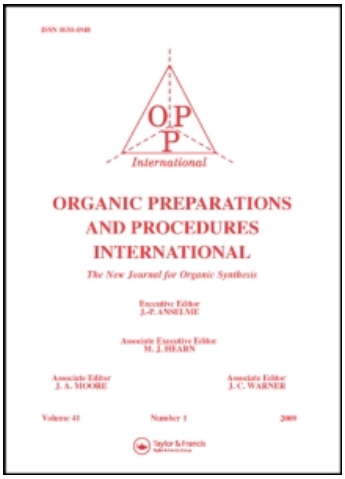

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PROGRESS IN THE MITSUNOBU REACTION. A REVIEW

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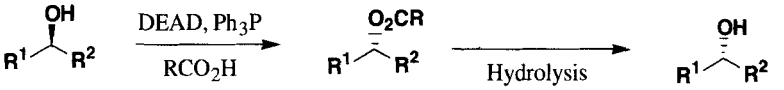
INTRODUCTION

In 1967 Mitsunobu and Yamada reported that carboxylic acids could be esterified with primary and secondary alcohols using the redox system diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP).[1] Four years later Mitsunobu and Eguchi demonstrated that the reaction with optically pure secondary alcohols proceeded with complete inversion of stereochemistry, meaning that the reaction could be used to invert the stereochemistry of optically active alcohols via an esterification/hydrolysis procedure (Eq. 1).[2] During the 1970's the Mitsunobu group and others expanded the



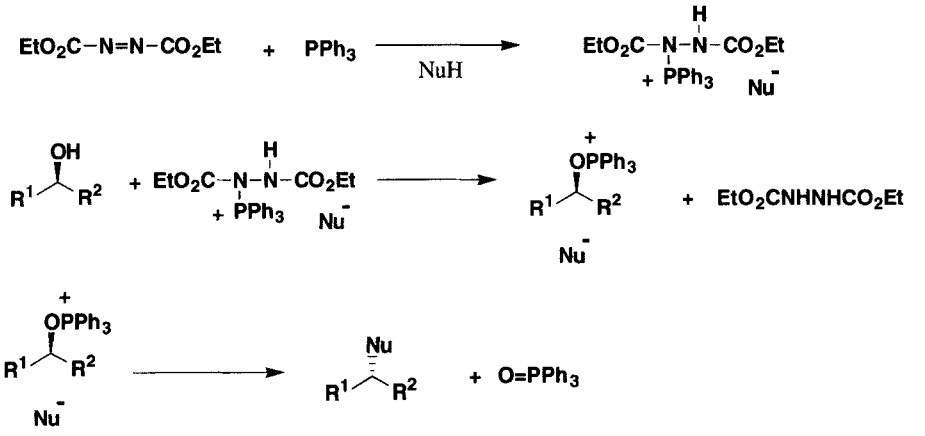
(1)

use of the DEAD/TPP/alcohol system to reactions involving acidic components other than carboxylic acids, including imides, heterocycles, carbon acids, phenols and inorganic nucleophiles such as azide, cyanide and halides. The reaction was reviewed by Mitsunobu in 1981,[3] and since then its use in organic synthesis has mushroomed, as evidenced by more than 2000 citations of the Mitsunobu papers. The clean stereochemical inversion, the compatibility of the reaction conditions with a wide range of functional groups and the simplicity of the experimental protocol are primary reasons for the popularity the reaction has enjoyed. Although the reaction was discovered almost three decades ago, new applications are still being found and the reaction has become one of the most versatile available in organic chemistry. A review of the Mitsunobu chemistry was published in 1992 and covered literature up to early 1990.[4] This review provides an update of significant advances since that time.

I. MECHANISM

The generalized 3-step mechanism of the Mitsunobu reaction is shown in Scheme I for reaction of a nucleophile (NuH) with a chiral secondary alcohol. In the first step, triphenylphosphine rapidly reacts with diethyl azodicarboxylate (DEAD) to form the zwitterionic P-N adduct, which is protonated in the presence of NuH to form the phosphonium salt. In the alcohol activation step, the phosphorus group is transferred to the alcohol to form the oxyphosphonium salt and the reduced hydrazine by-product. Finally, the deprotonated nucleophile reacts with the oxyphosphonium salt in an S_N2 reaction to provide the inverted product and triphenylphosphine oxide. The many mechanistic nuances associated with each step are outside the scope of the present review and are discussed in references 4 and 5. Other mechanistic complexities will be discussed in the following sections as they

apply to the synthetic transformation under discussion.



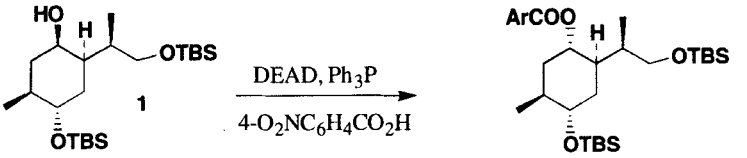
Scheme 1

II. CARBON-OXYGEN BOND FORMATION

1. Esters

A. Effect of the Carboxylic Acid.

Formation of inverted esters from chiral secondary alcohols is the largest use of the Mitsunobu reaction, accounting for nearly half of the applications of the reaction reported in the literature. For many substrates, the acid component is not critical and good yields can be obtained with the conventional acids such as acetic and benzoic acids. For sterically hindered alcohols, however, yields are often low with these acids and Martin and Dodge have found that yields of hindered alcohols are increased if 4-nitrobenzoic acid is used.[6] For example, the alcohol **1** gave a 27% yield of inverted ester with benzoic acid, but an 86% yield with 4-nitrobenzoic acid (Eq. 2). Similar yield improvements were noted with seven other secondary alcohols having substitution on the α-carbon.[6]

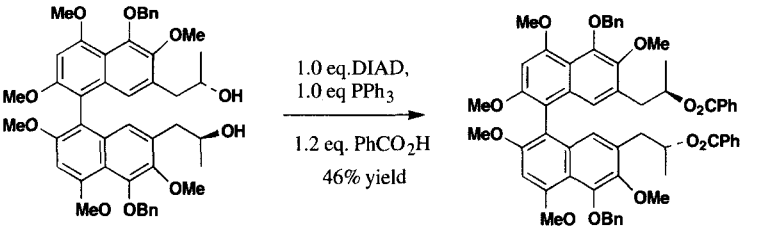


(2)

Bessodes and co-workers discovered that chloroacetic acid is also effective for esterification of sterically congested alcohols that have generally given low yields under the standard Mitsunobu conditions.[7] For example, the C-3 secondary alcohol of diacetone glucose under standard Mitsunobu conditions with benzoic acid results in esterification with retention of configuration, which presumably is caused by activation of benzoic acid with Ph_3P to form $PhCO_2PPh_3^+$, which then acylates the alcohol. With chloroacetic acid esterification proceeds with inversion and a yield of 67%. Bessodes provides four other examples where yields are improved by use of chloroacetic acid and a few other examples have since been reported.[8]

Dodge has systematically studied the effect of acid strength on yields of inverted esters of menthol.[9] In the series of acetic, chloroacetic and dichloroacetic acids, no reaction occurred with acetic acid and dichloroacetic acid gave only ester with retention of configuration; however, chloroacetic acid provided 60% of the inverted ester. With a series of benzoic acids, yields in the 60-83% range were observed with the most acidic (4-nitro, 3-nitro, 4-cyano, 4-methanesulfonyl) acids, while yields in the 20% range were obtained with the least acidic (H, 4-MeO, 4-Me, 4-F) acids. A large solvent effect was also noted in the reactions with 4-nitrobenzoic acid in that acetonitrile and dichloromethane gave yields under 5%, while benzene and THF gave yields near 80%. The rationale for these results is not clear. Camp and Jenkins[5a] have shown that the oxyphosphonium salt on the reaction pathway is favored over the phosphorane when progressively stronger acids are used, which could enhance the nucleophilic displacement reaction leading to product over side reactions which destroy the reagents.

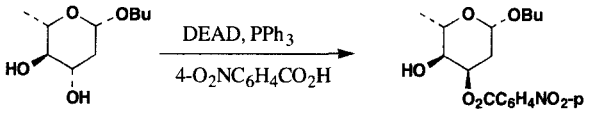
The failure or low yields obtained with sterically hindered alcohols is probably due to incomplete formation of the activated alcohol, $ROPPh_3^+$. Subjecting 1,1'-binaphthalenediol to standard Mitsunobu conditions at 25° provided only the mono-inverted ester, presumably due to steric congestion which prevented activation of the second alcohol (Eq. 3).[10] Since it has been shown that reducing the amount of excess acid present accelerates formation of the oxyphosphonium salt[5b] the ratio of benzoic acid to PPh_3 and diisopropylazodicarboxylate (DIAD) was adjusted to 1.2:1:1 and the reaction was run at -23°. Under these conditions the diester could be isolated in 46% yield.



(3)

B. Selectivity in Polyhydroxyl Compounds.

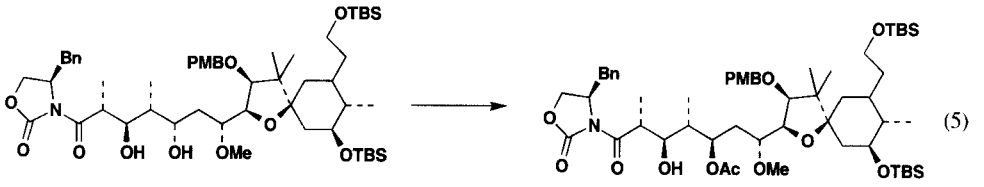
Selective esterification of diol **2** was accomplished using the conditions of Martin and Dodge,[6] resulting in esterifiction of only the least hindered secondary alcohol (Eq. 4).[11]



2

(4)

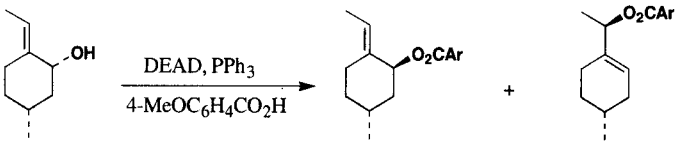
Likewise, in the synthesis of (+)-calyculin, the least hindered hydroxyl group was selectively inverted in 72% yield using di-tert-butyl azodicarboxylate, PPh_3 and acetic acid in benzene (Eq. 5).[12]



(5)

C. S_N2' Reactions

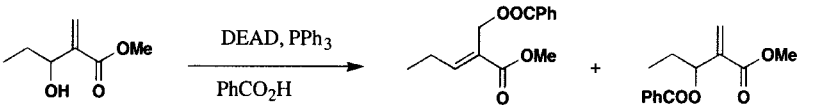
Allylic alcohols generally react in normal S_N2 fashion, but on occasion the S_N2' pathway predominates. Allylic alcohols with the double bond *exo* to a ring are particularly prone to S_N2' attack, as shown in the work of Burke[13] and Koreeda[14], shown in Eq. 6.



(6)

1 : 1.2

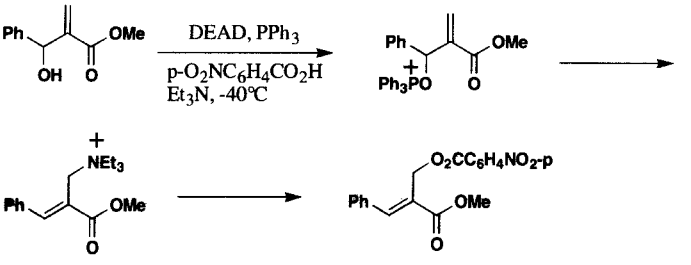
With an ester at the β-position, the Michael acceptor nature of the allylic alcohol now promotes predominant S_N2' attack (Eq. 7).[15a] The hindered acid, 2,4,6-trimethylbenzoic acid, gave the most S_N2' product at >50:1 ratio, while the most acidic acid tried, 4-nitrobenzoic acid, gave only a 10:1 ratio under the same conditions.



