4\text{-}p\text{-}(CH_2)_2(CF_2)_7CF_3$ **3f**. Fluorous phosphanes with longer chains or with three fluorous phenyl rings are also available, but the longer retention time and added molecular weight of these analogs offer no distinct advantage for separation by solid-phase extraction (SPE). The application of the fluorous phosphanes **3f** and **3g** will be discussed in detail in part III.1.

Considerable attention has been focused on using polymer-attached phosphanes to facilitate the removal of phosphane oxide. The polymer-supported solution-phase approach to the Mitsunobu reaction with the use of poly(ethylene glycol)-derived polyethers has been developed by Janda et al.[18,19] When applied to solution-phase synthesis phosphane **3h** gives alkyl aryl ethers in 75−88% yields by simple precipitation and filtration of the spent reagents. In contrast to the heterogeneous reaction, the yields are equivalent and reaction times are shorter. In addition, the polyether-supported phosphane proved more versatile than the polystyrene-supported phosphane since it reacts with all the substrates tested.

The use of solid-supported reagents, such as polystyrene-bound triphenylphosphane, that can be removed simply by filtration after the reaction has become a standard procedure.[20−22] Gentles et al. have developed an automated parallel protocol for the synthesis of alkyl aryl ethers, in which various aliphatic alcohols and phenols were treated with (diphenylphosphanyl)polystyrene and DBAD **4c**.[23] Problems that are encountered with solid-supported phosphanes in the Mitsunobu reaction include lower reactivity due to the sterically less accessible reactive centers. (Diphenylphosphanyl)polystyrene and DBAD **4c** can be combined together to form easy-to-handle preweighted tablets that can disintegrate during the course of the reaction.[24] The biphasic system often slows the rate of reaction and thus requires a large excess of phosphane reagent. This problem has been addressed by linking the triphenylphosphane to a non-crosslinked polymer. Charette et al. have prepared the phosphane **3i** from commercially available non-crosslinked polystyrene. This soluble polymer-bound phosphane is highly effective in the Mitsunobu reaction of secondary alcohols and in the S_N2' nucleophilic substitution of Baylis−Hillman adducts and can quantitatively be recovered after the reaction.[25]

2. Modified Azodicarboxylates

While the problem of separating the phosphane can be overcome, the removal of hydrazine can present also challenges. The use of crosslinked polystyrene-supported azodicarboxylate has been reported,[26] but applications in the Mitsunobu reaction with simultaneous use of a polymer-bound phosphane is limited by incompatibility due to phase separation.

Although diethyl azodicarboxylate (DEAD, **4a**) remains a traditional and frequently used reagent,[27] an increasing number of reports suggest that the less expensive diisopropyl azodicarboxylate (DIAD) is more advantageous.[28−33] Considering the economic factor and the ease of handling,

DIAD could become the preferred reagent for the Mitsunobu reaction.

Di-*tert*-butyl azodicarboxylate **4c** is also gaining popularity as it allows for the removal of the hydrazine by-product using acidic workup for decomposition to volatile by-products, followed by water extraction.[21b,34] DBAD **4c** has been used with phosphanes that are compatible with an acidic workup,[6,7] and finds applications in combinatorial synthesis.[23,24] One disadvantage is that compounds with basic functional groups may be affected by the accompanying workup.

An interesting approach, termed 'impurity annihilation', employed norbornene as a tag to enable selective derivatization by polymerization of contaminants, which are then removed by filtration. The synthesis of norbornene-tagged azodicarboxylate is outlined in Figure 3. Bis(5-norbornen-2-ylmethyl) azodicarboxylate (DNAD, **4d**) is synthesized in three steps from an *endo*/*exo* mixture of (5-norbornene-2-yl)methanol (**8a**). Reaction of **8a** with phosgene in toluene in the presence of *N*,*N*-dimethylaniline gives the chloroformate **9a**, which is then converted into the norbornene-derived hydrazine **7d**. Oxidation of **7d** with iodosobenzene diacetate in dichloromethane gives DNAD **4d** in an overall yield of 61%. For removal after the Mitsunobu reaction, ruthenium-catalyzed polymerization of olefin-containing compounds (ring opening metathesis) leads to insoluble by-products.[21d] However, compounds that coordinate with the Grubbs catalyst used for polymerization may not be compatible with this method.

