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Technical Reports
Volume 3, Number 19

A Whirlwind Tour of Current Mitsunobu Chemistry

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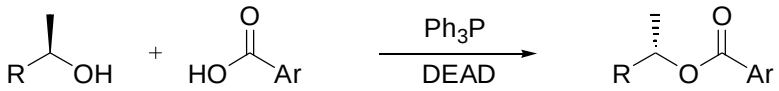
Abstract. *This review summarizes the recent developments in chemistry derived from the Mitsunobu Reaction over the last decade. Furthermore, some of the newest innovations based on premise of this reaction mechanism are presented along with some current examples of its use toward natural product and analog syntheses.*

Contents:

I. Introduction

In recent years, there have been numerous reports on the application of the Mitsunobu Reaction to organic synthesis. This method was first reported in the literature[1] as a novel protocol for the dehydrative bond-forming reaction between a carboxylic acid and an alcohol using a mixture of diethyl dicarboxylate (DEAD) and triphenylphosphine. In secondary alcohol substrates, this condensation reaction was shown to proceed with inversion of configuration at the alcohol center, leading to a general method for preparing derivatives of this type (Scheme 1).

Scheme 1

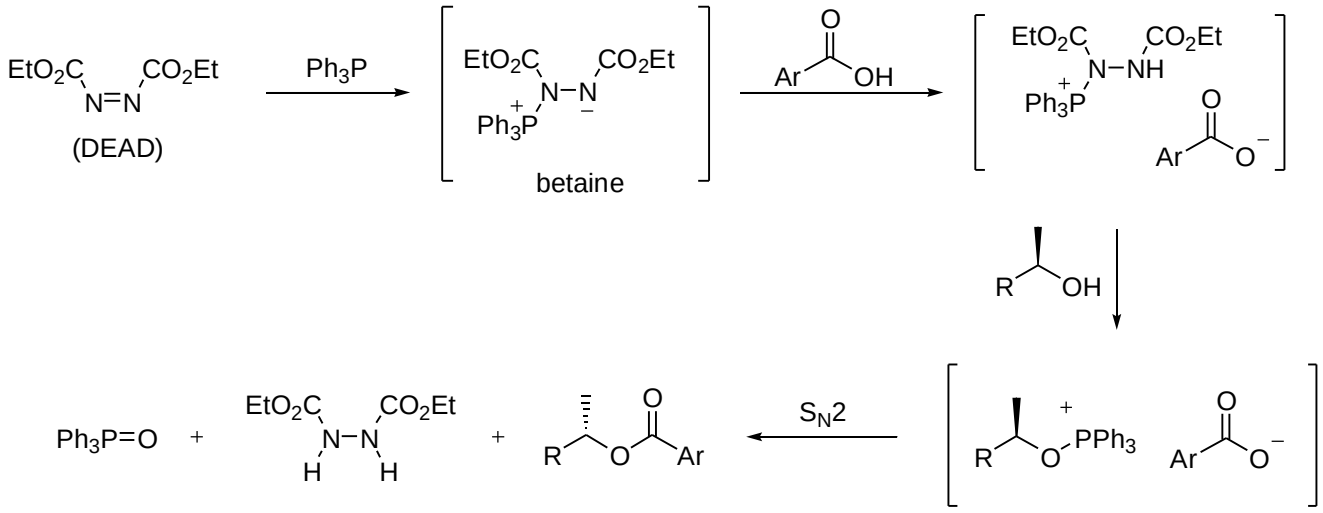


Over the years the scope of this reaction mechanism[2-4] and applications to natural product syntheses[5] have been extensively discussed and reviewed. Reviews covering the innovative utilization of the method to other kinds of bond constructions have also appeared.[6] This report is by no means a comprehensive review, but attempts to present a broad sampling of the most useful methods derived from the original Mitsunobu inversion procedure.

II. Alcohol Inversions — Intermolecular

In 1967, Oyo Mitsunobu reported a method for the condensation of a carboxylic acid and an alcohol, using a mixture of triphenylphosphine and diethyl dicarboxylate (DEAD), to provide an ester. This dehydrative bond forming reaction was based on the observation that a mixture of the phosphine and DEAD in solution produced a reactive betaine intermediate in situ, and was capable of both deprotonation of the acid nucleophile as well as activation of the alcohol electrophile toward substitution (Scheme 2). Furthermore, when a secondary alcohol substrate was used, the esterification reaction was shown to proceed with a net inversion of stereochemistry at the alcohol carbon. After the generality of this process was demonstrated in the literature, the use of this betaine intermediate in organic syntheses became widely known as the “Mitsunobu Reaction.”

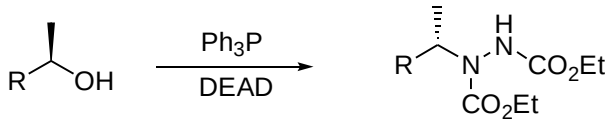
Scheme 2



The reaction occurs in under mild, essentially neutral reaction conditions (0 °C to room temperature), and tolerates a variety of functional groups. The p*K*a of the proton of the nucleophilic component must be lower than the betaine intermediate p*K*a (~ 13). Some of the more nonpolar solvents accelerate the conversion, and so THF, diethyl ether, methylene chloride and toluene are often preferred as solvents, though ethyl acetate, acetonitrile and DMF are sometimes used.

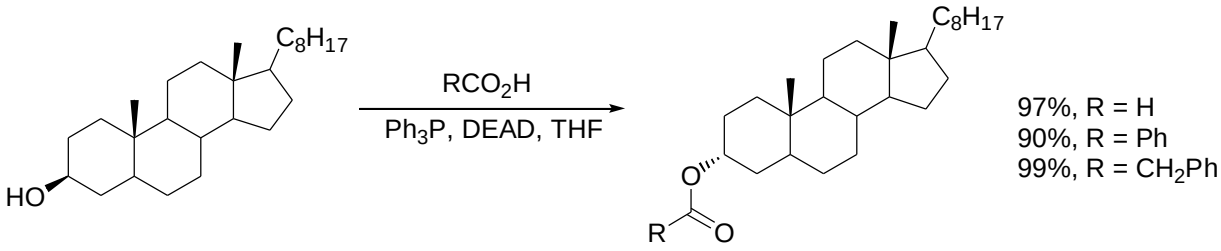
In cases where no nucleophile was added to the reaction mixture, or when the betaine was not able to abstract the proton of the nucleophilic precursor (p*K*a >13), the hydrazine portion of the reagent was shown to react with the alcohol substrate (Scheme 3).[5a]

Scheme 3



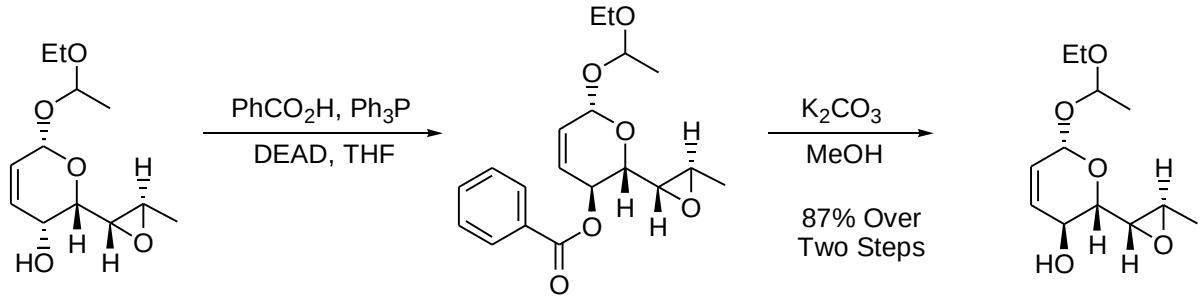
One of the first adaptations of this method to a natural product synthesis was the application of the inversion protocol to the preparation of sterols with benzoic acid. (Scheme 4).[7] Bose and coworkers showed that 5α-choletan-3β-ol could be converted to 5α-cholestan-3α-ol in one step, shortening the conventional synthesis by several steps, and extending this method to provide several new ester derivatives.

Scheme 4



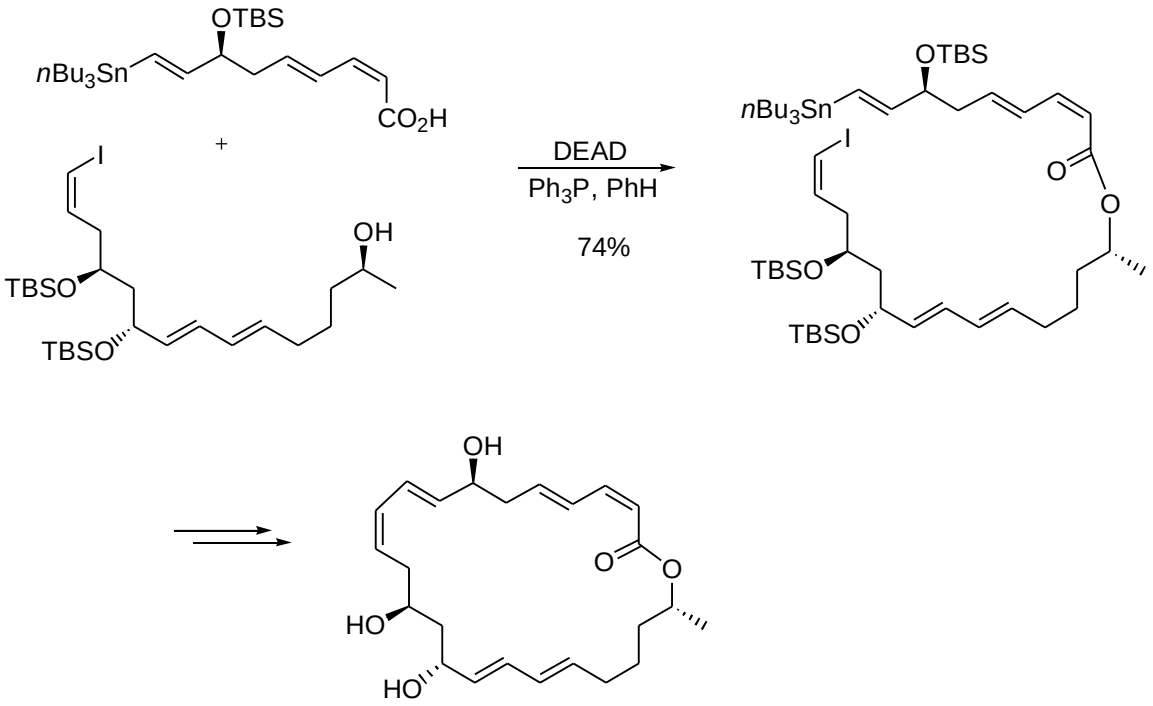
A more recent example showed how the alcohol inversion and hydrolysis procedure may be easily carried out in the presence of sensitive functionality (Scheme 5).[8,9]