(7a)

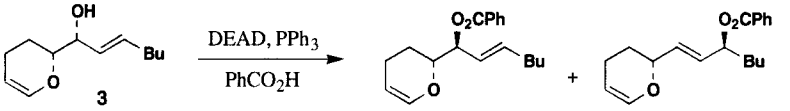
Major

With the phenyl substituted derivatives the Mitsunobu products were obtained in low yield with an $S_N2':S_N2$ ratio of only 2:1. Addition of a stiochiometric amount of triethylamine resulted in >80% yields with an improved $S_N2':S_N2$ ratio of 11:1. The authors postulate that triethylamine reacts initially in an S_N2' fashion to form the ammonium salt, which is then displaced by an S_N2 reaction with the carboxylate as nucleophile (Eq. 7b).[15b]



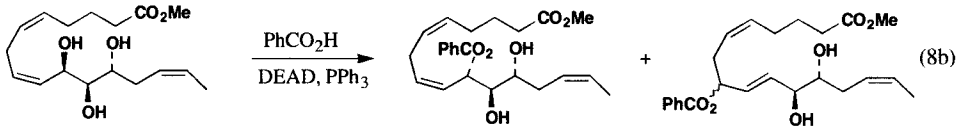
(7b)

Steric hindrance can also cause the S_N2' pathway to become viable, as the allylic alcohol **3** flanked with a large group adjacent to the alcohol reacted to give an equal mixture of S_N2 and S_N2' products (Eq. 8a).[16a] While both S_N2' isomers could be formed by attack at either face of the vinyl group, only the isomer shown was formed, which arises from attack opposite to the face of the phosphonium ion leaving group.

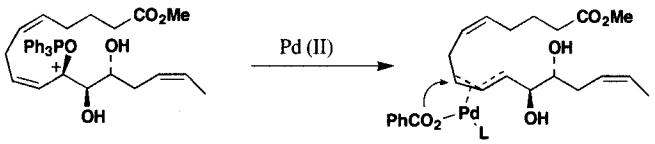


(8a)

The ratio of S_N2 and S_N2' products can also be influenced by the addition of a palladium complex. Mitsunobu reaction of the triol shown in Eq. 8b affords an equal mixture of the S_N2 and S_N2' benzoate products, with a 4:1 α:β ratio in the S_N2' product. However, Mitsunobu reaction in the presence of 10 mol % of freshly prepared $PdCl_2(MeCN)_2$ resulted in nearly exclusive formation of the S_N2' isomer in 73% yield with an α:β ratio of 10:1. A mechanistic rationale involves formation of a π-allyl palladium complex from the oxyphosphonium intermediate followed by *cis*-transfer of the coordinated benzoate to generate the major diastereomer (Eq. 8c).[16b]



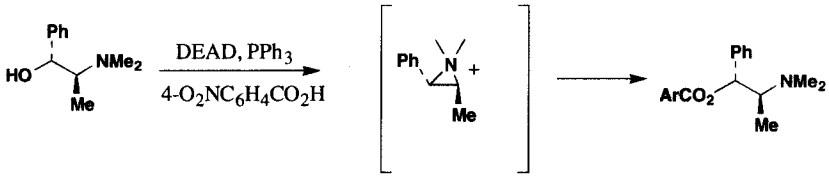
(8b)



(8c)

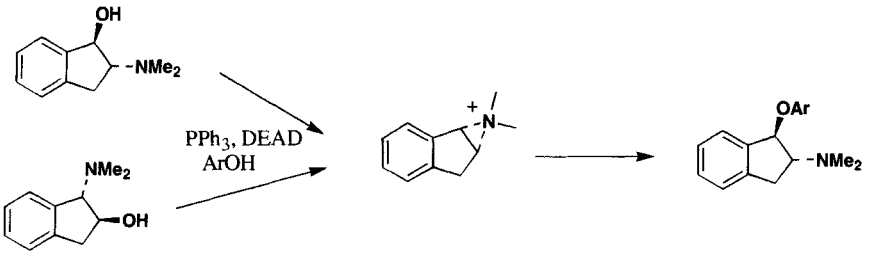
D. 1,2-Amino Alcohols and Related Compounds

N-Alkylephedrine derivatives react under Mitsunobu conditions with carboxylic acids, thiols and phthalimide to give retention of configuration at the reacting carbon.[17] The reaction proceeds through intermediate aziridinium ions, which cannot be isolated; thus, the overall reaction is a double inversion (Eq. 9).



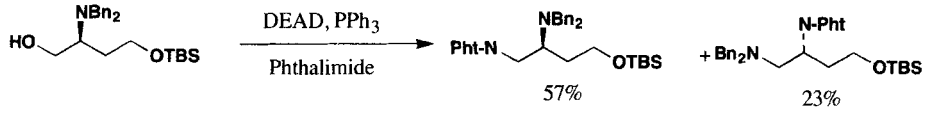
(9)

Similar behavior was observed for the indan amino alcohols in the Mitsunobu reaction with phenols. The *cis* amino alcohols produced the expected inverted *trans* product, but the *trans* alcohols reacted with retention of configuration . The *trans* regioisomer also reacted to give the same product, which is strong evidence for the intermediacy of the aziridinium ion, which reacts preferentially at the benzylic position (Eq. 10).[18]



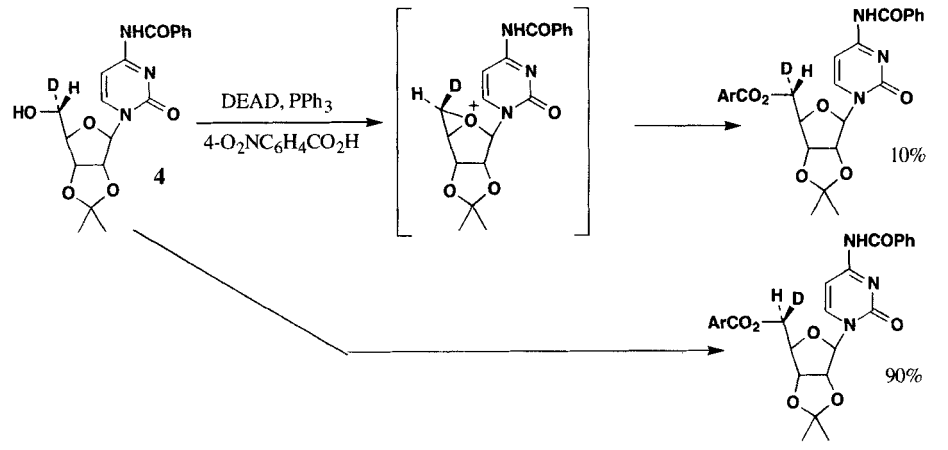
(10)

When there is no benzylic activation, a mixture of regioisomers occurs from reaction of the nucleophile at either carbon of the aziridinium ion. In the example shown in Eq. 11, the primary product is favored over the secondary product by 2.5-fold.[19]



(11)

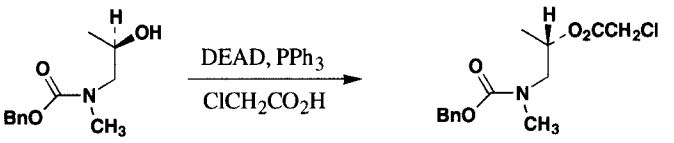
A similar explanation has been used to rationalize the partial loss of stereochemical integrity when the tetrahydrofuran derivative **4** was inverted using 4-nitrobenzoic acid. Although starting with diasteoropure **4**, the product had only 80% de, apparently due to formation of the oxonium ion intermediate (Eq. 12).[20a]



(12)

When the amine of an amino alcohol is protected as a carbobenzyloxy group, no intermediate aziridinium ion or oxazoline is formed, so clean inversion of stereochemistry is observed for the

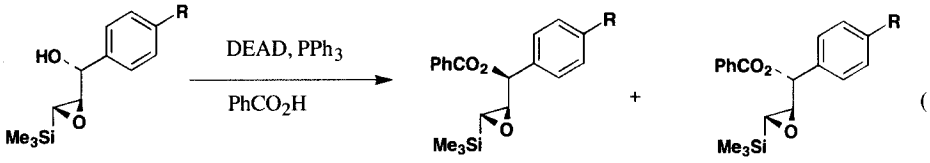
Mitsunobu reaction (Eq. 12b).[20b]



(12b)

E. S_N1-Type Reactions

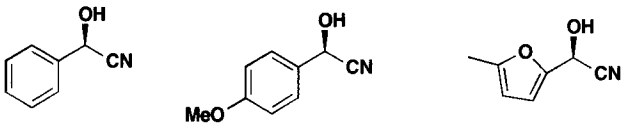
Mitsunobu reactions on benzylic alcohols are prone to esterification with substantial racemization, due to the stability of the incipient carbocation which promotes an S_N1 reaction. In the reactions of the para-substituted benzyl alcohols shown in Eq. 13, the *p*-methoxy alcohol suffers nearly complete racemization while the *p*-pivaloxy and *p*-acetoxy alcohols react with only minimal racemization.[21]



(13)

R = MeO	60	:	40
R = t-BuCO$_2$	96	:	4
R = MeCO$_2$	>98	:	2

Mitsunobu reaction of cyanohydrin **5** with acetic acid or substituted benzoic acids gave clean inversion with minimal racemization. However, cyanohydrin **6** reacted with complete racemization with both acetic acid and 4-nitrobenzoic acids, while cyanohydrin **7** gave product with 60% racemization.[22]

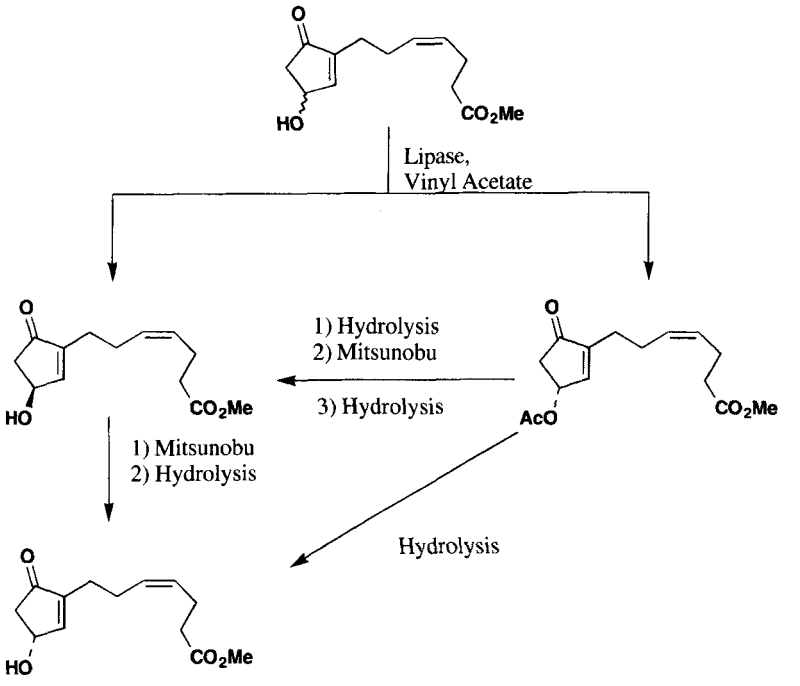


5 **6** **7**

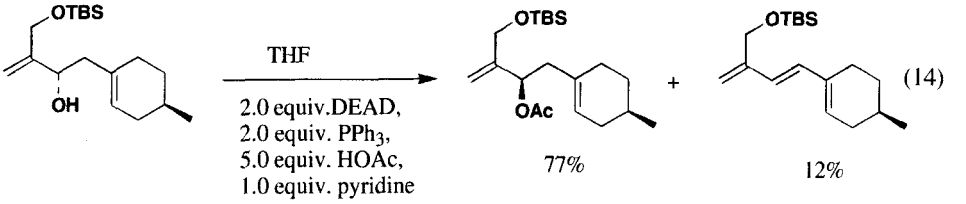
F. Miscellaneous

Enzymatic hydrolysis of racemic esters has become a valuable way of resolving alcohols. The drawback is that often only one enantiomer is desired, so the maximum yield of the desired isomer is only 50%. When a racemic alcohol is esterified enzymatically, the unreacted alcohol can be esterified with inversion by the Mitsunobu protocol to provide a theoretical yield of 100%. Using the enzymatic resolution coupled with the Mitsunobu chemistry, either enantiomer can be accessed in high yield. An example is shown in Scheme 2,[23] and other examples have been described in reference 24.