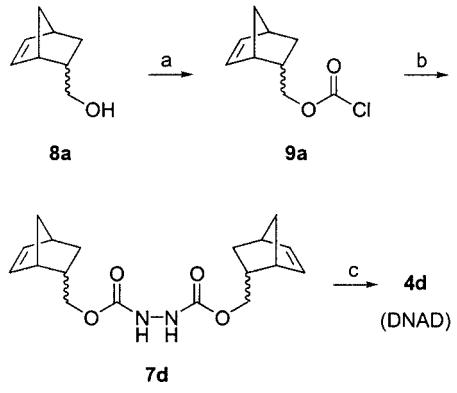

Figure 3. Synthesis of the norbornene-derived azodicarboxylate reagent DNAD **4d**; reagents: (a) $COCl_2$, $PhNMe_2$, toluene (83%); (b) $H_2NNH_2{\cdot}HCl$, Na_2CO_3, EtOH (88%); (c) $PhI(OAc)_2$, CH_2Cl_2 (83%)

The general approach for transformation of the Mitsunobu reaction for use under fluorous conditions includes the application of fluorophilic participating reagents, thus allowing phase separation of fluorous by-products from organic products. This has led to the synthesis of fluorous azodicarboxylates and the application of fluorous phosphanes. The fluorous azodicarboxylate (FDEAD, **4e**) was synthesized concurrently by two groups.[35,36] To prepare

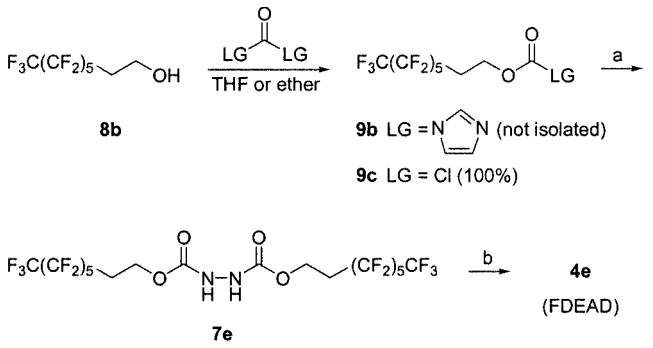

Figure 4. Synthesis of FDEAD **4e**; reagents: (a) from **9b**, $H_2NNH_2{\cdot}HCl$, Et_3N (85% for two steps); from **9c**, $H_2NNH_2{\cdot}H_2O$, EtOH (80%). (b) Br_2, pyridine, CH_2Cl_2 (100%), or *N*-bromosuccinimide, pyridine (79%)

FDEAD, 2-(perfluorohexyl)ethanol **8b** is treated with 1,1′-carbonyldiimidazole in THF or with phosgene in ether to give the fluorous imidazolide **9b** or chloroformate **9c**, respectively (Figure 4). Reaction of **9b** with hydrazine hydrochloride/triethylamine in THF or reaction of **9c** with hydrazine hydrate in ethanol yields the fluorous hydrazine **7e**. Oxidation of **7e** with bromine/pyridine in dichloromethane or *N*-bromosuccinimide in pyridine is superior to treatment with other reagents such as iodosobenzene diacetate, lead tetraacetate, or manganese dioxide.[36] The FDEAD **4e** is obtained in an 85−63% overall yield; the reagent is stable as a solid at ambient temperature for several months and in solution ($CDCl_3$) for at least two weeks.[35]

To explore the effects of varying the fluorine content, fluorous azodicarboxylates **4** that differ in the length of the spacer or perfluoroalkyl group [R″ = $F_3C(CF_2)_2CH_2O$, $F_3C(CF_2)_3(CH_2)_3O$, $F_3C(CF_2)_5(CH_2)_3O$] have been synthesized by the method shown in Figure 4.[35] Of those tested, the fluorous azodicarboxylates with the same amount of fluorine as in **4e** give similar results. When the fluorous content is reduced, as in R″ = $F_3C(CF_2)_3(CH_2)_3O$, the precursor hydrazine partitions between the organic and fluorous fractions during solid-phase extraction, thus making removal difficult. FDEAD **4e** with 60.9% fluorine content and an ethylene spacer group has been the most widely used.