Scheme 5



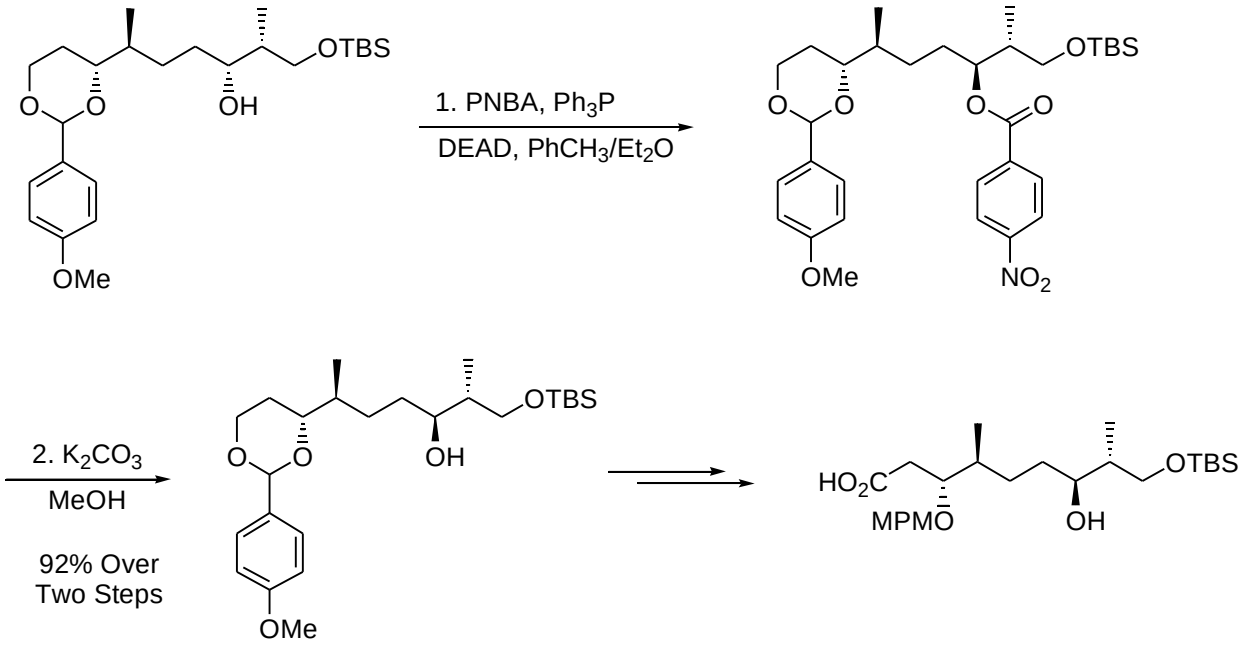
A recent paper by Smith and coworkers connected two unsaturated pieces by the Mitsunobu protocol in good yield, followed by a Stille coupling and further elaboration to the cytotoxic agent (-)-Mactrolactin A (Scheme 6).[10]

Scheme 6



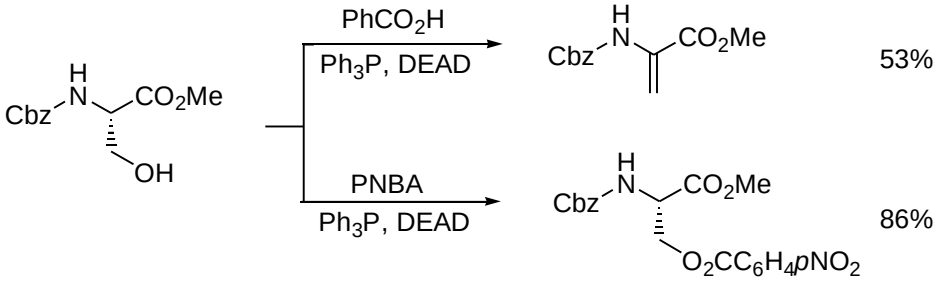
In 1991, Eli Lilly chemists Martin and Dodge showed that *p*-nitrobenzoic acid (PNBA) was a more effective nucleophile for the inversion of more sterically hindered alcohols.[11] This protocol was used by Buszek and Jeong to prepare the sterodefined linear precursor to Octalactin A and B (Scheme 7).[12]

Scheme 7



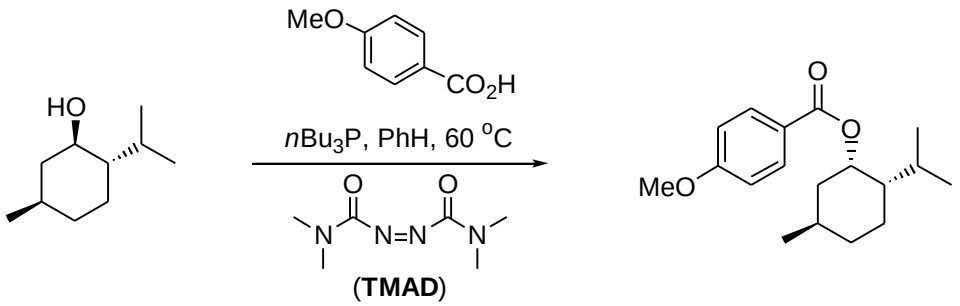
Workers at the DuPont-Merck Pharmaceutical Company found that PNBA was useful in preventing the elimination side reaction in the preparation of serine derivatives (Scheme 8).[13]

Scheme 8



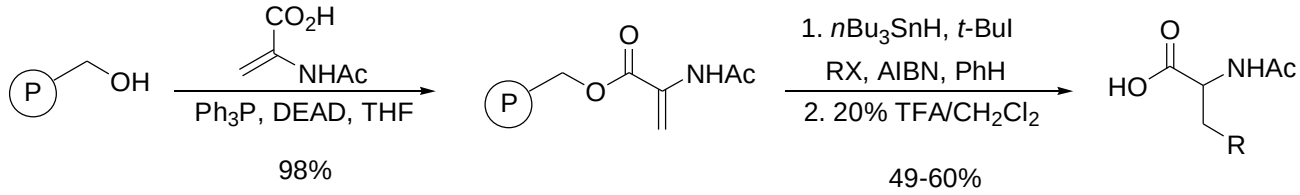
Tsunoda and coworkers also found that the use of *N,N,N'N'*-tetramethylazodicarboxamide (TMAD) and tributylphosphine was more tolerant of sterically congested alcohols, resulting in consistently better yields than the triphenylphosphine/DEAD combination (Scheme 9).[14]

Scheme 9



The Mitsunobu reaction has also entered the arena of solid-phase synthesis. Several groups have shown that acrylates may be bound to Wang resin using this chemistry after which further chemistry may be performed on the solid phase (Scheme 10).[15,16]

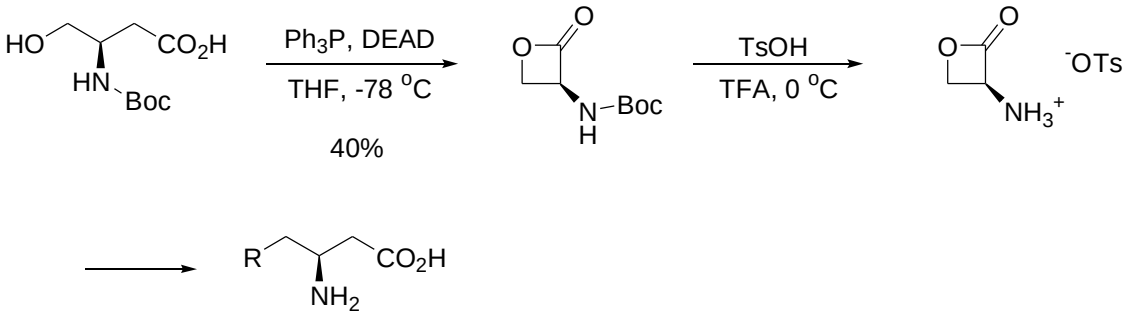
Scheme 10



III. Alcohol Inversion — Intramolecular

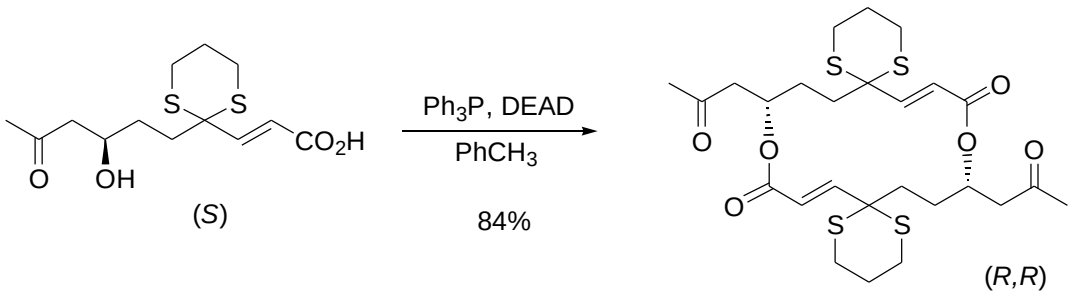
The Mitsunobu inversion protocol has been extended to intramolecular variations, providing a useful route to lactones. Vederas and coworkers showed that suitably protected L-serine could be converted to (*S*)-3-amino-2-oxetanone in two steps, providing a valuable precursor to amino acids (Scheme 11).[17,18]

Scheme 11



Seebach and Seuring showed that a double-displacement strategy could be employed to provide a series of bis-lactones from hydroxy acids (Scheme 12).[19] Intermolecular inversion of the (*S*)-alcohol moiety by a second acrylic acid molecule was rapidly followed by an intramolecular ring closure to provide (*R*,*R*)-vermiculin in good overall yield.

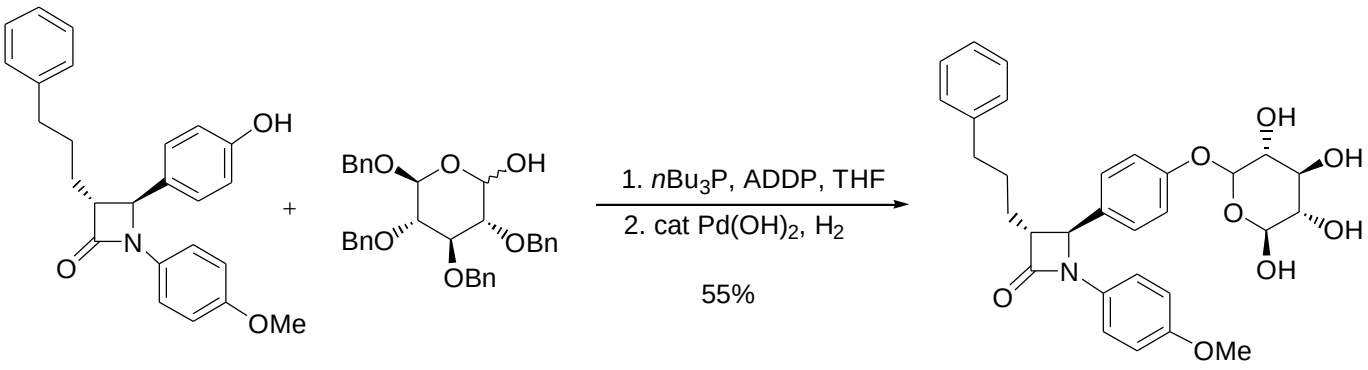
Scheme 12



IV. Other Oxygen Nucleophiles

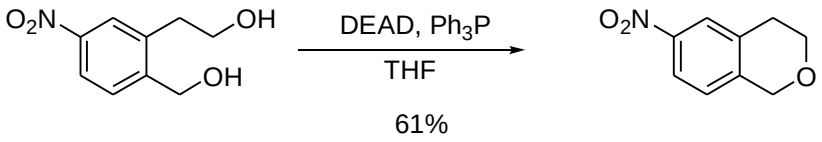
The alcohol moiety may also serve as a nucleophile for the Mitsunobu reaction, although usually limited to phenols and other alcohols of p*K*a < 13. In this case, Schering-Plough chemists showed that a Mitsunobu glycosylation between the β-lactam phenol and the protected sugar could be affected to provide the glucuronide in good yield after global deprotection (Scheme 13).[20,21] This β-lactam was prepared to confirm the structure of a cholesterol absorption inhibitor metabolite.