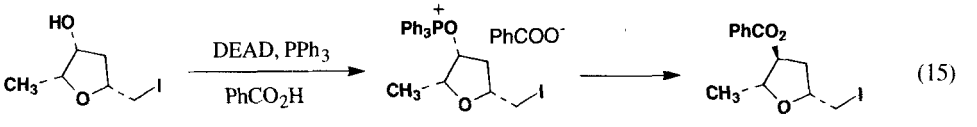
Elimination is often a problem in Mitsunobu reactions, especially when the incipient double bond is conjugated. Wovkulich and coworkers found that conducting the Mitsunobu reaction in the presence of pyridine suppressed the dehydration pathway (Eq. 14).[25]



Scheme 2



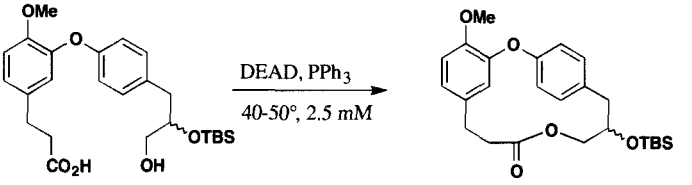
The excellent leaving group ability of the phosphonium ion intermediate formed in Mitsunobu reactions is evidenced by the esterification of secondary alcohols in the presence of primary iodides[26] and tosylates[27] (Eq. 15).



2. Lactones

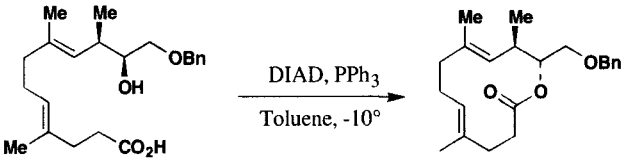
Lactones of nearly all ring sizes have been prepared by Mitsunobu chemistry and proceed with inversion of stereochemistry at the hydroxy carbon just as for intermolecular esterifications. For macrolactonizations, carefully optimized reaction conditions are often required to obtain reasonable yields of the macrocycle with minimal intermolecular products. In the synthesis of combrestatin D-2,

best results were obtained by adding the seco acid into the reaction mixture containing the preformed DEAD/PPh_3 reagent at 40-50° (Eq. 16).[28] The final dilution was 2.5 mM, compared to 0.5 to 1.5 mM used by earlier workers.[29] Using this protocol, no dimer was formed and the lactone was isolated in 81% yield after deprotection.



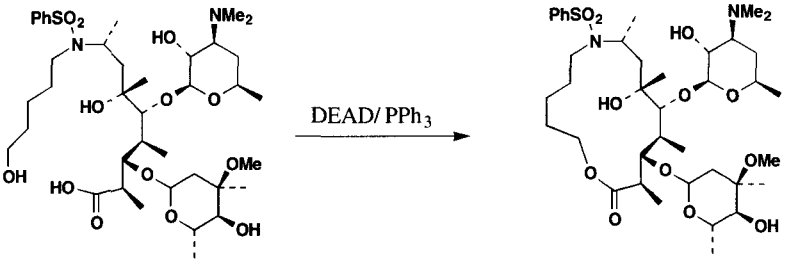
(16)

In the preparation of the polyether antibiotic Lonomycin A, the 12-membered macrocycle was obtained in 95% yield using DIAD/ PPh_3 at -10° for 15 min in toluene (Eq. 17).[30] When DEAD was used instead of DIAD, only the product arising from replacement of the alcohol with the DEAD component was obtained. The reaction in benzene at ambient temperature gave only a 47% yield.



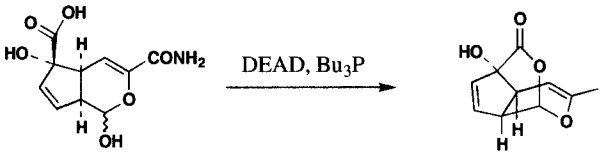
(17)

In the erythromycin-derived azalides, the glycosylated macrocycle was formed in 66% yield using the Mitsunobu reaction without having to protect the hydroxyl groups of the sugars (Eq. 18).[31] The reaction is surprisingly clean considering the lack of rigidity in the seco-acid, which generally results in complications due to intermolecular reactions.



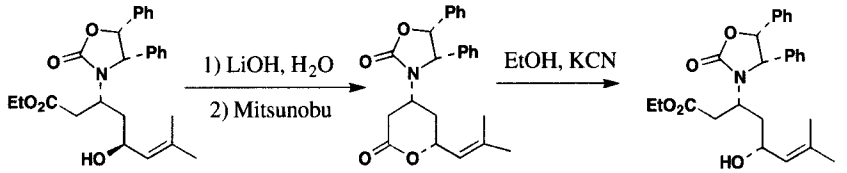
(18)

The highly strained lactone of (-)-echinosporin can be generated via intramolecular lactonization (Eq. 19). After surveying a range of phosphorus reagents and reaction conditions, the best results were obtained by addition of preformed DEAD-PBu_3 complex to a solution of the hydroxy acid at -15° in THF containing molecular sieves. After an overnight age at room temperature, the lactone was obtained in 28-31% yield.[32]



(19)

Attempted Mitsunobu inversion of the hindered allylic alcohol **8** using benzoic acid, 4-nitrobenzoic acid and chloroacetic acid, resulted in low yields of the inverted ester, with substantial loss of stereochemistry and production of sizable amounts of the diene from elimination.[33] These problems were circumvented by hydrolysis of the ester such that an intramolecular esterification could be done. In this case, a 64% yield of inverted lactone was achieved without loss of stereochemical integrity (Eq. 20).



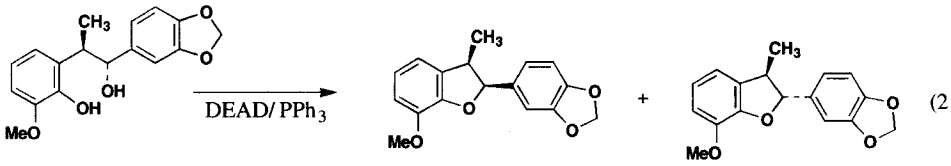
(20)

8

3. Ether Formation

A. Aryl Ethers

Much of the chemistry discussed above for esterification reactions, such as factors affecting a proclivity toward S_N1 or S_N2' reactivity, also applies to ether formation. For example, reaction with chiral benzylic alcohols often leads to racemized products, as shown for the intramolecular reaction in Eq. 21.[34]

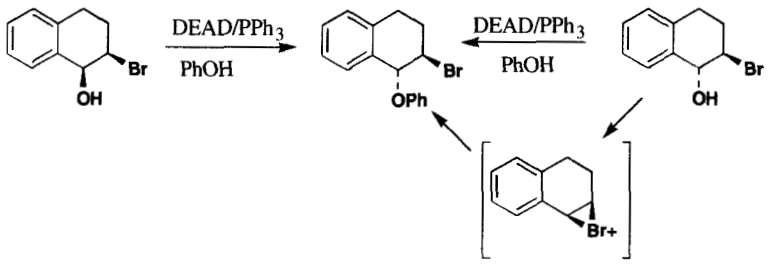


(21)

2:1

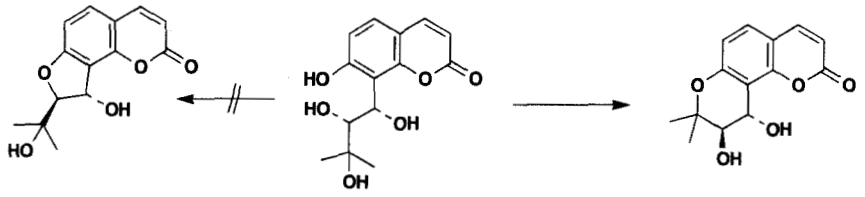
Both *cis* and *trans* isomers of the vicinal bromohydrin provided the *trans* aryl ether on Mitsunobu reaction with phenols. The retention of configuration for the *trans* isomer may be a result of an intermediate bromonium ion (Eq. 22).[35]

Mitsunobu reactions with tertiary alcohols are very rare since S_N2 displacements of tertiary systems are not sterically feasible. However, a handful of intramolecular cases have been reported. The example shown in Eq. 23 is particularly unusual in that two pathways are available, a reaction with a secondary alcohol to form a 5-membered ether or with a tertiary alcohol to form a 6-membered ring, yet only the product from latter pathway was isolated (15% yield).[36] This product is probably



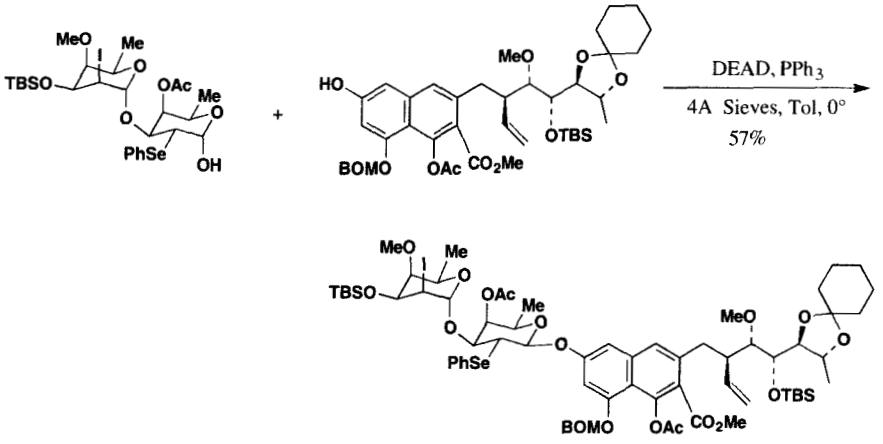
(22)

formed due to the Thorpe-Ingold effect of the gem-dimethyl groups which favors ring formation.[37]



(23)

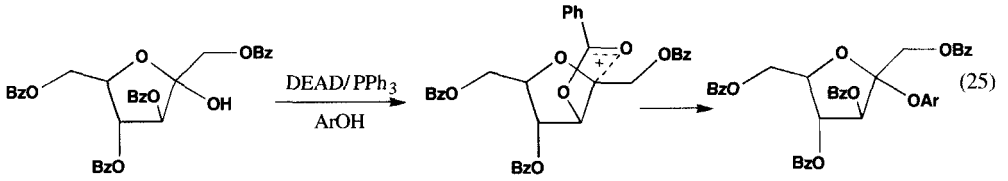
The Mitsunobu reaction has found a niche in the area of glycosidations using phenols. Roush and Lin have found that inversion of configuration occurs in the glycosidation of a range of pyranoses at 0°, which means that the rates of oxyphosphonium ion formation and nucleophilic displacement are faster than anomerization of the substrate.[38] The protocol was used in the preparation of the complex precursor to olivomycin (Eq. 24).[38]