The Mitsunobu reaction with the use of classical reagents is limited to rather acidic pronucleophiles with a $pK_a < 13$ (lower yields are observed for pronucleophiles with a $pK_a > 11$). Reagents, in which the alkoxy group is replaced by a secondary amine such as *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (**4f**, TMAD) and 1,1′-(azodicarbonyl)dipiperidine (**4g**, ADDP),[37] increase the basicity of the reaction intermediate and work well with carbon nucleophiles such as those containing activated methylene groups[4e,38] or amides.[39] Such reagents broaden the range of substrates and nucleophiles,[4a] and are usually combined with phosphanes of higher basicity such as Me_3P or Bu_3P.[4a,15,40−43]

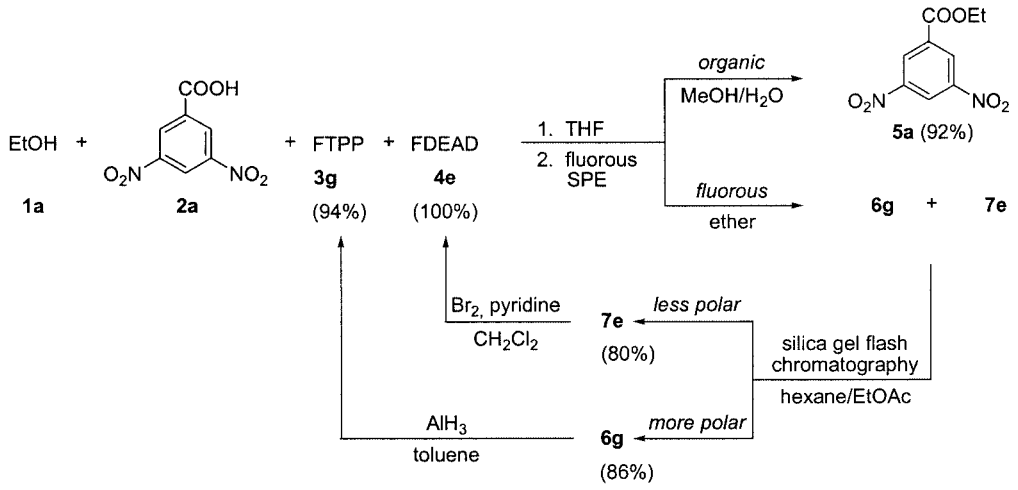

Figure 5. Separation and recycling of fluorous by-products in the Mitsunobu reaction with fluorous reagents (SPE = solid-phase extraction)

III. Fluorous Approach

1. Reactions with Fluorous Azodicarboxylate and Fluorous Phosphane

Most of the modified reagents discussed above allow solution-phase reaction, but they require additional chemical methods to separate the components. This adds time, limits the scope, and hampers the recycling of reagents. The fluorous approach offers convenient procedures for the separation of organic compounds from fluorophilic compounds. In the process of adapting to the Mitsunobu reaction, the efficiency of fluorous-modified reagents has been confirmed individually for fluorous phosphane FTPP **3g** with non-fluorinated DEAD **4a**[35] and for FDEAD **4e** with Ph_3P.[35,36] These reactions require more time but have yields similar to those with nonfluorous Mitsunobu reagents. Both reagents need to be fluorous for facile separation by solid-phase or liquid-liquid extraction. Accordingly, a fully fluorous reaction has been developed.