Scheme 13



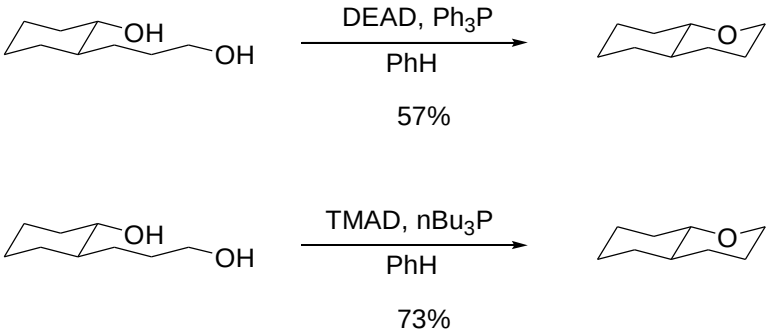
When the alcohol electrophile is sufficiently activated, or when the product is the result of an intramolecular addition, cyclizations may be performed with inactivated oxygen nucleophiles. A Pfizer, Inc. group employed the Mitsunobu reaction for the preparation of an electron-poor benzofuran as an intermediate to a novel pharmaceutical agent (Scheme 14).[22]

Scheme 14



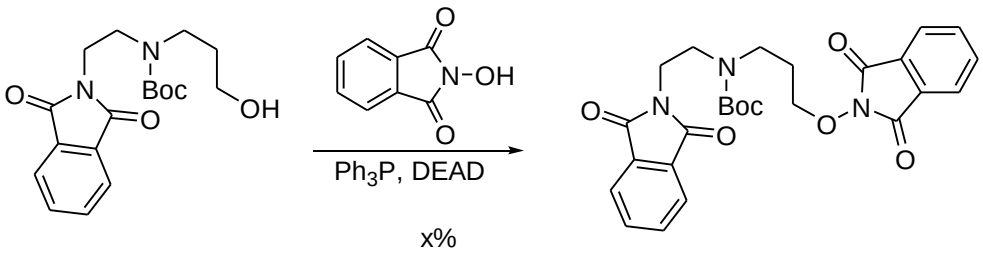
Similarly, Tsunoda and coworkers showed that intramolecular ether formation could be achieved in an inactivated system. Furthermore, the use of TMAD was shown to enhance the reactivity of these nucleophiles of larger p*K*a, leading to higher overall yields (Scheme 15).[23]

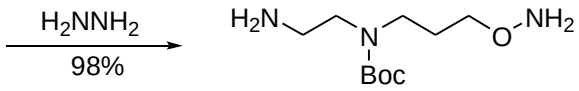
Scheme 15



Grochowski and Jurzcak showed that *N*-hydroxyphthalimide was also an excellent nucleophile for the intermolecular Mitsunobu reaction, providing good yields of hydroxylamines after hydrazinolysis of the phthalimide moiety (Scheme 16).[24,25]

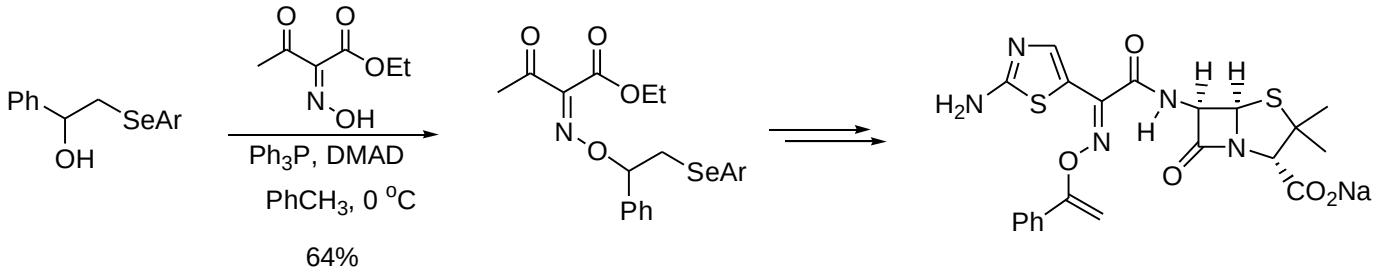
Scheme 16





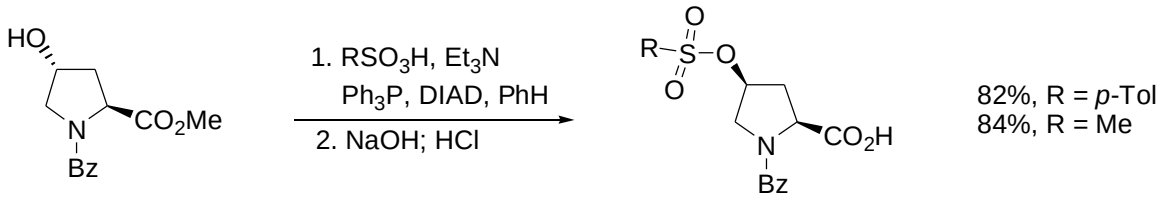
A group at SmithKline Beecham (UK) has shown that oximes also serve as oxygen nucleophiles, providing important precursors to *O*-vinyl penicillin derivatives (Scheme 17).[26]

Scheme 17



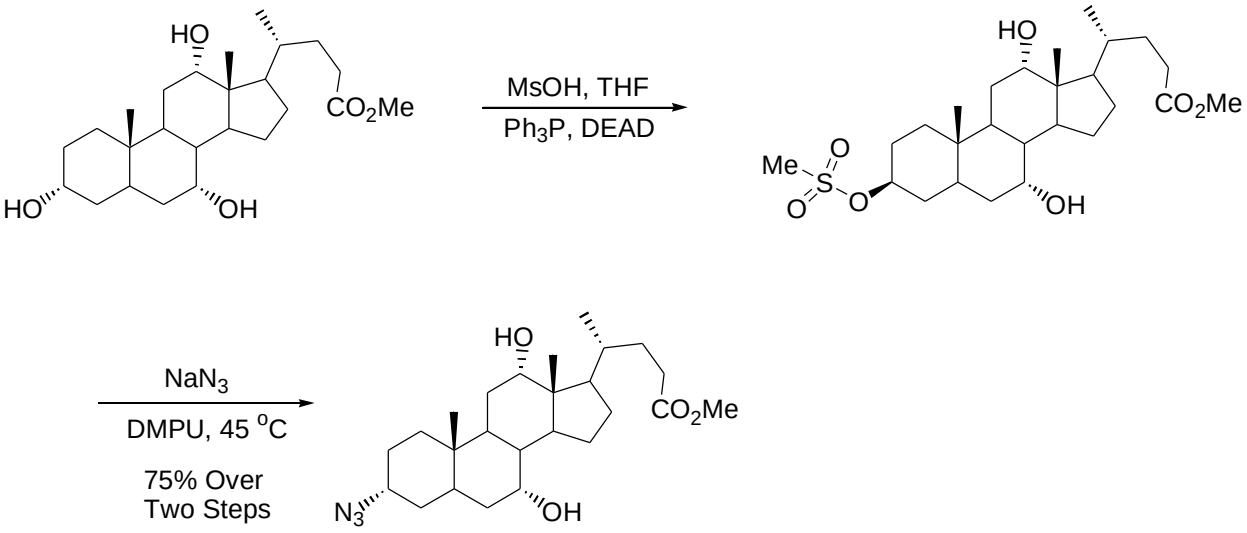
A group at Bristol-Myers Squibb has recently shown that the Mitsunobu reaction may be extended to preparation of sulfonates with the usual inversion of configuration in secondary substrates (Scheme 18).[27]

Scheme 18



Davis and coworkers took this idea one step further by displacing the resultant mesylate with sodium azide (Scheme19).[28] In this way, methyl cholate was transformed into the α-azide analog with an overall retention of configuration.

Scheme 19

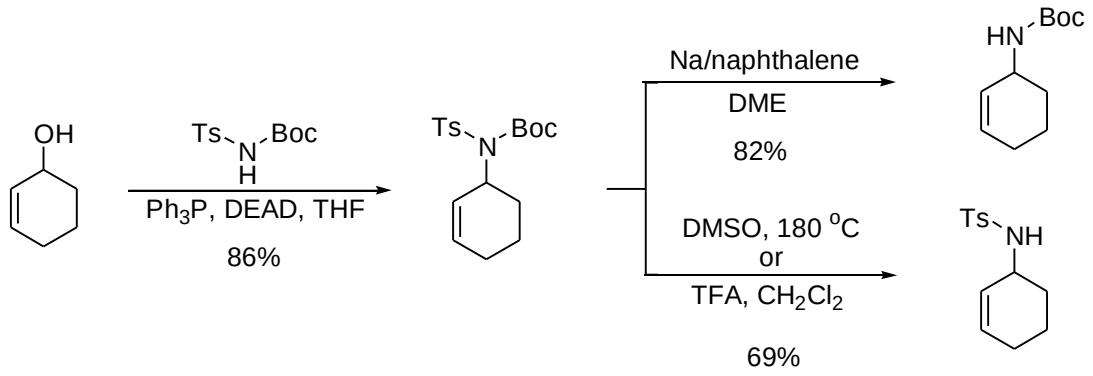


V. Nitrogen Nucleophiles

Mitsunobu type displacements of alcohols by amine nucleophiles has only recently appeared in the literature. Nucleophilic amines of sufficient acidity to be deprotonated by the triphenylphosphine/DEAD reagent (pKa < 13) may displace the activated alcohol to provide access to protected amines. Amides, sulfonamides, imides and azides can be used in this transformation.

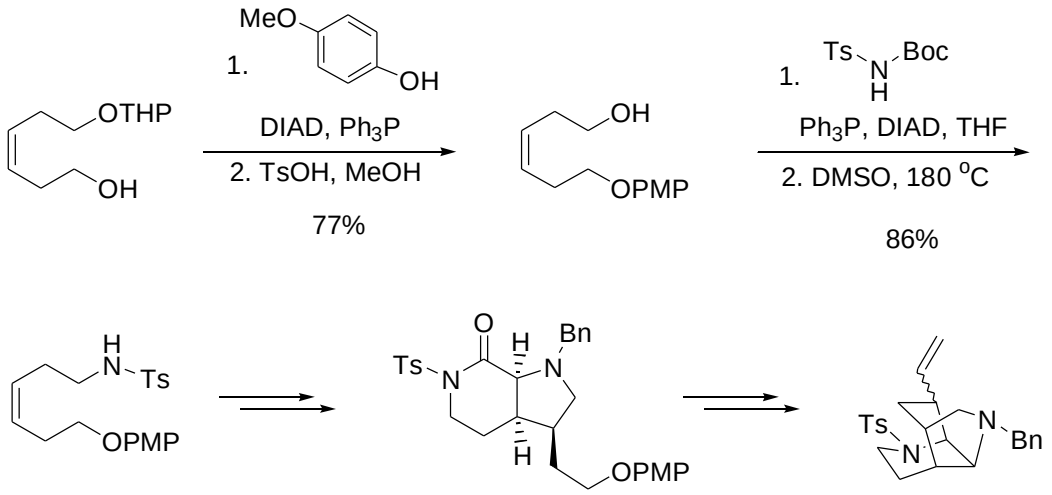
In 1989, Weinreb and coworkers showed that protected sulfonamides could undergo the Mitsunobu reaction to provide a variety of tertiary amines (Scheme 21).[29,30] A choice of reaction conditions provides access to either amine protection functionality.