(24)

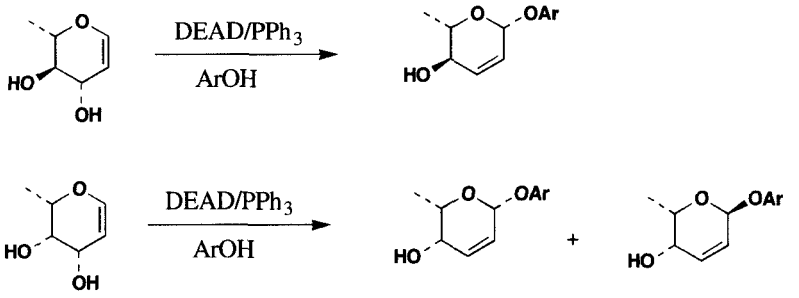
In another study, the glycosidations with a series of phenols and carboxylic acids of varying acidity indicated that the alpha to beta ratios of products were dependent on the pKa of the acid component. The least acidic reactant (pKa 4.8) gave exclusively the beta isomer while the most acidic (pKa 3.4) gave a 7:3 alpha to beta ratio. It was not determined whether this was due to acid-catalyzed anomerization before Mitsunobu reaction or to S_N1-type character in the displacement reaction.[39]

Bouali and coworkers have studied the Mitsunobu reaction of the tertiary alcohol, α-D-fructofuranose. The Mitsunobu reaction with MeOH proceeded smoothly to provide a 1:1 alpha:beta mixture of methyl D-fructofuranoside. The reaction with 2-nitrophenol gave the aryl analog in a 4:1 alpha:beta ratio while 4-nitrophenol reacted to give only the alpha isomer, indicating that retention of configuration predominates in these reactions. The authors propose participation of the benzoyl group to form an acyloxonium intermediate to account for the retention of stereochemistry (Eq. 25). Alternatively, the reaction may be proceeding through an S_N1 mechanism with the alpha isomer being the favored product thermodynamically since the benzoyl group and aryloxy group have a *trans* relationship.[40]



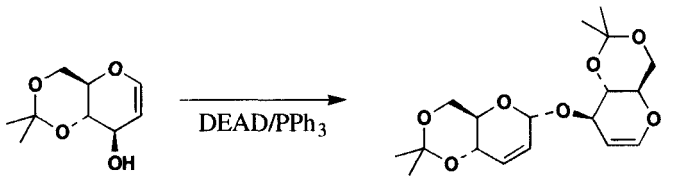
(25)

Glycosides can also be prepared via S_N2' reactions, taking advantage of the tendency of glycals to undergo allylic substitution in preference to direct displacement. In addition, the other hydroxyl groups in the sugars need not be protected. Reaction of either 4-nitrophenol or 4-methoxyphenol with L-rhamnal in the presence of PPh_3/DEAD exclusively provided the alpha isomers in 78-80% yields. In contrast, L-fucal gave a 2:1 mixture of beta: alpha isomers (Eq. 26).[41]



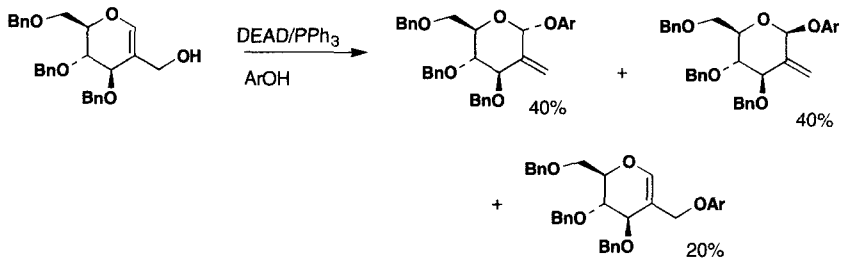
(26)

When the protected glucal is reacted in the absence of a nucleophile, the self-condensation disaccharide product was obtained in 10:1 alpha:beta ratio (Eq. 27).[42]



(27)

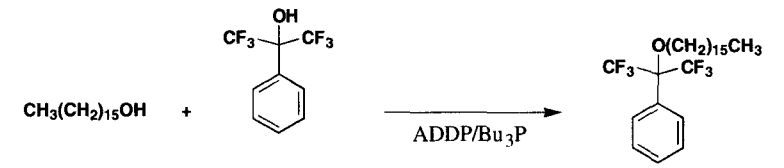
In a similar study, mixtures of S_N2 and S_N2' products were obtained on Mitsunobu reaction of primary allylic glucals. The equal mixtures of anomers in the products indicates the reaction is proceeding via an oxonium intermediate (Eq. 28).[42]



(28)

B. Aliphatic Ethers

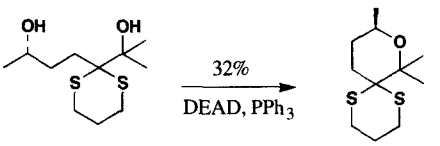
The Mitsunobu reaction generally cannot be used to make aliphatic ethers from two alkyl alcohols since one of the alcohols must act as the acid component and the pKa of alcohols (15-16) are too high to be deprotonated by the hydrazine anion intermediate formed from DEAD and PPh_3. However, Falck has demonstrated that etherifaction of polyfluoroalcohols is successful using the Mitsunobu reaction. Simple primary alcohols reacted with primary, secondary and tertiary fluoroalcohols using tributylphosphine and 1,1'(azodicarbonyl)dipiperidine (ADDP) to provide the ethers in 90-95% yields (Eq. 29). The least acidic primary fluororalcohols such as trifluoroethanol required heating to 65° for best results, due to their relatively low acidity (pKa 11-12). The more acidic secondary and tertiary fluoroalcohols reacted at ambient temperature.[43]



(29)

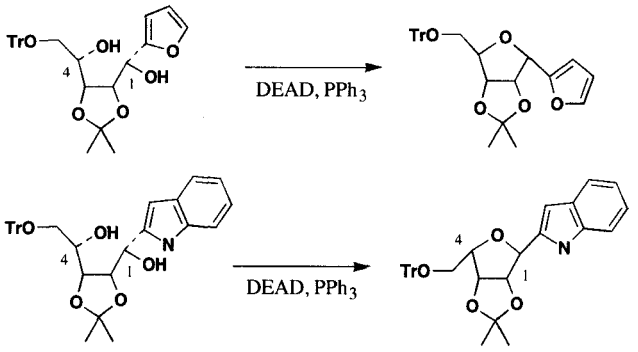
C. Cyclic Ethers

Although intermolecular etherification of two alkyl alcohols is not feasible using the Mitsunobu reaction, intramolecular reactions provide 3- to 7-membered rings. An example of the formation of a 6-membered ring is shown in Eq. 30, where a tertiary alcohol is the nucleophile, displacing the secondary alcohol with 99% inversion of stereochemistry.[44]



(30)

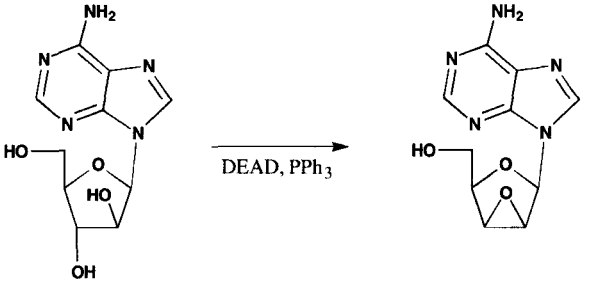
When both alcohols are secondary, it is often not clear which hydroxyl group will be the nucleophile and which the leaving group. Yokoyama and colleagues have prepared a series of ribonucleosides using the intramolecular Mitsunobu etherification to form the tetrahydrofuran ring (Eq. 31). When the heterocycle at position 1 was furyl or thienyl, the oxyphosphonium leaving group was formed at the 1-hydroxyl position and the 4-hydroxyl group was the nucleophile, so that the 1R-diol reacted to produce the alpha-tetrahydrofuran. However, incorporation of a nitrogen heterocycle at the 1-position resulted in oxyphosphonium ion formation at the 4-hydroxyl group, so that the 1R-diol now reacted to



(31)

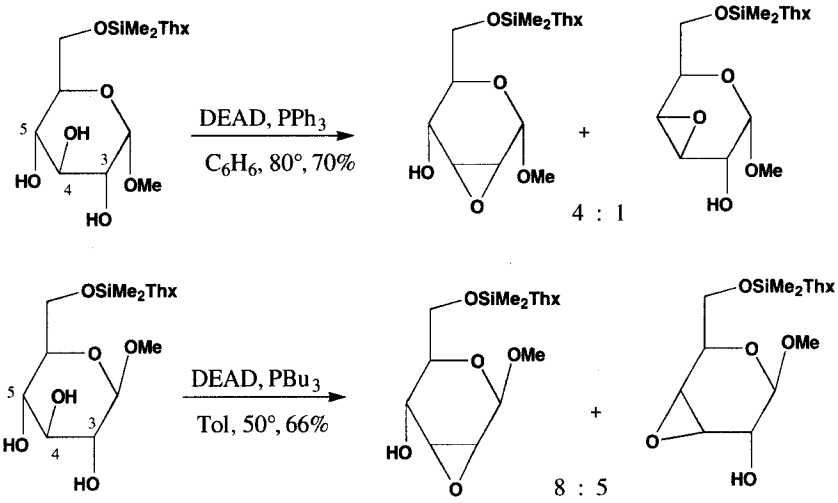
form the beta-tetrahydrofuran. The latter reaction was rationalized by invoking hydrogen bonding between the nitrogen of the heterocycle and the 1-hydroxyl group which inhibited formation of the oxyphosphonium ion at the 1-position. [45]

Similar considerations apply to the formation of epoxides from 1,2-diols. Generally, the least hindered alcohol is the one activated, while the most hindered one acts as the nucleophile. An example is shown in Eq. 32, where the hydroxyl group at the 3-position cannot be readily activated due to the steric crowding of the adjacent adenine moiety. Therefore, the hydroxyl at the 4-position becomes the leaving group, leading exclusively to the regioisomer having the epoxide on the beta face. The primary hydroxyl group is positioned to form a 4-membered ring, but the epoxide is always favored instead of the oxetane, probably because of the proximity of the adjacent hydroxyl which favors epoxide formation.[46]



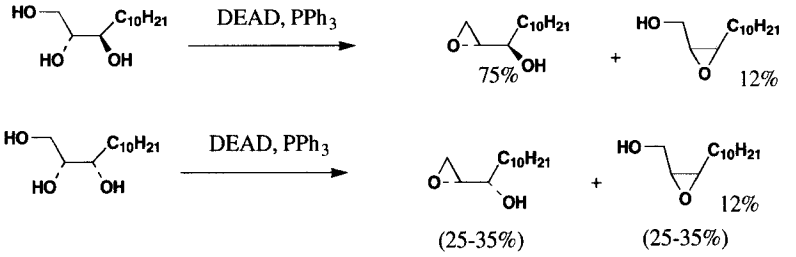
(32)