Dandapani and Curran have established an elegant separation procedure for organic products and fluorous by-products, with recycling of the latter (Figure 5).[35] After a Mitsunobu reaction with ethanol **1a**, 3,5-dinitrobenzoic acid **2a**, FDEAD **4e**, and fluorous phosphane FTPP **3g**, the solvent is removed and the crude reaction mixture is subjected to solid-phase extraction on fluorous silica. Elution with methanol/water gives the organic Mitsunobu adduct **5a** in a 92% yield. Further elution with ether gives a mixture of the fluorous phosphane oxide **6g** and the fluorous hydrazine **7e**. This mixture of fluorous by-products is readily separated on regular silica gel by eluting with hexane/EtOAc. The less polar hydrazine **7e** is eluted first and isolated in 80% yield and the more polar phosphane oxide **6g** follows in 86% yield. Both the reduction of the fluorous phosphane oxide **6g** with AlH_3 to regenerate **3g** and the oxidation of the fluorous hydrazine **7e** to reconstitute **4e** (also a step in the synthetic route to FDEAD, cf. Figure 4) are quantitative reactions.

The order in which the reagents are added can affect the course of the Mitsunobu reaction.[2] A solution of the phosphane and the alcohol can be added to a solution of the azodicarboxylate and the nucleophile (procedure A). Classically, the phosphane, the alcohol, and the nucleophile can be dissolved in the solvent, and the azodicarboxylate added dropwise (procedure B). Finally, the azodicarboxylate and the phosphane can react first to form an adduct, followed by addition of the alcohol and the nucleophile (procedure C). These three procedural variations have been investigated in reactions of simple alcohols and nucleophiles with FDEAD **4e** and FTPP **3g**. All the reactions provide very good yields, although procedure C is significantly advantageous over procedure B for the reaction with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide.[35]

2. Synthesis and Separation of Fluorous Esters and Ethers

The "tagging" methodology is based on the presence of a fluorous "ponytail" in the product that is exploited during separation, followed by "detagging" to yield a final product. This approach is highly suitable for the Mitsunobu reaction, and allows for efficient separation of products from by-products and spent reagents without column chromatography.

The use of a fluorous-tagged nucleophile in the Mitsunobu reaction has been investigated by Dembinski et al.[44] The best results for fluorous partitioning are obtained when the total fluorine content of the molecule is 60% or more. The number of perfluoroalkyl groups is also an important factor as appropriate shielding of the hydrocarbon domain leads to better fluorous solubility and partitioning. Accordingly, a tagging unit has been developed from inexpensive gallic acid. The 3,4,5-tris{4-(perfluorooctyl)butoxy}benzoic acid (**2b**, Figure 6) is obtained by etherification of gallic acid methyl ester, and subsequent hydrolysis.[45] The three perfluoroalkyl ponytails provide appropriate shielding and a fluorine content of 60.9% for the ArCOO unit, thus exceeding the requirements for good fluorous partitioning.

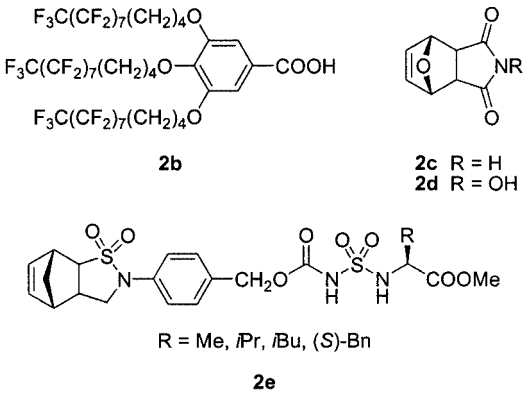

Figure 6. Nucleophilic reagents NuH **2** that facilitate separation in the Mitsunobu reaction

The use of the fluorous-tagged nucleophile **2b** in the Mitsunobu reaction offers two other advantages: (i) the fluorous esters are solids and can easily be isolated by organic liquid/fluorous solid precipitation, thus eliminating the use of fluorous solvents, and (ii) the fluorous-tagged nucleophile (Nu) can readily be dissociated from the organic products by saponification,[44,45] thereby providing the opportunity to recycle.