Scheme 20



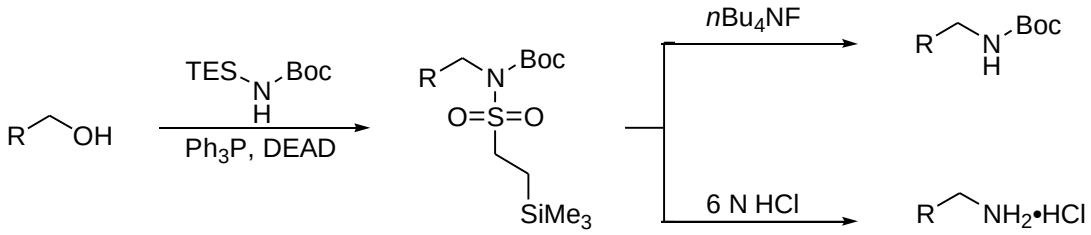
Weinreb's group has applied this method to the synthesis of the fused tricyclic inner core of the natural product Sarain A (Scheme 22).[31] In this strategy, the key amine was constructed from monoprotected 3-hexenediol using two consecutive Mitsunobu reactions.

Scheme 21



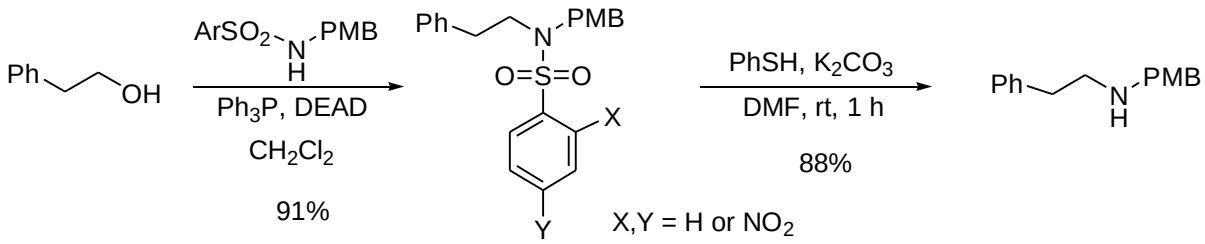
Several other Mitsunobu amination substrates have been developed since that time, providing products that may be deprotected by various methods to accommodate sensitive molecular functionality. Hart and Campbell showed that the 2-[(trimethylsilyl)ethyl]sulfonyl protecting group (SES) provides a useful sulfonamide for this coupling reaction, leading to Boc-protected amines upon deprotection with tetrabutylammonium fluoride (Scheme 22).[32] Furthermore, Decicco and Grover at DuPont Merck showed that this type of sulfonamide could be treated with concentrated hydrochloric acid to directly provide the resulting amine hydrochloride.[33]

Scheme 22



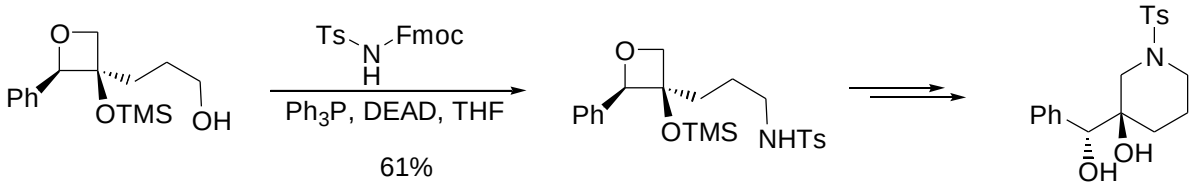
Fukuyama and coworkers then showed that nitroarylsulfonamides could undergo Mitsunobu amination and could easily be deprotected with thiophenol under mildly basic conditions (Scheme 23).[34] This method was later used by Fukuyama as part of a total synthesis of some of the iboga alkaloids.[34b]

Scheme 23



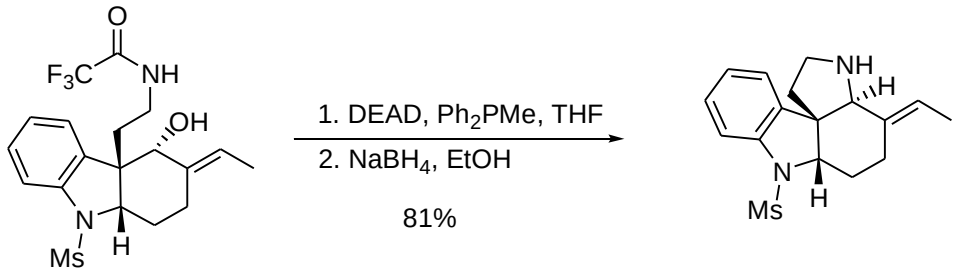
More recently, Bach and Kather showed that Fmoc-protected sulfonamides could undergo the Mitsunobu coupling reaction with concomitant removal of the Fmoc group to provide sulfonamides directly (Scheme 24).[35,36]

Scheme 24



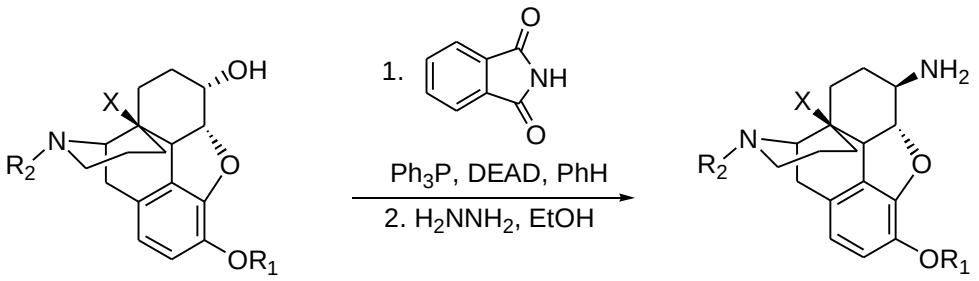
Amides and imides may also undergo the Mitsunobu reaction. Murphy and coworkers constructed a tricyclic core by an intramolecular amination of a tryptamine-derived amide (Scheme 25).[37,38]

Scheme 25



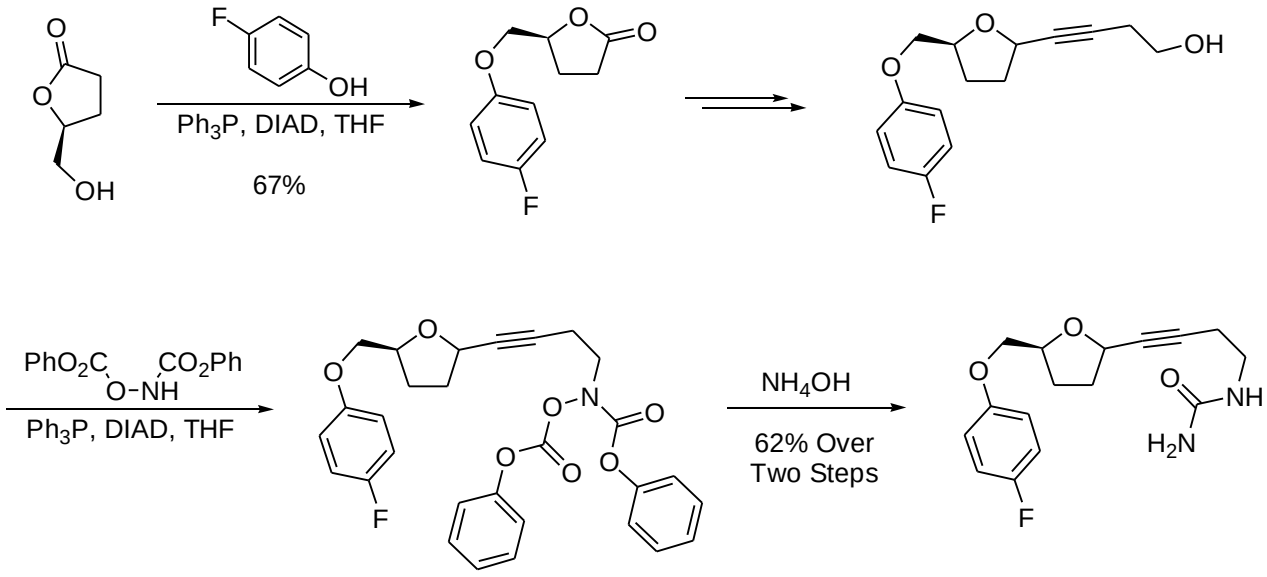
The use of phthalimide for the Mitsunobu reaction has become a popular method for the direct substitution of an alcohol to a primary amine.[39-42] Makleit and coworkers used this method for the preparation of β-naltrexamine derivatives from dihydrocodeine (Scheme 26).[39c]

Scheme 26



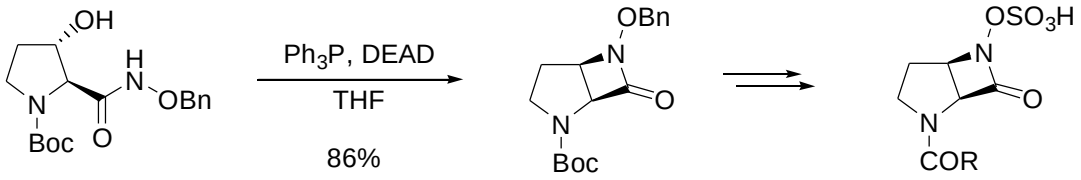
Alcohols may be replaced by appropriately activated hydroxylamines by the Mitsunobu protocol. A collaboration by groups at CytoMed, Inc. and Steroids, Ltd. has shown that the total synthesis of the potent 5-lipoxygenase inhibitor CMI-977 was achieved by two Mitsunobu reactions (Scheme 27).[43] First, displacement of the lactone alcohol with 4-fluorophenol provided the aryl ether in good yield. After functional elaboration, displacement of the homopropargyl alcohol with *N,O*-bis(phenoxycarbonyl)hydroxylamine was followed by aminolysis to provide CMI-977 in multi-gram quantities.