A mixture of epoxides often arises from 1,2,3-triols. In the example shown in Eq. 33, four epoxides are possible, but only two are formed. The hydroxyl at the 3-position is not activated due to the steric crowding of the adjacent methoxyl group. The major isomer arises from activation of the 4-hydroxyl group and displacement by the 3-hydroxyl group. It is unusual that no epoxide arising from displacement by the 5-hydroxyl is observed. Instead, the minor isomer arises from activation of the 5-hydroxyl position and displacement by the 4-hydroxyl group.[47] In the case where the methoxyl group is on the beta face, only the 4-hydroxyl group is activated and the two regioisomers arise from either displacement by the 3-hydroxyl group or the 5-hydroxyl group. In this case, tributylphosphine was used instead of triphenylphosphine.[47]



(33)

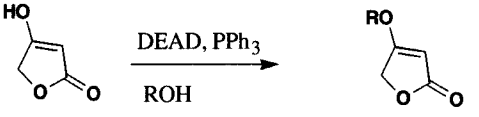
With acyclic 1,2,3-triols, the regiochemistry of the Mitsunobu epoxidation is dependent on the stereochemistry of the triol. As depicted in Eq. 34, the RR-diastereomer gives mainly the epoxide arising from activation of the primary alcohol and displacement by the adjacent hydroxyl. The 2,3-epoxide is formed in 12% yield. With the RS-diastereomer, both the 1,2-epoxide and the 2,3-epoxide are generated in 25-35% yields. The reason for the lower selectivity is not understood, but it was speculated that the 2,3-epoxide might arise from the 1,2-epoxide via Payne rearrangement.[48]



(34)

D. Enol Ethers

Reactions of 1,3-diketones or 1,3-ketoesters under Mitsunobu conditions generally leads to *O*-alkylation with *C*-alkylation being the minor or unobserved product. β-Tetronic acids can be alkylated at oxygen in high yields by a wide variety of alcohols using the Mitsunobu reaction. Only the regioisomer shown in Eq. 35 was isolated.[49]

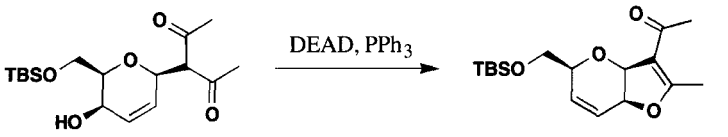


(35)

R = primary or secondary

Bicyclic dihydrofurans are produced from the S_N2' reaction *cis*-4-alkyl cyclohexen-2-ols (Eq. 36). Best yields resulted when tributylphosphine was used instead of triphenylphosphine and the potential

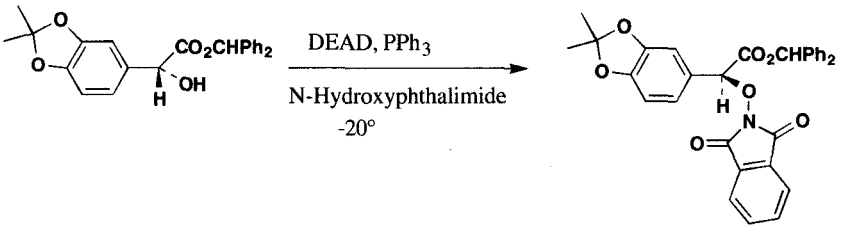
cyclopropane from *C*-alkylation was never observed. Good yields were also obtained with the *trans*-alcohol.[50]



(36)

E. N-Hydroxyphthalimide

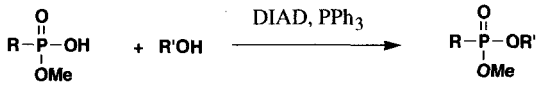
Having an aqueous pKa value of 6.91, N-hydroxyphthalimide readily participates in Mitsunobu reactions. When the reaction shown in Eq. 37 was conducted in ethyl acetate at room temperature, the inverted product was obtained in only 46% yield and 30% ee. However, when the reaction was run at -20° in dry solvent, the yield improved to 95% and the ee was 99.4%.[51]



(37)

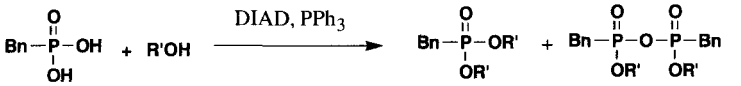
4. Phosphonate Esters

In a new application of the Mitsunobu reaction, Campbell has reported the formation of phosphonate esters from the reaction of alcohols with methyl alkyl phosphonate (Eq. 38).[52] When



(38)

conducted in anhydrous THF at ambient temperature, sterically undemanding alcohols such as ethanol and isopropanol react within 0.5 hr, while more hindered alcohols such as methyl mandelate require 2 hrs to complete. *bis*-Esterification of benzylphosphonic acid was also successful using these conditions (Eq. 39). With primary alcohols the reaction was instantaneous and yields of the diester were 80-90%.

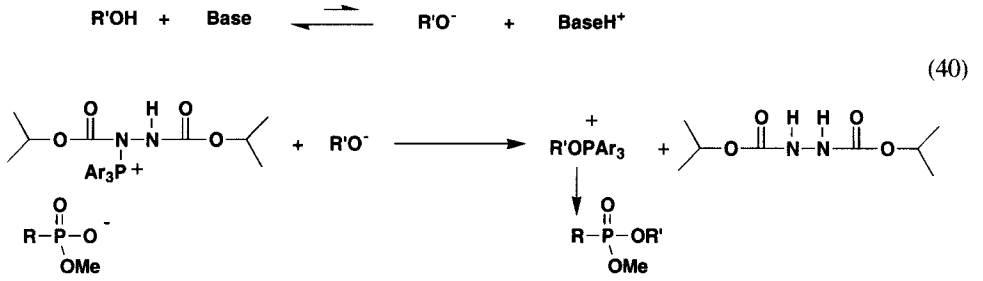


(39)

With 2-propanol the pyrophosphate was the major product when 2.5 equiv. of alcohol was used, but the desired diester could be obtained in 76% yield in the presence of 25 equiv. of alcohol.[52]

In general poor yields resulted when the condensations were conducted under alcohol-limiting conditions, which would be problematic if the alcohol were expensive or difficult to prepare. Two modifications were developed to overcome this problem. First, 5.0 equivalents of triethylamine were added to the reaction. A base is required to convert the alcohol to the oxyphosphonium salt. Usually, this is accomplished by the counterion of the acid used in the reaction, but the phosphonate anion is

too weakly basic to facilitate this reaction (Eq. 40). Addition of triethylamine accelerates the conversion of the alcohol to the oxyphosphonium ion and reduces the reaction time from 72 hrs to 8 hrs. The



other modification was use of the more electrophilic phosphine, tris(4-chlorophenyl)phosphine, which further reduced the reaction time to 0.5 hr.[53] These modifications provide good yields of phosphonate esters even with sterically hindered phosphonic acids and alcohols. In addition, the method is applicable to solid phase synthesis of peptidylphosphonates using an alcohol anchored to a resin and has thus found a use in the preparation of a combinatorial library.[54]

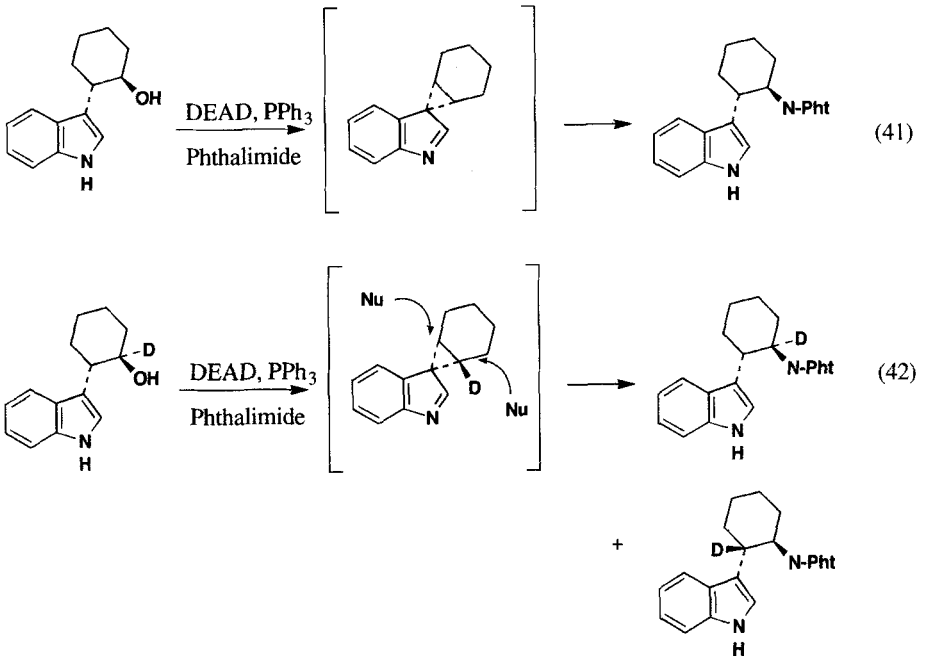
Two groups have used the Mitsunobu reaction for phosphorylation of the primary hydroxyl group at the 5'-position of nucleosides. Saady and coworkers found that anhydrous pyridine was the only solvent that provided adequate yields of the phosphate ester, which may be due to the basicity of pyridine which aids the activation of the alcohol, as discussed above.[55] Farquhar found that the 5'-position of nucleosides could be phosphorylated selectively without protection of the 3'-OH group. These reactions were run in dimethylacetamide at 60° for 5 days, providing the phosphate in 57-59% yield.[56]

III. CARBON-NITROGEN BOND FORMATION

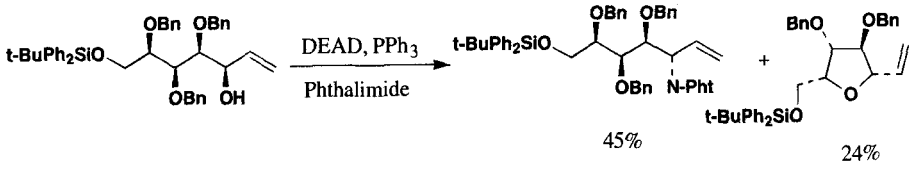
1. Cyclic Imides

The Mitsunobu reaction of alcohols with phthalimide followed by deprotection with hydrazine has found widespread use for the conversion of alcohols to inverted amines. While a majority of these reactions proceed uneventfully to provide the expected inverted product in high yield, a few give products arising from retention, S_N2' reaction, or rearrangements, similar to those discussed above for reactions to form esters and ethers. A few noteworthy examples are discussed below.