The reactions of representative alcohols with different carbon skeletons have been investigated.[44] All reactions have been carried out with Ph_3P and DIAD **4b** under homogeneous conditions, since **2b** is soluble in THF. After reaction via procedure B, separation is carried out according to the organic liquid/fluorous solid principle. The highly fluorous products are immiscible with the organic phase and readily precipitate from chloroform/methanol. The analytically pure esters are separated from the organic by-products by filtration. Most of the reactions with alcohols go to completion and afford an almost quantitative isolation of esters (83−96%). This approach eliminates the use of fluorous solvents and complements SPE, especially for separation of fluorous esters with a large organic component.

Hydrolysis of the fluorinated ester allows isolation of the alcohol in high yields and recovery of the fluorous tag. 5α-Cholestan-3α-ol is isolated in a 94% yield after saponification of the fluorous ester obtained from **2b** and 5α-cholestan-3β-ol. This example also confirms the expected inversion of configuration. The tagging acid **2b** is recovered in a 78% yield. Thus, the highly fluorinated carboxylic acid **2b** is a useful fluorous tag for the acylation of alcohols in the Mitsunobu reaction with a chromatography- and fluorous solvent-free separation protocol and excellent yields.

Rábai et al. have shown that the Mitsunobu reaction can effectively be used for the synthesis of fluorous ethers from fluorine-containing components.[46] The reaction of the 2-aryl-hexafluoropropanols in the presence of DEAD and Ph_3P with aliphatic perfluoroalcohols containing different spacers has been examined. The reaction is sensitive to electron-withdrawing effects. The 3-(perfluorooctyl)propanol can be used as the alcohol component with commendable yields; however, conversion to an ether is significantly reduced with 2-(perfluorooctyl)ethanol due to dehydration. The three methylene groups in 3-(perfluorooctyl)propanol are necessary to provide sufficient insulation, since ether formation with (perfluoroheptyl)methanol is not observed. With respect to the nucleophiles, 3-(trifluoromethyl)phenol and perfluoro-*tert*-butyl alcohol have also been used. These reactions were carried out using procedure B in benzotrifluoride (α,α,α-trifluorotoluene), in which all reaction components are sufficiently soluble. After removal of solvent, the formed fluorophilic ethers are efficiently separated from the reagent-driven organic by-products by partitioning in a two-phase solvent system of perfluorohexanes (FC-72) or perfluoro(methylcyclohexane) and methanol.

IV. Other Recent Advances

1. Modified Nucleophiles

In addition to the fluorous approach discussed above (part III.2) products can be recovered using polymerization. In this method, oxanorbornenyl-tagged succinimide derivatives (**2c**,**d**, Figure 6) or norbornenyl-tagged sulfonamide nucleophiles **2e** were used for a solution-phase Mitsunobu reaction. As is the case for the removal of DNAD **4d** (part II.2), post-reaction phase-switching is accomplished by in situ ring-opening metathesis polymerization, followed by precipitation of the polymer with methanol. Release of the product from the polymers gives amines, alkyl hydrazines,[47] *O*-alkylhydroxyamines,[48] or cyclic sulfamides.[49]

Obviously, either substrate **1** or **2** can be attached to a solid phase to facilitate separation.[4f,28,40,50,51]

2. Alternative Reagents

Novel reagents that challenge the traditional phosphane/azodicarboxylate approach have recently been introduced or applications using these reagents have been developed. The alkoxytriphenylphosphonium ion intermediate in the Mitsunobu reaction can be generated using bis(triphenylphosphonio)oxide bis(trifluoromethanesulfonate) (**10**, Hendrixon reagent, Figure 7).[52] Reagent **10** can be used for the