Scheme 27

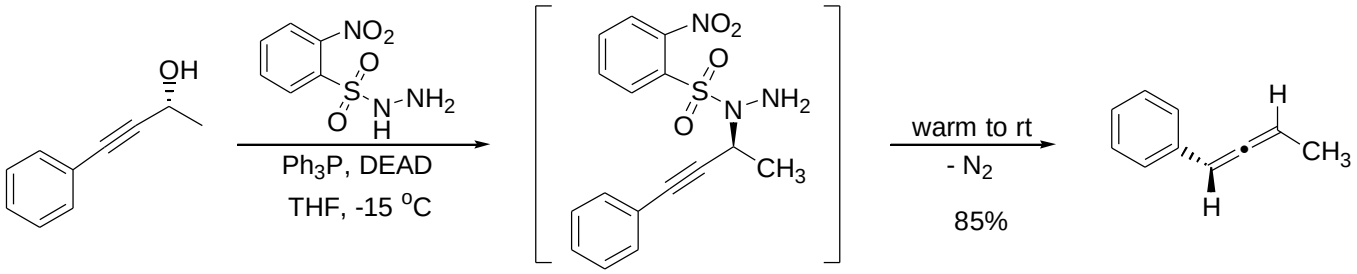


Miller and Bellettini showed that a new class of bicyclic β-lactamase inhibitors could be constructed by an intramolecular Mitsunobu reaction with an acyl hydroxylamine (Scheme 28).[44]

Scheme 28



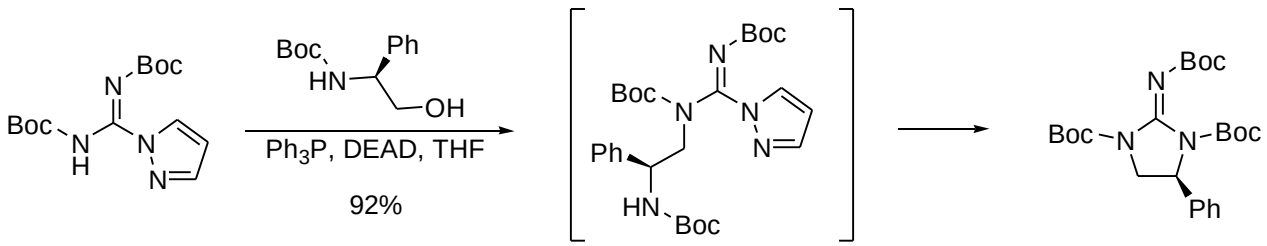
The Myers group has shown that the sulfonyl hydrazine could undergo the Mitsunobu reaction to provide a propargyl hydrazine, a precursor in the stereospecific synthesis of allenes (Scheme 29).[45,46] The secondary amine has the more acidic proton and is thus the nucleophile in this reaction. Upon warming to room temperature, nitrogen and arylsulfinic acid are extruded to provide the allene.



Scheme 29

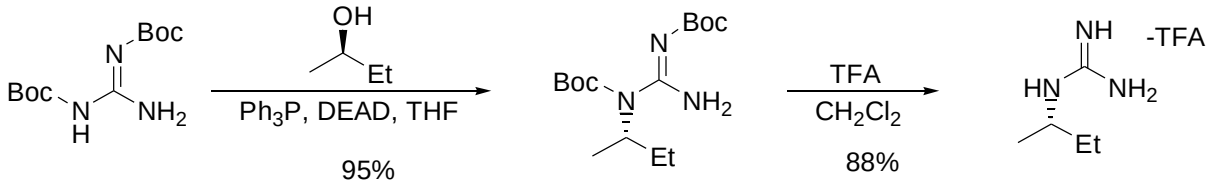
Guanidines may also act as nucleophiles, displacing alcohols activated by Mitsunobu conditions (Scheme 30).[47] This method is very practical for the preparation of disubstituted guanidines, for which only limited literature procedures exist. Chemists at Molecumetics, Ltd. showed that when the appropriate substrate is used, the intermediate spontaneously cyclizes.

Scheme 30



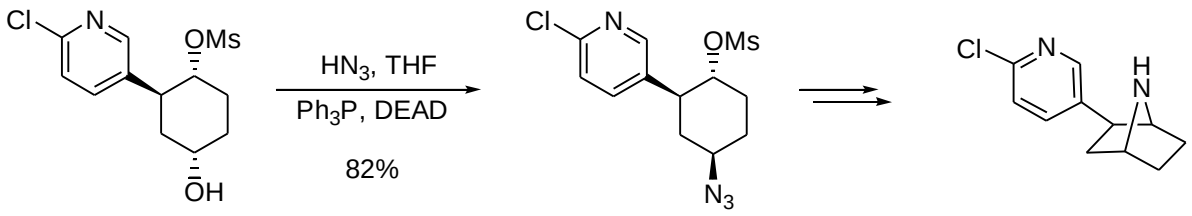
Published at the same time, Kozikowski and coworkers showed that bis-protected guanidine was also a good nucleophile for the Mitsunobu amination, providing primary guanidines directly (Scheme 31).[48]

Scheme 31



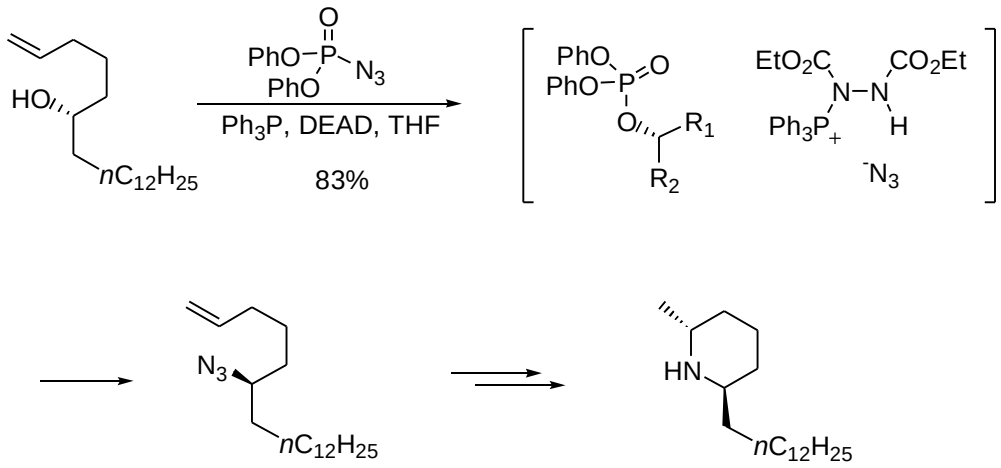
Another way to accomplish direct amination of an alcohol is to utilize the azide functionality in the Mitsunobu reaction. One of two methods for this transformation makes use of hydrazoic acid[50,51] or a metal azide[52] as a nucleophile for the dehydrative coupling. Maycock and coworkers used this amination method to build the nitrogen bridge in the core structure of (+)-epibatidine (Scheme 32).[50]

Scheme 32



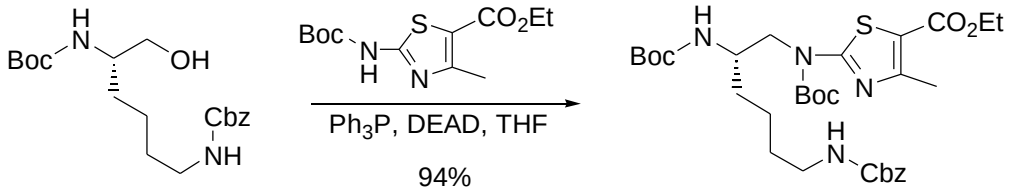
A second method for this transformation makes use of a diarylphosphoryl azide reagent as the azide source.[53] Taber and Deker, in conjunction with workers at the NIH, showed that inversion of an alcohol with diphenylphosphoryl azide (DPPA) let to the azide in good yields. This intermediate was ultimately elaborated to provide the first enantioselective synthesis of (*R*,*R*)-solenopsin B (Scheme 33).[54] Other phosphoryl azide reagents have also been used with success.[55]

Scheme 33



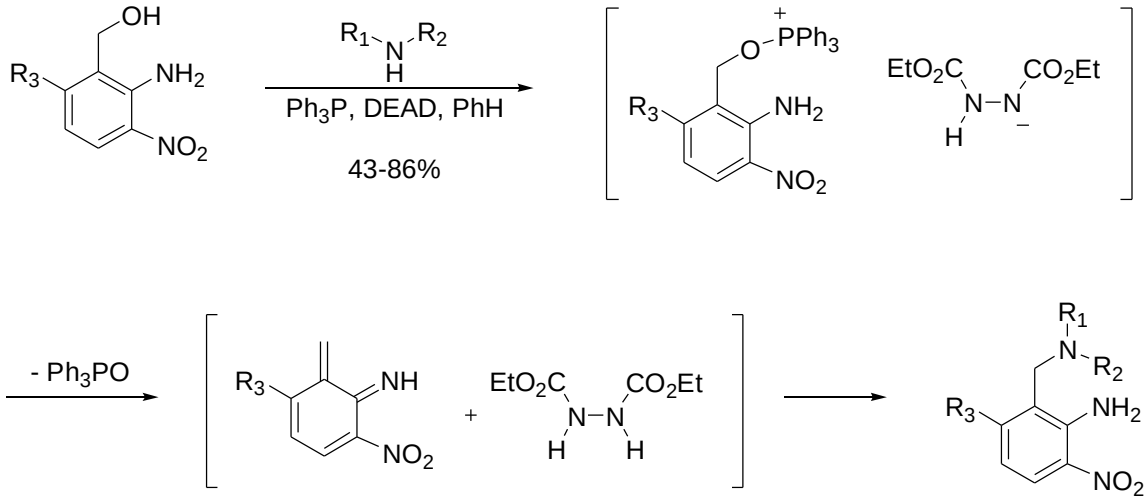
Recently Molecumetics Ltd. chemists Kim and Kahn showed that suitably protected aminoazole esters may undergo the Mitsunobu amination reaction, providing a series of lysine and arginine analogs (Scheme 34).[56]

Scheme 34



Parke-Davis chemists Nikam and coworkers showed that secondary and tertiary benzylamines may be constructed using the Mitsunobu protocol, but are only effective with activated aryl substrates (Scheme 35).[57,58] The authors propose that the 2-amino-3-nitro substitutions on the aromatic ring produce an azaquinomethane intermediate, which can successfully undergo substitution. These benzylamines were cited as useful precursors to biologically active benzimidazole pharmaceuticals.