In chemistry aimed at preparing serotonin analogs, two groups independently found that a Mitsunobu reaction with phthalimide produced a product arising from retention of stereochemistry (Eq. 41).[57,58] A spiro-cyclopropane was proposed as an intermediate, the opening of which would lead to the observed stereochemistry. The likelihood of the purported intermediate was established by a labelling experiment. Since the spirocyclic intermediate is symmetrical, the ring-fused carbons are identical toward attack of a nucleophile. When the deuterated alcohol was subjected to the reaction, the product had the deuterium label scrambled (about a 1:1 mixture), as expected if the spiro-cyclopropane were an intermediate (Eq. 42).[58]

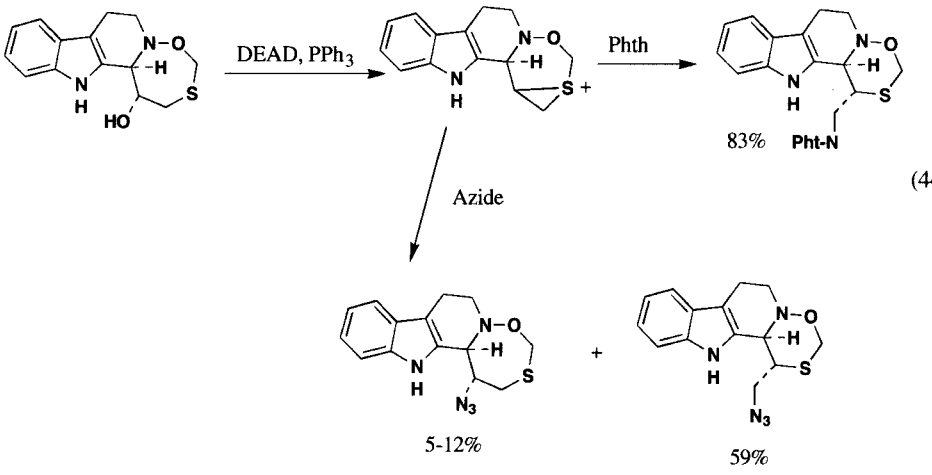


Mitsunobu reaction using phthalimide as nucleophile on alcohols having a γ-benzyl ether results in competitive phthalimide formation and debenzylation with concomitant cyclization to tetrahydrofurans (Eq. 43). The likely mechanism for debenzylation is attack of the phthalimide anion



on the benzyl group, which was supported by isolation of N-benzylphthalimide in 16% yield.[59,60]

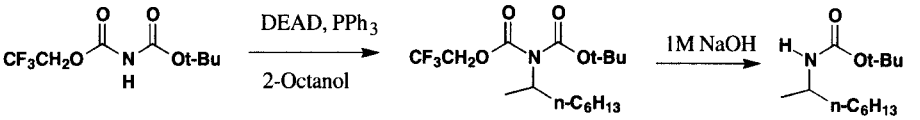
Attempted introduction of nitrogen nucleophiles into the *trans* 1-hydroxy eudistomins via the Mitsunobu condensation resulted in high yields of rearranged products arising via a thiiranium intermediate (Eq. 44). With phthalimide as nucleophile only attack at the secondary carbon to give the 6-membered ring was observed. With azide, 5-10% attack at the tertiary carbon occurred to regenerate the 7-membered ring, with the stereochemistry retained.[61]



(44)

2. Iminodicarbonates

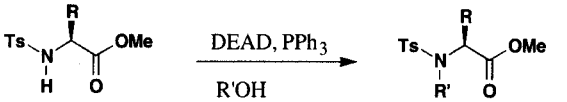
Iminodicarbonates are useful substitutes for phthalimide in Mitsunobu reactions as they can be deprotected under milder conditions than the phthaloyl group. Ragnarsson[62] and Chong[63] noted that the iminodicarbonates having electron-withdrawing groups gave higher yields in the Mitsunobu reaction and also provided more flexibility in deprotection schemes. For example, the trifluoroethyl *t*-butyl iminodicarbonate could be condensed with 2-octanol in 88% yield using DEAD/PPh_3, then deprotected to the BOC-protected amine by mild base hydrolysis (Eq. 45). On the other hand, the di-*t*-butyliminodicarbonate gave only a 40% yield with 2-octanol under the same conditions.[63] A study of acidity of the iminodicarbonates in DMSO and yields in the Mitsunobu reaction with ethyl lactate showed a rough correlation, with the most acidic dicarbonates giving the best yields.[64]



(45)

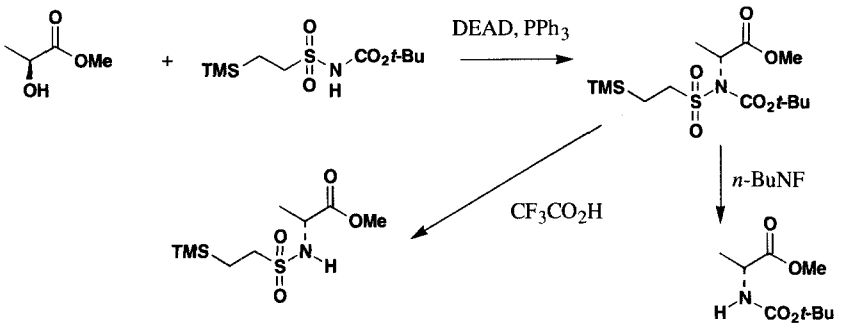
3. Sulfonamides

Aryl sulfonamides, acyl sulfonamides and trifluoromethanesulfonamides undergo condensations with alcohols under Mitsunobu conditions. N-Tosylamino acids and peptides react with simple alcohols to provide the N-alkylated products in good yields with no racemization (Eq. 46).[65]



(46)

2-[(Trimethylsilyl)ethyl]sulfonyl *t*-butoxycarbonylamine (SES-NH-BOC) is a useful amine surrogate for conversion of alcohols to amines, since either the SES group or the BOC group can be selectively removed (Eq. 47).[66]

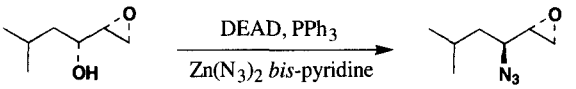


(47)

Trifluoromethanesulfonamides,[67] N-BOC toluenesulfonamides,[68] and sulfamides[69] also react with alcohols under Mitsunobu conditions.

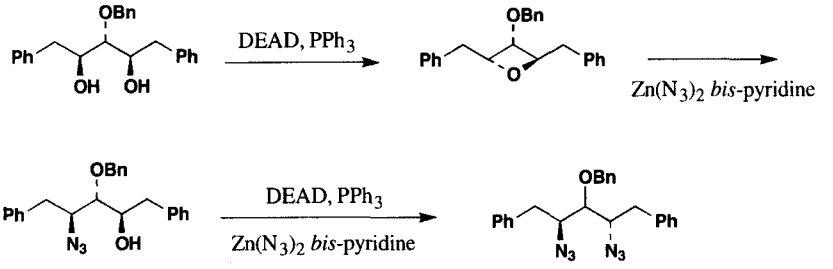
4. Azides

Azides are formed via Mitsunobu reaction of alcohols with either hydrazoic acid or diphenylphosphoryl azide as the nucleophilic component. Rollin has recently reported that *bis*-pyridine complex of zinc azide can also be used as an azide source,[70] and in the reactions of epoxyalcohols, Bessodes and coworkers found that use of hydrazoic acid led to ring opened products while zinc azide provided the inverted azide in high yield (Eq. 48).[71]



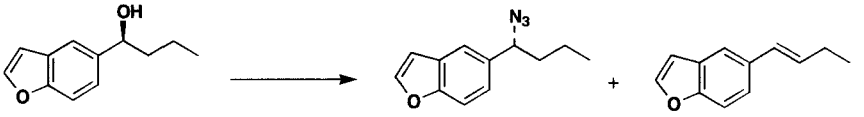
(48)

Reaction of a 1,3-diol with zinc azide results in formation of the *bis*-azide wherein one center has reacted with inversion and the other with retention. This unusual outcome was explained by initial formation of an oxetane ring with inversion, followed by ring-opening to form the azido alcohol, followed by substitution of the remaining alcohol with inversion (Eq. 49).[72]



(49)

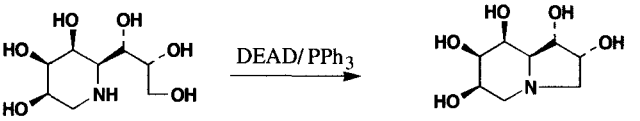
When using diphenyl phosphorazidate (DPPA) as the azide source, DEAD and PPh_3 are not needed for the displacement reaction if a base is added. In this case an intermediate phosphate is formed, characterized by NMR, which is displaced by the resulting azide counterion. For benzylic substrates, this method gave less racemization than the DEAD/PPh_3/DPPA protocol (Eq. 50).[73] The procedure has also been used for displacement of the hydroxyl group in α-hydroxylglycines.[74]



(50)

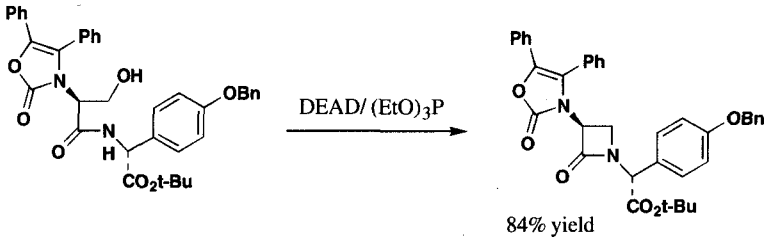
5. Intramolecular Carbon-Nitrogen Bond Formation

While intermolecular reactions of amines with alcohols are rare in Mitsunobu chemistry, intramolecular reactions to form 3- to 6-membered cyclic amines are common.[75] A noteworthy example is shown in Eq. 51, wherein an aminoalcohol containing 6 unprotected hydroxyl groups was selectively reacted with DEAD/PPh_3 in pyridine at 0° to form the fused pyrrolidine in 85% yield.[76]



(51)

Hydroxy amides and related compounds can also be cyclized under Mitsunobu conditions to form lactams. Miller has made extensive use of the reaction to form beta-lactams, as reviewed in 1986.[77] Mitsunobu lactamization of a derivatized serine was a key step in Townsend's syntheses of a family of Norcardicins (Eq. 52).[78] Protection of the amino group was essential to prevent competing

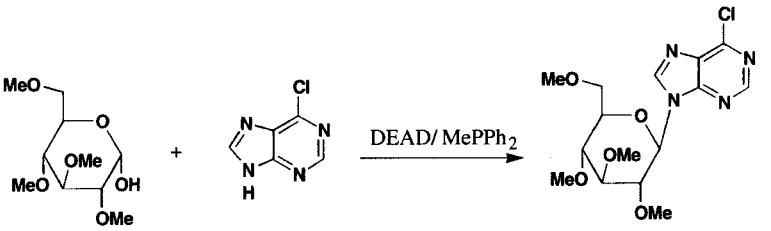


(52)

formation of an aziridine, yet the protecting group selected had to be removable under mild conditions to prevent racemization of the C-5 center. The 4,5-diphenyl-4-oxazlin-2-one group proved to be satisfactory. Preventing racemization of the C-5 center under the Mitsunobu cyclodehydration was accomplished using triethylphosphite instead of triphenylphosphine and using the *t*-butyl group to protect the carboxyl group. The oxazolinone was then be removed by hydrogenation.