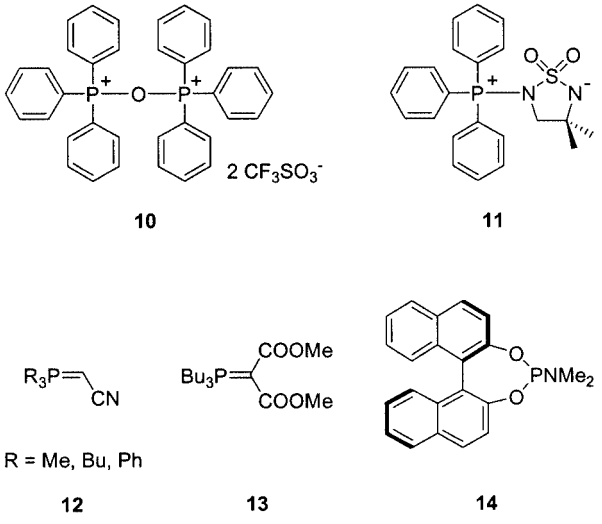

Figure 7. Alternative reagents for the Mitsunobu reaction

etherification of tetronic acids with primary and secondary alcohols[53] or for the esterification of primary alcohols.[54] However, secondary alcohols such as menthol undergo *anti*-elimination during esterification. This effect has been attributed to the presence of the triflate ion in the reaction medium.[54]

Triphenylphosphane-cyclic sulfonamide betaine (**11**, Figure 7)[55] gives better results for the synthesis of alkyl aryl ethers than Ph_3P with DEAD or DIAD.[55,56] This reagent is especially useful for reactions where sensitivity of the heterocyclic substrates such as thiazolidine-2,4-dione[57] or 1,2,4-dithiazolidine-3,5-dione[58] precludes the use of traditional reagents. The betaine **11** reduces the number of components in the reaction mixture and flash chromatography is sufficient for product purification.[55,58]

Applications of (cyanomethylene)trialkyl- or triphenylphosphoranes (**12**, Figure 7), spearheaded by Itô and Tsunoda, have extended C−C bond formation reactions.[4e,41,42,59,60] With the use of cyanomethylenetrimethylphosphorane **12** (R = Me) primary and secondary alcohols can be transformed into nitriles with acetone cyanohydrin,[41] primary alcohols can be converted into amines[61] or into one-carbon-atom extended nitriles,[62] and primary, secondary, and tertiary alcohols can be used for alkylation of 1*H*-indole and 9*H*-carbazole derivatives.[63] The phosphorane reagents are generally less active at room temperature.

Dimethyl tributylphosphoranylidenemalonate (**13**, Figure 7) has been introduced by McNulty et al.[64] and can be prepared in one step from trialkylphosphane and 2-chlorodimethylmalonate. With reagent **13** esterification of simple primary or secondary alcohols proceeds with a 70−98% yield. By manipulating the reaction conditions or tuning of the electronic and steric natures of the reagents, the reaction involving chiral secondary alcohols can be controlled to give either a high level of inversion or retention of the configuration.

Alkoxydiphenylphosphanes can be prepared in situ from tertiary alcohols via reaction with chlorodiphenylphosphane. When treated with 2,6-dimethyl-1,4-benzoquinone, esters are formed in high yields (76−90%) with inversion of the stereochemistry.[65] Secondary and primary alcohols react in a similar way.[66] Analogously, 2,3-dichloro-5,6-dicyanobenzoquinone combined with Ph_3P can be used as the mediator for conversion of diethyl α-hydroxyphosphonates into α-thiocyanatophosphonates.[67]

3. Additives

Additives such as tertiary amines can increase the yields for etherification of phenols. For Mitsunobu reactions carried out in the presence of a crosslinked commercial polystyrene-supported phosphane, addition of triethylamine increases the conversion.[21a] When hydroxymethyl polystyrene resin is treated with protected tyrosine in the presence of *N*-methylmorpholine, the formation of an ether bond proceeds in almost quantitative yields.[22] Imidazole improves the yields for the synthesis of alkylthioethers in the presence of Me_3P and ADDP **4g**.[43]

The addition of zinc bis(*N*,*N*-dimethylthiocarbamate) [$(Me_2NCOS)_2Zn$, Ziram®] in toluene to a classical mixture of Ph_3P and DEAD allows for the conversion of 1,2-disubstituted 1,3-diols to corresponding oxetanes. The starting 1,3-diols can contain a tertiary phenylsulfanyl, phenylsulfonyl, or *tert*-butyl group adjacent to the secondary hydroxyl group. Mechanistic studies and optimization of reaction conditions have been reported.[29]