Scheme 35



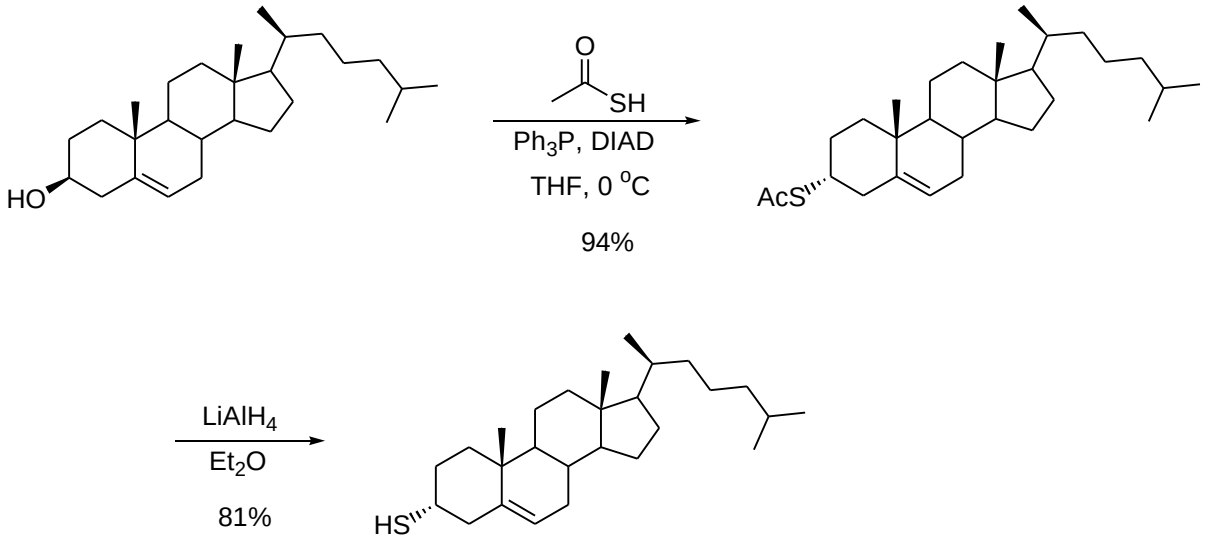
In a very recent communication, Jackson and coworkers have utlitized the Mitsunobu reaction for the preparation of aryl and hindered alkyl isocyanates (Scheme 36).[59] When primary amines were treated with the betaine reagent in the presence of carbon dioxide in methylene chloride at low temperature, excellent isolated yields of isocyanates were observed. This procedure was an extension of a little known method for the preparation of carbonate esters from alcohols and carbon dioxide by the Mitsunobu protocol.[60]

Scheme 36

VI. Sulfur Nucleophiles

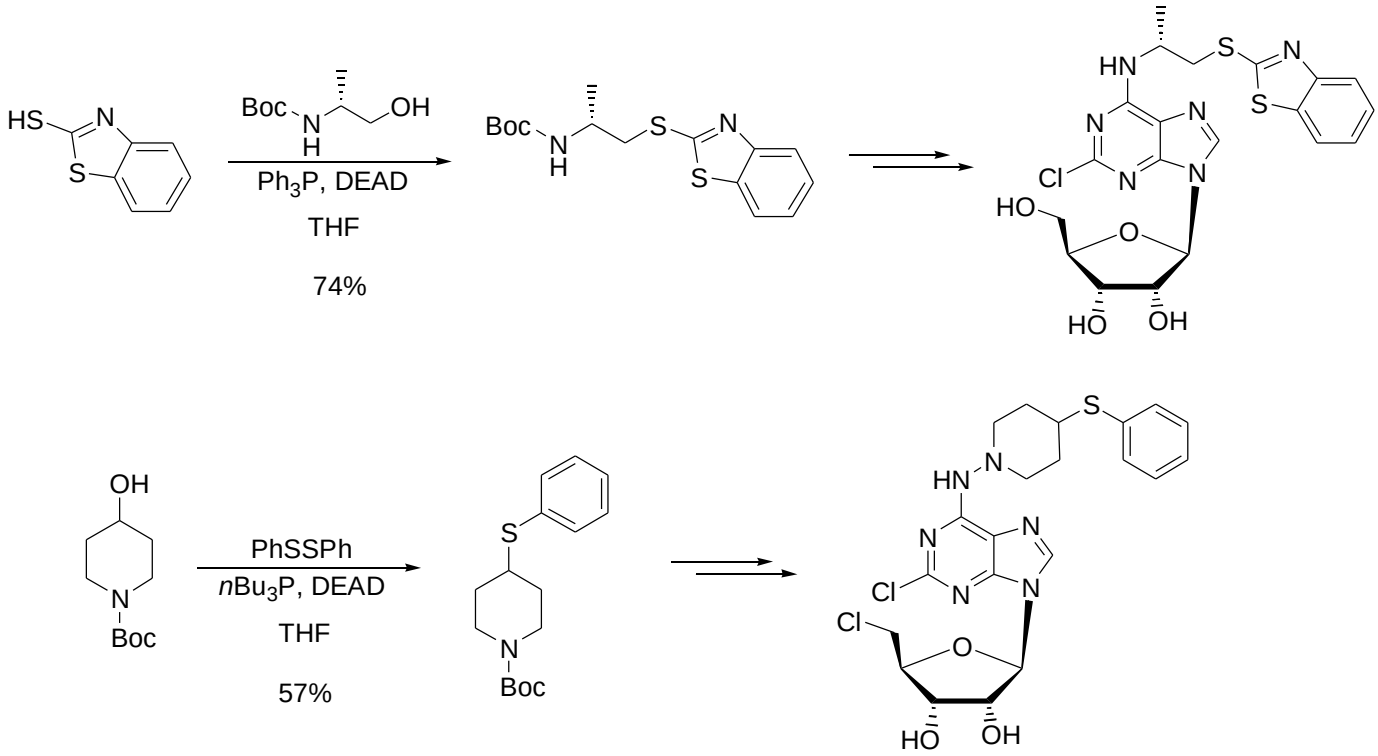
Activated sulfur nucleophiles also may participate in the Mitsunobu reaction, to provide thioester and thioethers with inversion of configuration. Merck chemist Volante was the first to show this utility in the preparation of several steroidal thiols (Scheme 37).[61]

Scheme 37



Aryl thiols are also suitably active for this transformation. In a recent publication, Novo Nordisk chemists Knutsen and coworkers described a method for preparing several novel neuroprotective A_1 agonists using the Mitsunobu protocol, using two different aryl thiols (Scheme 38).[62,63]

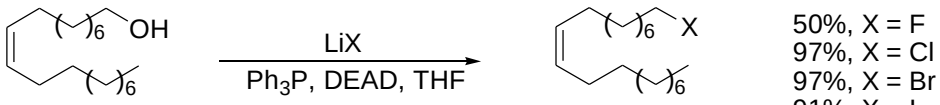
Scheme 39



VII. Halogenations

The substitution of an alcohol with a halogen using the Mitsunobu protocol has been known for some time, but is not widely reported in the organic synthesis literature. Falck and coworkers showed that hydroxy compounds may undergo this substitution to provide all of the alkyl halogens (Scheme 39).[64]

Scheme 39

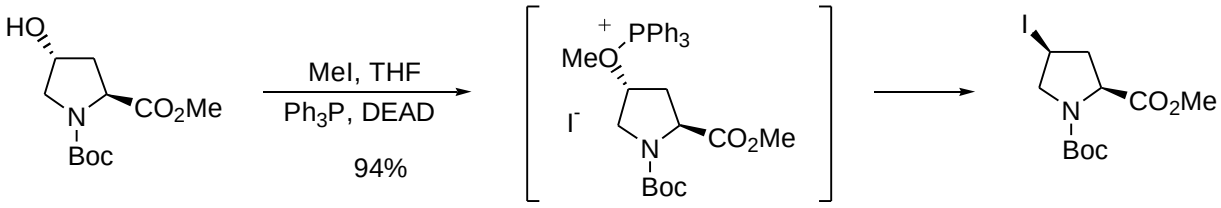


50%, X = F
97%, X = Cl
97%, X = Br
91%, X = I

Joullié and coworkers showed that a proline derivative could be converted to the epimeric iodide at C-4 in good yield by a two-step transformation (Scheme 40).[65,66] Deprotonation of the 4-hydroxyproline with the Mitsunobu betaine facilitates the alkylation of iodomethane in the usual fashion. Residual triphenylphosphine activates the resulting ether to displacement by iodine,

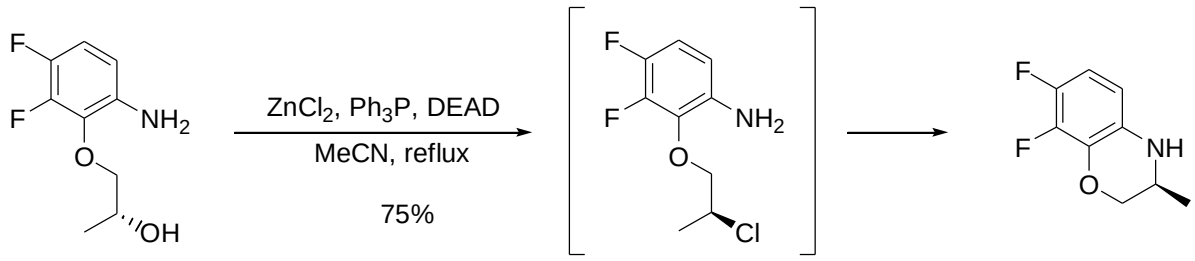
resulting in inversion of stereochemistry. This iodide was prepared as a key intermediate to the total synthesis of the marine natural products astins A, B and C.

Scheme 40



When an aniline substrate failed to cyclize under the Mitsunobu conditions, Kim and coworkers found that zinc (II) chloride catalyzed the ring closure with an overall retention of stereochemistry (Scheme 41).[67] A mechanistic study revealed that the zinc reagent was able to induce a chlorination of the pendant secondary alcohol with the usual inversion of stereochemistry. Intramolecular attack of the aniline nitrogen then displaced the chloride, leading to good overall yield of the dihydrobenzoxazine, a key component in the synthesis of the quinolone antibacterial agent levofloxacin.

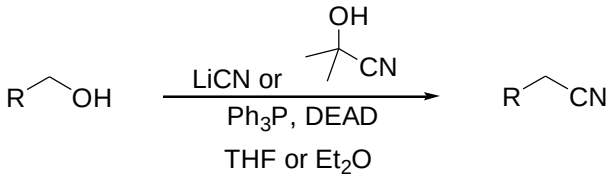
Scheme 41



VIII. Carbon-Carbon Bond Formations

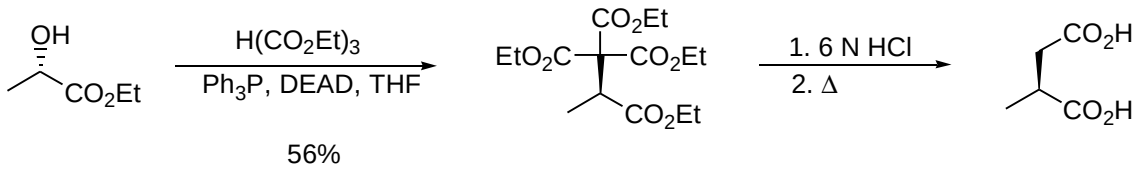
The formation of carbon-carbon bonds by the Mitsunobu reaction has only been reported in a small number of communications. Although an early report by Falck showed that lithium cyanide could displace an alcohol activated by the Mitsunobu betaine to provide nitrile products,[64] only a few advances in this area have only appeared in the last few years. Szántay and coworkers have recently shown that acetone cyanohydrin was able to effect nitrile substitution by the Mitsunobu protocol, but was limited to primary alcohols and sterically unencumbered secondary substrates (Scheme 42).[68]

Scheme 42



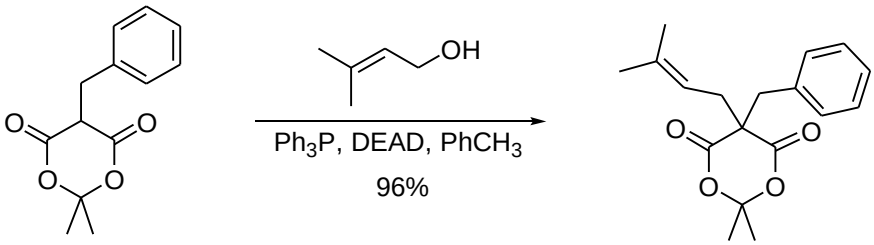
Palmisano and coworkers have recently shown that triethyl methanetricarboxylate may act as a nucleophile in this dehydrative alkylation, leading to intermediates with a handle for various synthetic manipulations.[69] In one case, (*S*)-(-)-ethyl lactate was converted to the tetraester, followed by acidic hydrolysis and decarboxylation to provide 2-methylsuccinic acid with no detectable loss in optical purity (Scheme 43).