6. Formation of Nucleosides

Mitsunobu reaction of the nucleoside bases purine, uracil, guanine and thymine with sugar alcohols provides a way to make nucleosides (Eq. 53).[79] With the interest in the anitviral activity of the related carbocycles, the reaction has been used extensively in the past 5 years to make a variety of carbocyclic nucleosides. The chart below shows a representative example of the range of carbocycles used to prepare these nucleoside derivatives. The most common bases used are 6-chloropurine and 2-amino-6-chloropurine, which can be used without protection. In most cases, only the N-9 isomer was



(53)

isolated, while clean stereochemical inversion at the reacting carbon of the cyclopentanol was always observed. To improve the regioselectivity for the N-9 position vs. the N-7 position, Samuelsson and coworkers preformed the DEAD/PPh_3 complex at -78°, added the alcohol and purine cold, then warmed to 0° overnight.[80] Benner's group has also reported improved results by cold preformation of the DEAD/PPh_3 complex.[81]

The notion that exclusive N-9 alkylation occurs with purines has been challenged by a group of Japanese workers. Using benzyl alcohol, ethanol and 1-hydroxy-3-*t*-butyldimethylsiloxy-cyclopent-4-ene, this group found that 11-25% N-7 isomer was formed with the reaction of 6-chloro-purine in THF.[93] A further study using benzyl alcohol with 6-F, 6-I, 6-, 2,6-Cl_2 and 2-I-6-Cl purines

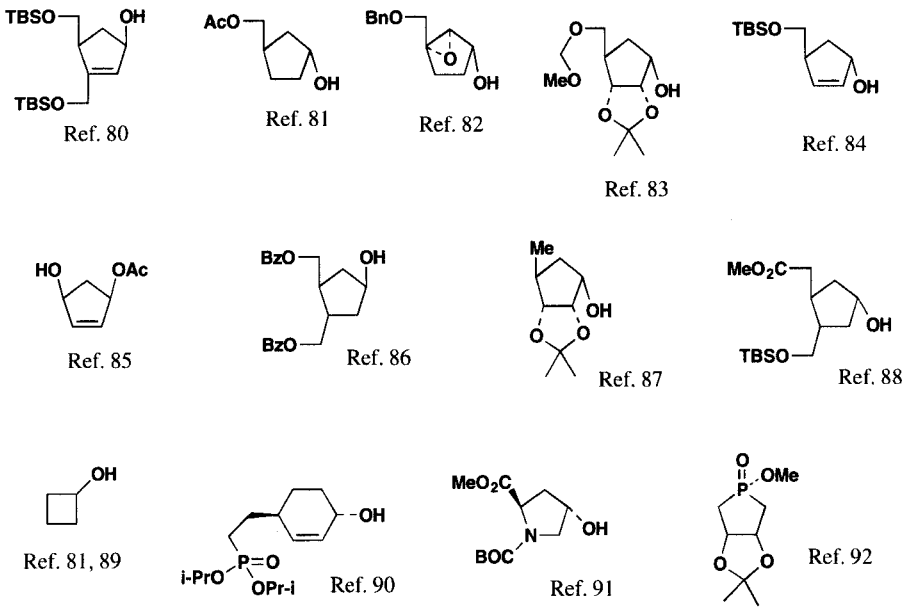


Chart 1

showed that the N-7 isomer was formed in 9-26% yield while the yield of the desired N-9 isomer was 64-85%. The 6-azido isomer formed the N-7 product in 69% yield with the N-9 isomer in only 24% yield. The 6-dimethylamino derivative also produced the N-3 isomer in 36% yield along with 64% of the N-9 isomer.[94] Reactions with variously substituted cyclopentanols provided the N-7 isomer in 48-87% yield, the N-9 isomer in 3-12% yield and the N-3 isomer in 0-10% yield. Thus, the regiochem-

istry is dependent on the structure of the alcohol plus the substitution pattern on the purine derivative, as well as other experimental variables such as solvent, temperature and order of addition.

7. Other C-N Bond Forming Reactions

A diverse assortment of nitrogen nucleophiles having acidic N-H protons have been successfully condensed using the Mitsunobu reaction and are summarized in Chart 2. The nitrogen in bold is the reacting center in the examples shown.

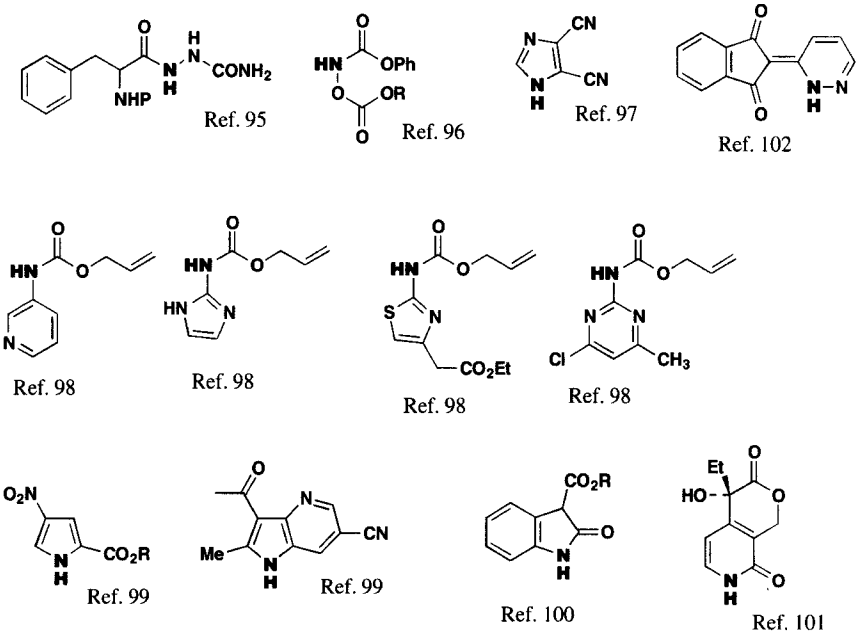
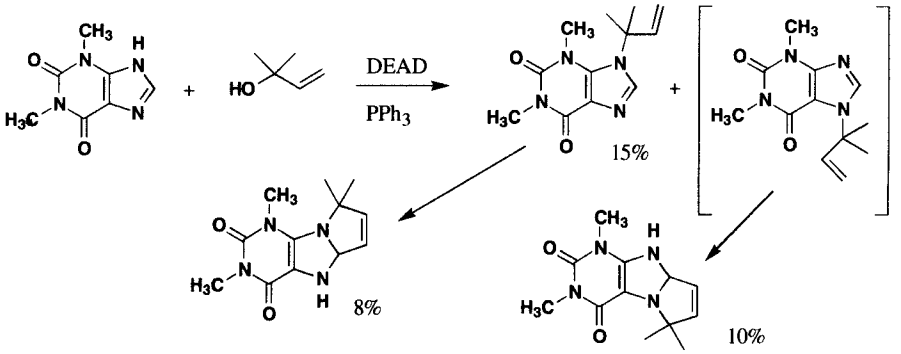


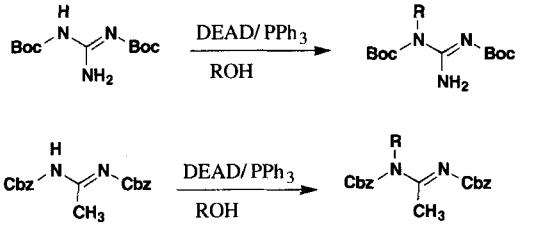
Chart 2

Although reactions of tertiary alcohols are rare in Mitsunobu reactions, theophylline reacted with 2-methyl-3-buten-2-ol to give three products derived from N-7 and N-9 alkylation. Only products arising from S_N2 reaction were observed, although the hindered nature of the alcohol would have led one to predict S_N2' reactivity (Eq. 54).[103]



(54)

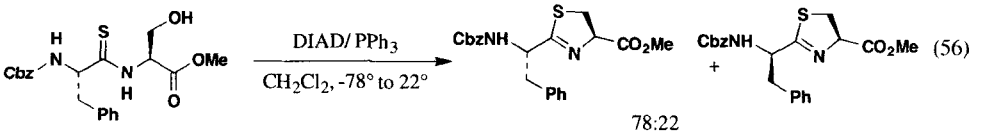
Amidines[104] and guanidines[105] react with alcohols under Mitsunobu conditions to provide the substituted amidine or guanidine in high yield with inversion of configuration (Eq. 55).



(55)

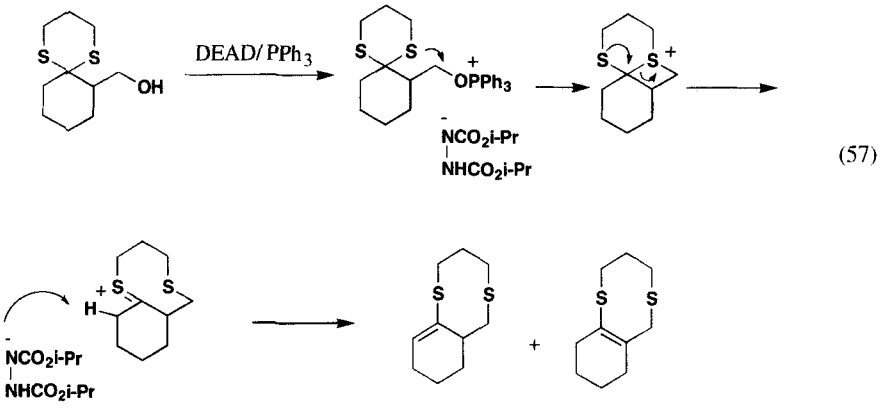
IV. CARBON-SULFUR BOND FORMATION

The most common sulfur nucleophile used in Mitsunobu reactions is thioacetate,[106] although several other sulfur compounds having acidic protons have been used.[4] The thioacetate Mitsunobu reaction can also be carried out on a resin.[107] In the reaction with unprotected glycosides with 2-mercaptobenzothiazole, the primary alcohol was selectively condensed in pyridine with DEAD/PPh_3 to form the 6-thioether in 72% yield. Reaction with 2 equiv. of the thiol gives the 3,6-dithioether in 42% yield, with inversion at the 3-position.[108] Likewise, unprotected cyclodextrins can be selectively reacted with several thiols or thioacetic acid at the primary 6-hydroxyl positions.[109] Thiazolines were prepared from intramolecular cyclization of β-hydroxythioamides in 65-80% yields;[110,111] however, substantial side chain epimerization occurred giving product of only 56% de (Eq. 56).[112]



(56)

[1,3]-Migration occurred on the dehydration reaction of the hydroxy dithiane shown in Eq. 57 to provide the ring expanded product. This product is rationalized by intramolecular nucleophilic



(57)

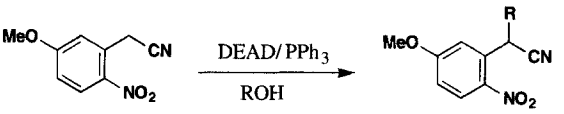
4:1, 60% overall

displacement of the phosphonium intermediate to form a sulfonium salt, which then rearranges to the ring-enlarged product.[113]

V. CARBON-CARBON BOND FORMATION

Carbon-carbon bond formation by Mistunobu reaction is rare since few carbon acids have an aqueous pKa value below 12, which is required for reactivity. Most carbon compounds used thus far are doubly activated, such as in 1,3-diketones and these often react on oxygen instead of carbon.[4]

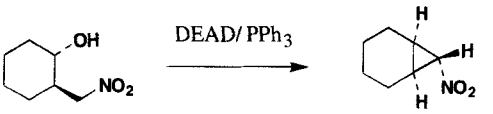
o-Nitroarylacetonitriles were reacted with alcohols to form the carbon alkylated product (Eq. 58). Benzylic, allylic and propargylic alcohols reacted faster than primary alcohols, which in turn



(58)

reacted faster than secondary alcohols, which was the order expected for S_N2 reactivity, suggesting that displacement of the oxyphosphonium ion was the rate limiting step.[114]

γ-Nitroalkanols were converted via the Mitsunobu reaction to α-nitrocyclopropanes with inversion of configuration (Eq. 59).[115]



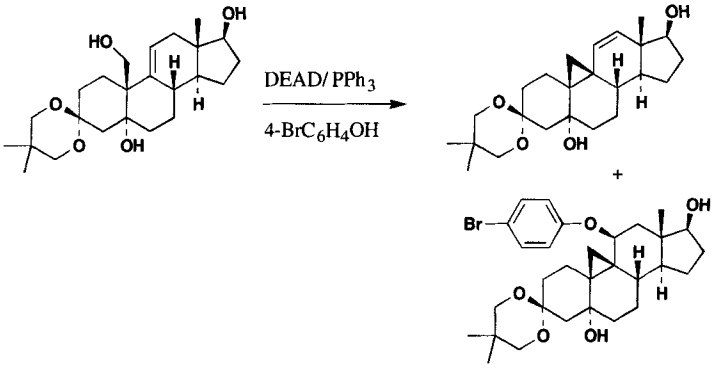
(59)