4. Regioselectivity

The Mitsunobu reaction can exhibit selectivity between primary alcohol and phenyl hydroxyl groups in esterification reactions,[68] or between primary and secondary hydroxyl groups (by manipulation of the sterically different phosphanes) in amination reactions.[15] Azidation reactions of 1,2- and 1,3-diols predominantly lead to substitution of the secondary rather than the primary hydroxyl group, while reactions of 1,4-diols give cyclic ethers under the same reaction conditions.[69] Two adjacent secondary hydroxyl groups of *syn*-2,3-dihydroxy esters can be distinguished in benzoylation, azidation, and tosylation reactions.[70] The two nitrogens with different acidities in 3,4-dihydropyrimidin-2(1*H*)-ones can be differentiated in alkylation reactions in the presence of Bu_3P/TMAD.[71]

5. Stereochemistry

Typical inversion of configuration has been confirmed in several classical-style applications of the Mitsunobu reaction, and in fluorous processes.[35,36,44] Inversion, using regular reagents, of chiral tertiary alcohols that can be converted to chiral alkyl aryl ethers in 51−58% yields has been observed with >99% *ee* at elevated temperatures.[72]

Recently, the isolation of products with retention of configuration under standard Mitsunobu conditions has been reported in reactions of sterically shielded secondary alcohols.[73−76] The most likely reason for this is the failure of the Ph_3P-DEAD complex to activate the secondary hydroxyl group due to steric inaccessibility. The deprotonated nucleophile then displaces the hydrazide ion to afford the acyloxyphosphonium ion; nucleophilic attack of the substrate hydroxyl group on the activated acyl group leads to a product that retains the configuration (Figure 8).

6. Enantioselective Reactions

Moderate enantioselectivity has been observed when racemic secondary alcohols react with carboxylic acids (14−73% yield, 11−39% *ee*)[77] or phthalimide (26−45% *ee* after conversion into amine)[78] in the presence of DEAD and a chiral cyclic phosphoramidite derived from (+)-(*R*)-1,1′-binaphthalene-2,2′-diol (**14**, Figure 7).

Kinetic resolution of racemic secondary alcohols proceeds when esterification is carried out in the presence of a chiral (1*S*)-(+)-ketopinic acid and Ph_3P/DEAD. The chiral secondary alcohol is recovered in a 38−44% yield with

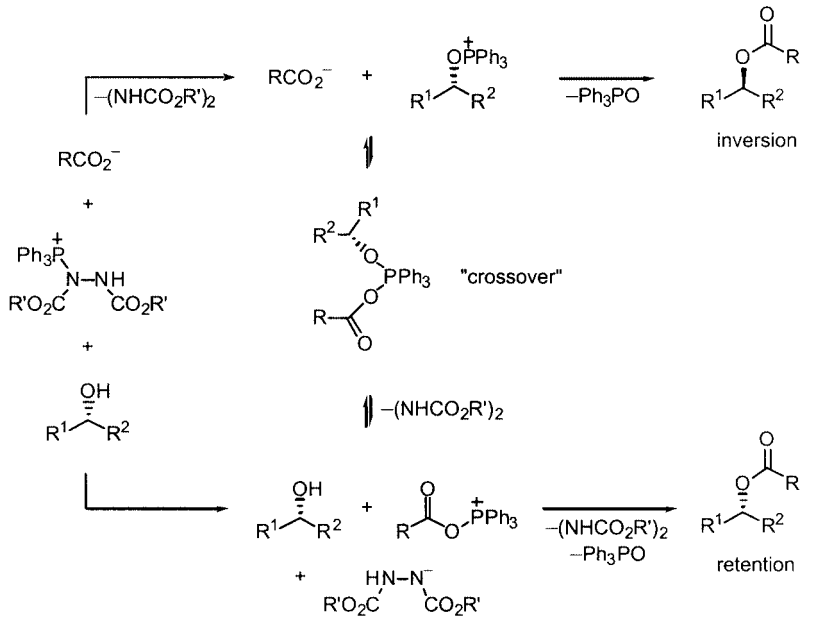

Figure 8. Outline of mechanistic pathways for the Mitsunobu esterification reaction