Scheme 43



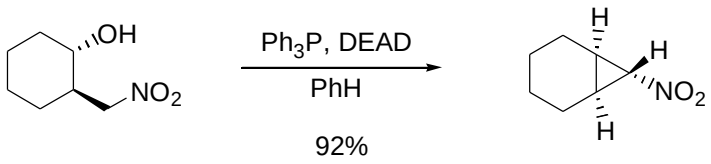
Shing and coworkers showed that the Mitsunobu reaction could be successfully applied to the C-alkylation of monosubstituted Meldrum's acids (Scheme 44).[70]

Scheme 44



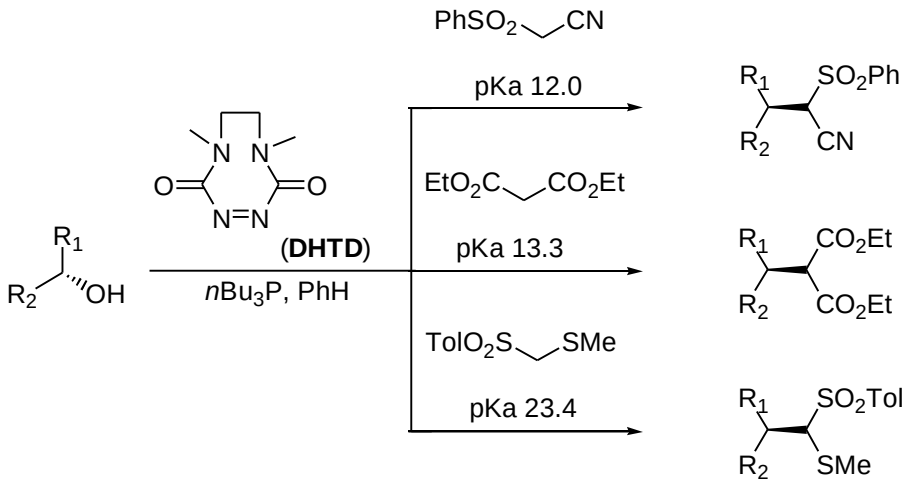
Falck and coworkers have recently reported a method for the preparation of α-nitrocyclopropanes by Mitsunobu chemistry in generally excellent yields (Scheme 45).[71] Deprotonation of the activated carbon center allows intramolecular displacement of the activated alcohol.

Scheme 45



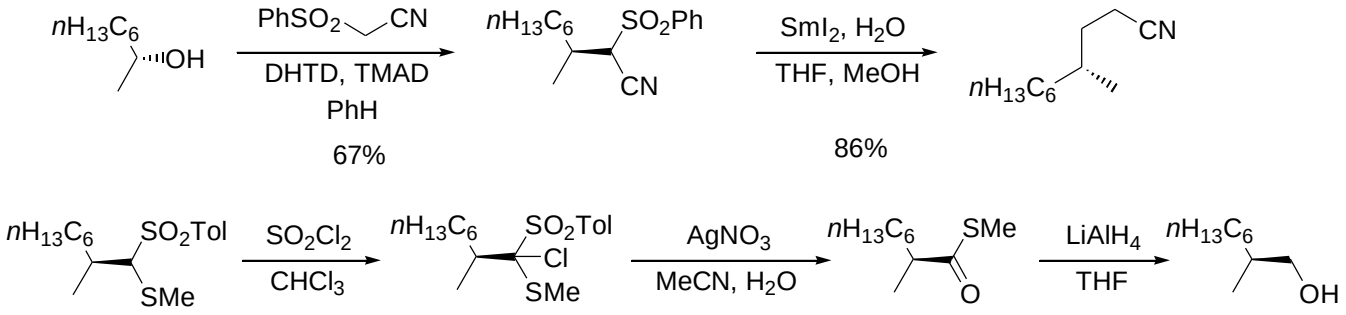
A recent report by Tsunoda and coworkers has shown some promise in the area of carbon-carbon bond formation by the Mitsunobu protocol.[72] These studies show that a combination of tributylphosphine and the azo reagent 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD) were effective for the deprotonation of activated methylene substrates with p*K*a values above the generally accepted range for nucleophiles in this transformation (Scheme 46). Thus, diethyl malonate and two α-activated sulfone nucleophiles were found to undergo C-alkylation under the Mitsunobu conditions to provide a variety of primary and secondary products with minimal loss of optical activity.

Scheme 46



Some of the examples shown for this method were further elaborated to show the synthetic utility of the requisite functional groups. In this case, the α-cyano sulfone product from the coupling reaction with (*2S*)-2-octanol was desulfurized to provide the nitrile required for the formal synthesis of the red flour beetle pheremone (Scheme 47). Likewise, the α–sulfonyl thioether coupling product was elaborated to the alcohol necessary for the synthesis of the saw fly sex pheremone.

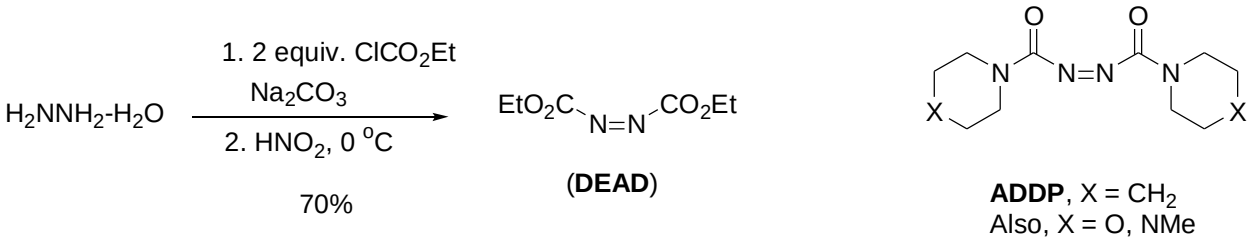
Scheme 47



IX. Alternative Reagents – Azodicarbonyl Portion

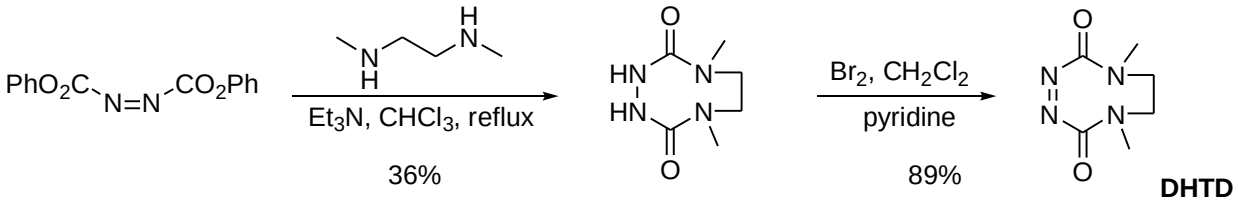
Some mention should be given to the availability of reagents for the Mitsunobu chemistry, and to highlight some of the advances toward higher efficiency in the reaction protocol. Both DEAD and DIAD are readily available from the usual reagent vendors, although they can be made easily from hydrazine by bis-carboalkoxylation followed by oxidation (Scheme 48).[73] Any excess DEAD and corresponding byproduct hydrazine (see Scheme 2) from the Mitsunobu reaction is usually easily removed from the product mixture by a chromatographic separation. Tsunoda and coworkers have recently shown that 1,1'-(azodicarbonyl)dipiperidine (ADDP) is a useful alternative azodicarbonyl equivalent, which can be readily filtered off from the reaction mixture (along with the corresponding hydrazine byproduct) after dilution of the completed reaction mixture with hexanes.[74] This reagent is also commercially available but at a higher cost. Some other diazocarbonyl equivalents derived from morpholine and *N*-methylpiperazine have also been reported.[5]

Scheme 48



Tsunoda's reagent 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD), used for carbon-carbon bond forming reactions as described in Scheme 47, is easily prepared in two steps and in a somewhat moderate overall yield (Scheme 49).[72]

Scheme 49

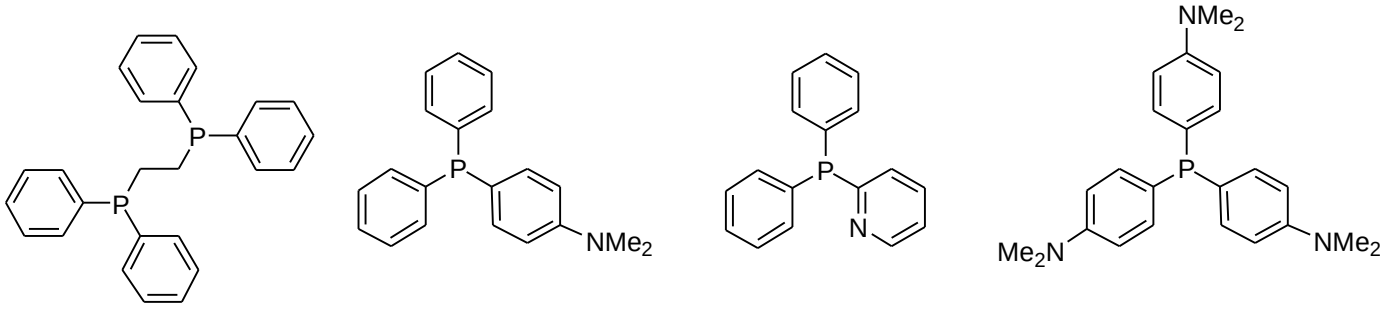


X. Alternative Reagents – Trisubstituted Phosphine Portion

Removal of the byproduct triphenylphosphine oxide (see Scheme 2), as well as excess triphenylphosphine, has been the single most problematic facet of Mitsunobu chemistry. In some cases, the byproduct may be filtered from the reaction mixture, but often the byproducts must be removed by a chromatographic separation. Some research groups have found the use of tributylphosphine to be a useful improvement for this method with little or no effect on the reaction yield.[75] In this case, the byproduct tributylphosphine oxide is water soluble and may be largely removed by an aqueous workup. Excess tributylphosphine is volatile and is usually removed during removal of the reaction solvent.

Other methods have been developed to increase the ease of workup of Mitsunobu chemistry, and a great deal of effort has been put toward the development of triarylphosphines. Modification of the phosphine portion has allowed for reagents that are easily removed from the completed reaction mixture, along with the corresponding phosphine oxide byproducts (Scheme 50).