92%, only trans

bis-Sulfones condensed with alcohols both in intramolecular and intermolecular reactions using the Mitsunobu protocol and proceeded with the expected inversion of stereochemistry.[116] (Phenylsulfonyl)acetonitrile also condensed with alcohols using Me_3P or Ph_3P with 1,1'-(azodicarbonyl)dipiperidine. For secondary alcohols, imidazole was required to obtain useful yields.[117]

Conversion of alcohols to nitriles can be achieved using the Mitsunobu reaction, but requires the use of HCN. However, Wilk has found that HCN can be replaced with the safer acetone cyanohydrin, with yields comparable to those found with HCN.[118] Szantay and coworkers reported that yields with acetone cyanohydrin could be improved by the experimental protocol of adding reagents in the following order: DEAD, alcohol, then acetone cyanohydrin, to a cold solution of PPh_3.[119]

Double bonds are also capable of being nucleophiles, as shown in Eq. 60. The carbocation,



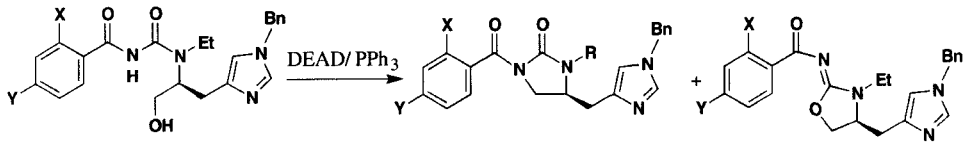
(60)

resulting from displacement of the phosphonium ion by the double bond, can either lose a proton to regenerate a double bond or be trapped by an added nucleophile, in this case 4-bromophenol.[120]

VI. AMBIDENT NUCLEOPHILES

Most of the examples of ambident reactivity pertain to *N* vs. *O* alkylation. Mitsunobu condensation of 2-pyridone with a variety of alcohols gave exclusive or predominant oxygen alkylation with 2-phenylethanol, 1-phenyl-2-propanol, 1-phenylethanol and 2-phenylpropanol, but produced mainly the nitrogen alkylation product with benzyl alcohol and 2-naphthalenemethanol in THF as solvent. A solvent study was carried out with 2-phenylethanol, with the finding that clean oxygen alkylation occurred in DME and chloroform, while mixtures were obtained in dichloromethane, acetonitrile, DMSO and benzene.[121]

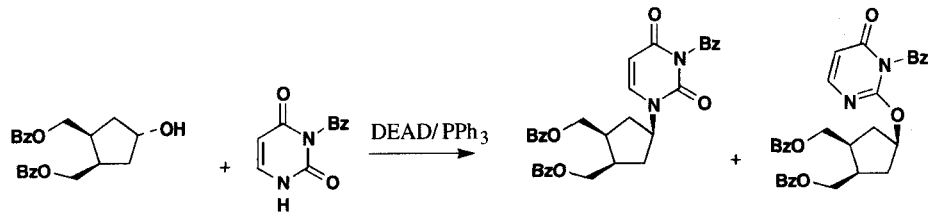
Rapoport reported mixtures of nitrogen and oxygen alkylation in the intramolecular reaction of acyl ureas (Eq. 61). Increasing the acidity of the N-H group by adding electron-withdrawing substituents to the aryl group increased the extent of *N*-alkylation.[122]



(61)

X	Y	N-alkyl	O-alkyl
H	H	56	44
H	Cl	57	43
Cl	Cl	80	20

Ambident reactivity with 3-benzoyluracil with cyclopentanol derivatives was dependent on the temperature (Eq. 62). At 0° only oxygen alkylation was observed, but at -40° equal amounts of nitrogen and oxygen alkylation occurred and at -78°, the nitrogen product predominated by a 2:1 ratio. These results were rationalized by postulating that *N*-alkylation is more sensitive to steric effects and that restricted rotation of the benzoyloxymethyl groups on the cyclopentanol at low temperature would reduce steric effects and favor *N*-alkylation.[123]

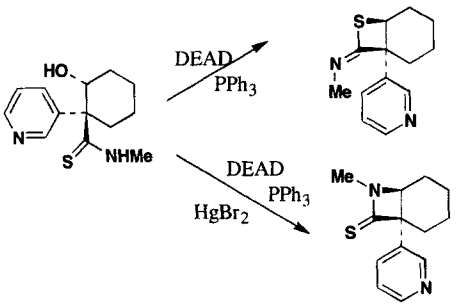


(62)

Reaction of several substituted benzoyl carbamates with either benzyl alcohol or ethyl lactate in the presence of PPh_3/ DEAD gave mixtures of *N*- and *O*-products, with the amount of O-alkylation ranging from 9% to 58%.[124]

The intramolecular Mitsunobu cyclization of γ-hydroxythioamides gave roughly a 2:1 mixture of S- vs. N-product.[125] On the other hand, β-hydroxythioamides provided the S-isomer under

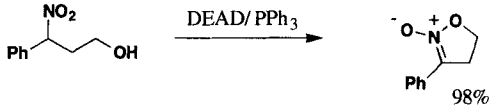
standard Mitsunobu conditions, or the N-isomer under Mitsunobu conditions with mercuric bromide added (Eq. 63).[126]



(63)

VII. OTHER REACTIONS

Nitroalkanes with electon-withdrawing substituents at the α-postition undergo O-alkylation both intra- and intermolecularly with alcohols to form alkyl nitronates (Eq. 64). For best results in intramolecular reactions, the DEAD/PPh_3 adduct was formed first, followed by addition of the nitroalkanol.[127] In contrast, as shown above (Eq. 59), unactivated γ-nitroalkanols undergo C-C bond formation to produce cyclopropanes.[115]

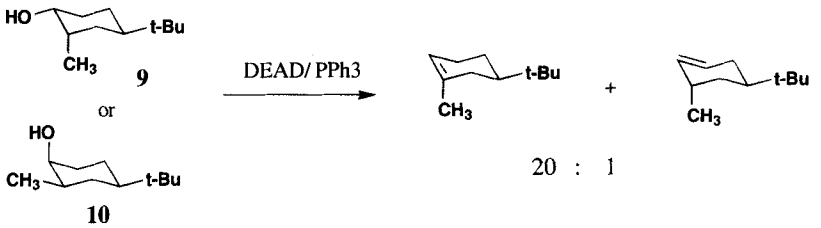


(64)

Silyl ethers can also be prepared by Mitsunobu chemistry by reaction of phenols and alcohols with silanols (Eq. 65).[128]

(65)

When no nucleophile is added to Mitsunobu reactions, elimination can occur to produce alkenes. In a series of cyclohexanols that could form either Saytzeff or Hoffman elimination products, Iimori and coworkers found that the Saytzeff product predominated with 18:1 to 50:1 selectivity (Eq. 66). In compound **10**, which has an axial hydrogen, the dehydration can proceed by an anti-elimination to give the observed Sayzteff product. For compound **9**, the elimination was proposed to proceed



(66)

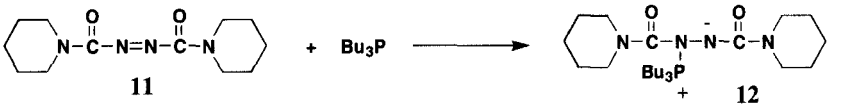
via a skew boat conformation in which the hydroxyl is pseudo-axial and thus an anti-periplanar arrangement is possible.[129]

Fluorophosphoranes, which are useful fluorinating agents, were produced from reaction of triphenylphosphine and DIAD with potassium hydrogen fluoride (Eq. 67).[130]

$$PPh_3 + DIAD + KHF_2 \longrightarrow Ph_3PF_2 \qquad (67)$$

VIII. NEW REAGENTS

During the past 5 years, Tsunoda and coworkers have developed a number of new redox reagents that have extended the Mitsunobu reaction to previously inert or poorly reactive substrates. The first system reported was tributylphosphine with 1,1'-(azodicarbonyl)dipiperidine (ADDP, **11**). The increased basicity of the Bu_3P/ADDP adduct **12** (Eq. 68) was expected to extend the range of compounds that would react in the Mitsunobu reaction and this was borne out by the finding that diethyl malonate (pKa 13.3) and N-benzyl trifluoroacetamide (pKa 13) reacted with benzyl alcohol in 50-55% yield, while only 2-3% yields were obtained with DEAD/ PPh_3.[131]



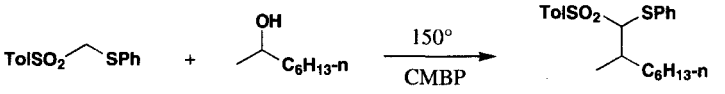
(68)

In addition, Tsunoda found that N,N,N',N'-tetramethyl- and tetraisopropylazodicarboxylates (abbreviated as TMAD and TIPA, respectively) were as effective as ADDP and better than the traditional DEAD, when used in conjunction with tributylphosphine.[132] For the hindered alcohols, 5-α-cholestan-3β-ol, 5-α-cholestan-3α-ol, (-)-menthol and (-)-8-phenylmenthol, the TMAD/ Bu_3P system gave good yields and complete conversion in the esterification reactions with 4-methoxybenzoic acid, whereas the DEAD/ PPh_3 system gave lower yields, especially with menthol and 8-phenylmenthol.[133]

Yet another redox alternative devised by Tsunoda was the reagent cyanomethylenetributylphosphorane, which mimics the zwitterionic adduct between DEAD and Ph_3P (Eq. 69).[134]

$$N\equiv C-\overset{-}{C}H-\overset{+}{P}Bu_3 + HA + ROH \longrightarrow \overset{+}{R}OPBu_3 + CH_3CN + A^- \qquad (69)$$

The reactions tend to be slower than typical Mitsunobu reactions, requiring heating at 100° in some cases. This reagent was capable of effecting the condensation between (methylthiomethyl)tolylsulfone (pKa in DMSO of 23.4) and several alcohols at 100-150° (Eq. 70).[135] This carbon acid is too weakly acidic to react to any appreciable extent with any of the other Mitsunobu redox reagents. Ethoxycarbonyl- and cyanomethylenetriphenylphosphoranes also performed well in some condensation reactions, but gave somewhat lower yields than cyanomethylenetributylphosphorane.



(70)

As an alternative to triphenylphosphine, von Itzstein and coworkers have introduced (4-dimethylaminophenyl)diphenylphosphine. The oxide of this reagent can be removed by an acid wash,

thus facilitating product purification.[136]

SUMMARY

Although the Mitsunobu reaction was discovered nearly three decades ago and extensively developed during the 1970's by Mitsunobu and his group, novel applications of this versatile reaction continue to be discovered. A few of the more notable highlights reported within the last five years include the following: (1) 4-nitrobenzoic acid has become the acid of choice for use in inverting the stereochemistry of secondary hydroxyl groups, providing higher yields than the conventional benzoic and acetic acids, especially with hindered substrates; (2) selective formation of glycosidic bonds has found widespread use in carbohydrate chemistry; (3) primary, secondary and tertiary polyfluoroalcohols can serve as the acidic component in Mitsunobu reactions with other alcohols to form aliphatic ethers; (4) aliphatic alcohols can be phosphorylated by reaction with methyl alkyl phosphonate under Mitsunobu conditions; (5) the search for anti-viral agents has spawned an explosive use of the Mitsunobu reaction for coupling nucleoside bases with sugar alcohols; (6) the reaction has been shown to be amenable to solid phase chemistry, thereby becoming a tool in combinatorial chemistry; and (7) Tsunoda and coworkers have developed a family of new redox reagents, including 1,1'-(azodicarbonyl)dipiperidine, which has extended the Mitsunobu reaction to otherwise refractory substrates.

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