70−90% *ee*, and the ketopinate ester is obtained in a 37−75% yield with 76 to > 95% *de*.[79]

7. Mechanistic Studies

Mechanistic studies have provided a more comprehensive understanding of the various factors that influence the reaction outcome. An acylphosphonium salt intermediate has been confirmed for retention of the stereochemistry.[80] Imamoto investigated the reaction of primary and secondary alcohols with enantiomerically pure P-chiral cyclohexylmethyl(1-naphthyl)phosphane (**3j**, Figure 2). Experiments in which the reaction conditions and the nature of the alcohol and carboxylic acid are varied suggest competition between two alternative mechanisms: one proceeding via a phosphonium salt (DEAD−**3j** adduct) and the other via a pentacoordinate phosphorane during the second stage of the reaction.[81] Evidence for direct acylation and a base-mediated crossover step under both neutral and basic conditions has been provided.[82] Additional insights into the formation of pentacoordinate phosphorus intermediates have been furnished by ^{31}P NMR spectroscopy.[78,83,84] The general mechanism for the Mitsunobu reaction is outlined in Figure 8.

8. Product Expansion

The products available via the Mitsunobu reaction have been expanded or the procedure has been improved to include styrene oxides with a high level of stereoretention,[32] oxetanes,[29] lactones from hindered chiral alcohols with retention of configuration,[73] aldehydes from 1,1-disubstituted-1,2-diols,[85] carbamate esters,[57,86,87] γ-lactams from amino alcohols,[88] primary amines,[89] tertiary benzylamines,[40] alkylated hydrazines,[90] nitriles,[41,61] isocyanates,[31] thiocyanates,[91] hydroxyalkyl azides,[69,92] and *cis*- or *trans*-1,2-diazides from epoxides or *trans*-diols.[93] Hydrazine derivatives can be obtained directly from the azodicarboxylate and an alcohol,[94] vinylhydrazinecarboxylates from ketones in the presence of dimethyl azodicarboxylate,[95] and hydrazylmethyl uracil derivatives from N^3-benzyluracil, TMAD, and *N*-hydroxymethylphthalimide.[96] Mitsunobu reagent-induced pinacol rearrangement leads to sesquiterpenes.[97] Epimerization of the glucose derivative is accompanied by the substrate-dependent rearrangement; addition of base and the use of nonpolar solvents favor epimerization.[98] An interesting ring contraction of 6-hydroxy-1,4-diazepan-2-one leads to a 1,4-piperazine-2-one.[99]

A literature search for the Mitsunobu reaction using SciFinder® produces over one hundred citations per year. It is not possible here to provide citations for synthetic applications of the Mitsunobu reaction that use standard conditions, but it should be noted that interesting chemistry, structures, and properties have been achieved with the help of this reaction.

V. Conclusions

Recent modifications of the reagents for the Mitsunobu reaction have opened new avenues for the separation of products, by-products, and spent reagents. Appropriately modified reagents can be removed by acid or base extraction, by decomposition to volatile products, by sequestration, or by phase-switching. Progress has been made toward regio- and enantioselective reactions. Mechanistic studies have yielded a better understanding of the key factors that influence the reaction, particularly as they affect the stereochemical outcome. New classes of products are available and synthetic procedures have been improved.

The fluorous approach offers an appealing solution to problems involving isolation of the products in the Mitsu-

nobu reaction by simplifying separation protocols, which include reduced reliance on column chromatography, by improving yields, and/or allowing recycling of reagents. When fluorous DEAD and fluorous phosphanes are used, solvent evaporation followed by solid-phase extraction over fluorous silica gel affords the products. The depleted fluorous reagents can readily be recovered from the SPE column, separated by standard flash chromatography, and recycled. The use of highly fluorinated carboxylic acids or alcohols as pronucleophiles for the acylation or etherification of alcohols also offers advantages with regard to separation. In addition, organic liquid/fluorous solid separation eliminates the need for fluorous solvents.

There are a variety of modified reagents and recycling processes available that will help in scaling up the Mitsunobu reaction.

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