Scheme 50



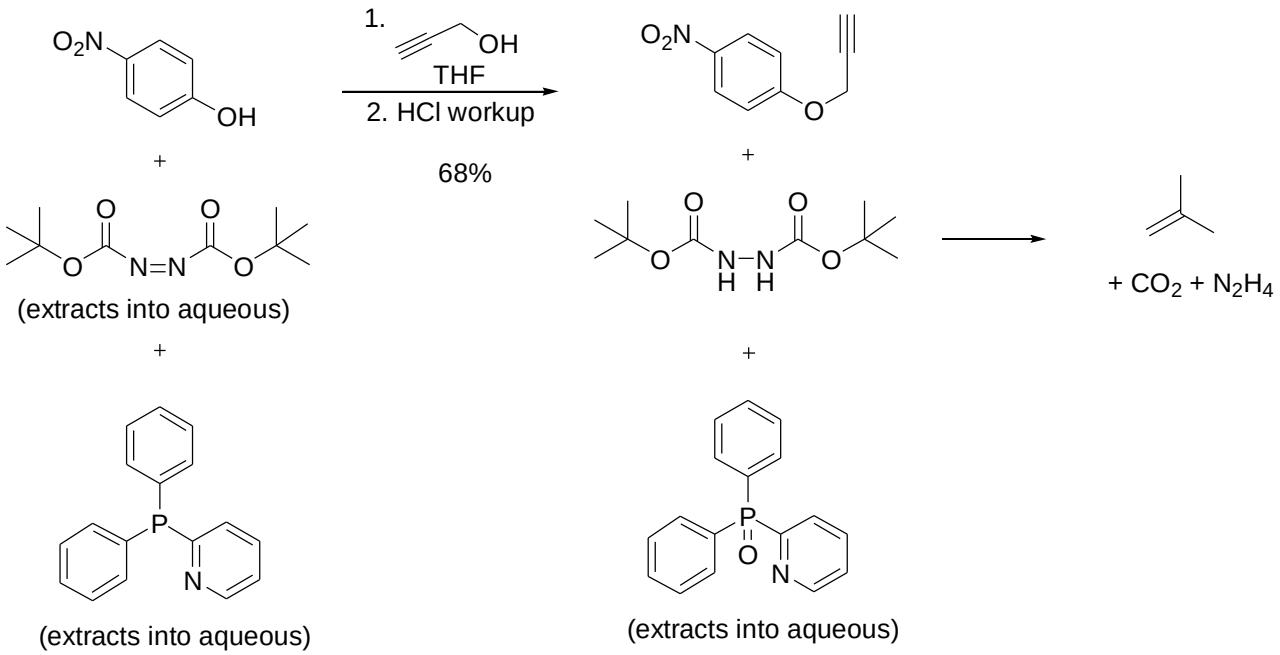
DPPE **DAP-DP** **Ph_2P-Py** **Tris-DAP**

O'Neil and coworkers have shown that 1,2-bis(diphenylphosphino)ethane (DPPE) is a convenient replacement for triphenylphosphine in the Mitsunobu reaction.[76] Due to the greater polarity of the resulting bis-phosphine oxide byproduct, this component is usually insoluble to the point at which

it can be easily removed from the reaction mixture by a simple filtration prior to workup and purification. Other phosphine equivalents include (*p*-dimethylaminophenyl)-diphenylphosphine (DAP-DP),[77] diphenyl(2-pyridyl)phosphine (Ph_2P-Py)[78] and tris(dimethylamino)phosphine (tris-DAP).[79]

A very recent example from Neurocrine Biosciences chemists Kiankarimi and coworkers have shown that the use of a diphenyl(2-pyridyl)phosphine and the acid labile di-*tert*-butyl azodicarboxylate are very convenient reagents for the Mitsunobu reaction (Scheme 51).[80] The advantage to these materials, as well as for the respective byproducts, is that they are either

Scheme 51



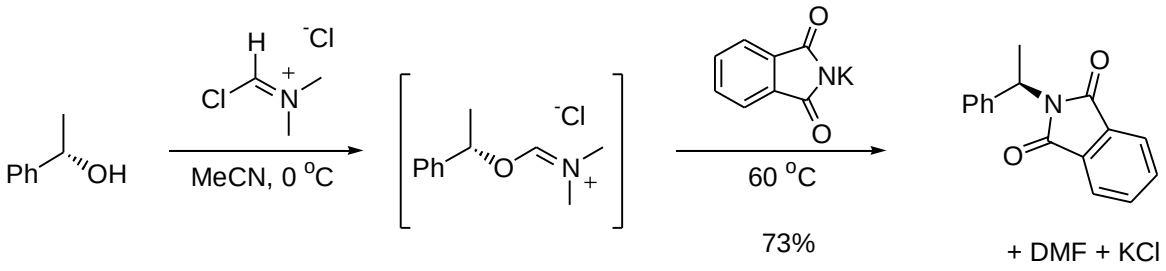
directly soluble in aqueous acid or are converted to gaseous byproducts and water soluble materials upon treatment with acid. In a typical experimental procedure, the completed reaction mixture is worked up by adding 4 M HCl in dioxane to ensure complete decomposition of the azodicarboxylate products followed by an aqueous acid wash. In most cases, the crude product residue did not require any further purification, or was obtained after a filtration through a short plug of silica gel. This modification should be useful in large scale process chemistry where the removal of the reagents in an efficient manner is crucial to timely throughput.

XI. Some Alternatives to Mitsunobu Chemistry

Valuable alternative methods to the Mitsunobu protocol have recently appeared. Barrett and coworkers utilized the Vilsmeier reagent, (chloromethylene)dimethylammonium chloride (generated in situ from DMF and oxalyl chloride) to activate secondary alcohols. The intermediate imidate salt is displaced by a nucleophile to generate amines with inversion of

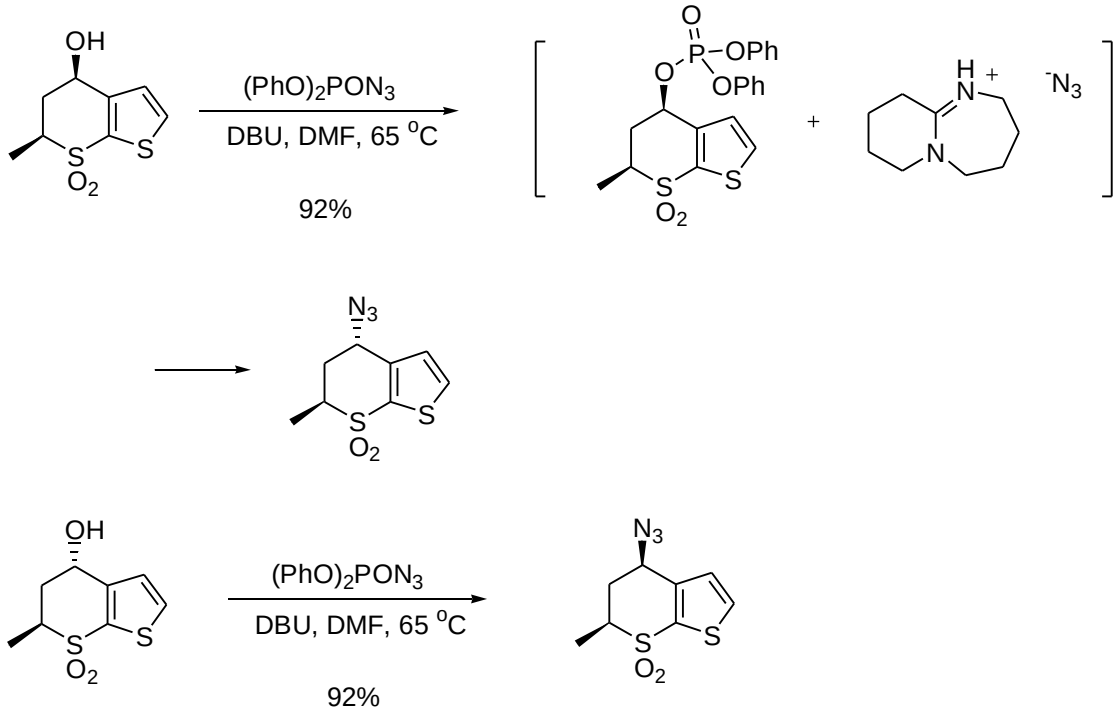
stereochemistry (Scheme 52).[81] The side products include regenerated DMF and potassium chloride. This method has also been extended to the preparation of esters from alcohols,[82] and an intramolecular reaction to provide dihydrobenzopyrans has been reported.[83]

Scheme 52



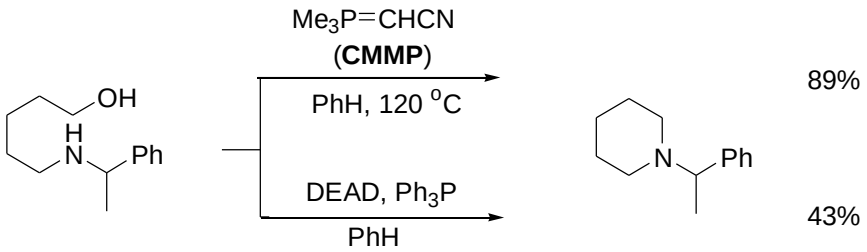
Merck chemists Thompson and Grabowski utilized DPPA with DBU to prepare azides from secondary benzylic alcohols (Scheme 53).[84] With Mitsunobu chemistry, benzylic substrates may undergo an erosion of enantiomeric purity due to the formation of benzyl cation intermediates. The use of this reagent mixture not only suppresses the S_N1 chemistry, but allows for removal of excess reagents and byproducts by an aqueous workup and a quick filtration through a plug of silica gel. In this case, the cyclic sulfone underwent displacement to provide the azide in good yield. As a control experiment, the sulfone bearing a secondary alcohol of the opposite stereochemistry was subjected to the reaction conditions providing the epimeric azide in equally good yield. These azides prove to be key intermediates in the Merck carbonic anhydrase inhibitor program.

Scheme 53



Finally, the work by Tsunoda and coworkers has shown that the use of cyanomethylenetrimethylphosphorane (CMMP) and cyanomethylenetributylphosphorane (CMBP) provided a useful variant to the Mitsunobu reaction (Scheme 54).[72,85] This method proceeds by an intermediate phosphorane which is able to deprotonate nucleophiles that are harder to ionize than are generally tolerated as Mitsunobu nucleophiles (p*K*a greater than 13). One drawback of this method is that the reactions must usually be performed well above the boiling temperature of the reaction solvent requiring resealable reaction vessels. In this case, a piperidine formation was shown to proceed in better yield than with the usual Mitsunobu betaine reagent.

Scheme 54



XII. Appendix of Abbreviations & Acronyms

PNBA – *p*-Nitrobenzoic Acid

DPPA – diphenylphosphoryl azide

DEAD – Diethyl Azodicarboxylate

DIAD – Diisopropyl Azodicarboxylate

DMAD – Dimethyl Azodicarboxylate

ADDP – 1,1'-(Azodicarbonyl)dipiperidine

TMAD – *N*,*N*,*N'*,*N'*-Tetramethylazocarboxamide

DHTD – 4,7-Dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione

DAP-DP – (*p*-Dimethylaminophenyl)diphenylphosphine

DPPE – 1,2-Bis(diphenylphosphino)ethane

Ph_2P-Py – Diphenyl(2-pyridyl)phosphine

tris-DAP – tris(dimethylamino)phosphine

CMMP – Cyanomethyltrimethylphosphorane

CMBP – Cyanomethyltributylphorphorane

Acknowledgment

This Author would like to thank Dr. Larry Yet for his invaluable editorial suggestions and insightful input on the content of this Review.

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