Mitsunobu and Related Reactions: Advances and Applications

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1. General Introduction

The substitution of primary or secondary alcohols with nucleophiles mediated by a redox combination of a trialkyl- or triarylphosphine and a dialkyl azodicarboxylate is popularly known as the Mitsunobu reaction. Since its discovery in 1967 by Professor Oyo Mitsunobu (1934−2003),[1,2] this reaction has enjoyed a privileged role in organic synthesis and medicinal chemistry because of its scope, stereospecificity, and mild reaction conditions. Several important variations were discovered by Mitsunobu and his co-workers in the early stages of its development as a synthetic tool.[3−14] This reaction is often used as a key step in natural product syntheses. Its importance and utility can be gauged from the fact that in *SciFinder*, for explicit use of the phrase "Mitsunobu reaction", there were 1615 citations from 1996 to 2008 including 186 patents. This topic has been reviewed in several places earlier, and during the last several years, the focus has been to cover specific areas.[15−39] In this review, we have made an attempt to give an overall picture, taking examples mostly from the literature during the last ten years. Apart from esters, a wide range of compounds that include amines, azides, ethers, cyanides, thiocyanides, thioesters, and thioethers can be synthesized using a Mitsunobu protocol (*cf.* Scheme 1). The azido or phthalimido derivatives so obtained can be readily transformed into amines while thioesters can be converted to thiols in a single step, allowing facile conversion of an alcoholic −OH group to a $-NH_2$ or −SH group. It is also possible to readily convert primary amines to isocyanates using CO_2 as an additional component. Thus, this reaction permits C−O, C−S, C−N, or C−C bond formation by the condensation of an *acidic component* with a primary or a secondary alcohol in the presence of triphenylphosphine (or another suitable phosphine) and

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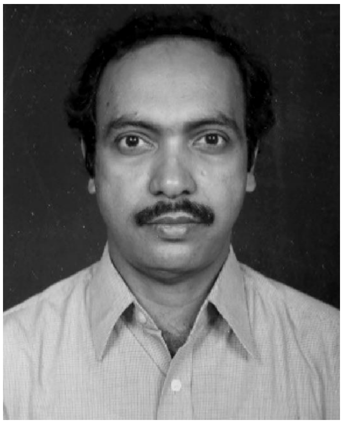

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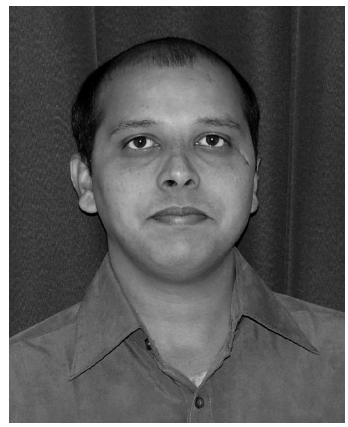

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diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD).

Given below are some of the salient features of this reaction:

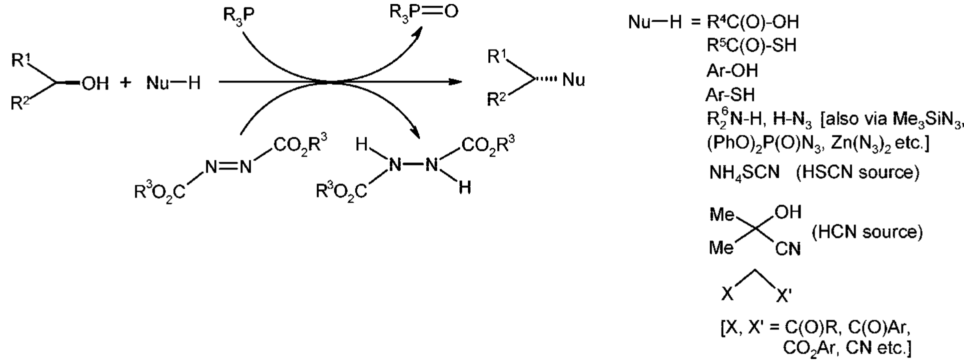
(i) The *substrates* are primary or secondary alcohols. Chiral secondary alcohols undergo a *complete inversion* of configuration unless sterically very congested.[40−42] This aspect has been positively exploited in numerous reactions. In general, tertiary alcohols are less reactive, but there is at least one report of the synthesis of alkyl-aryl ethers (with complete inversion of configuration) starting from tertiary alcohols.[43]

(ii) The *nucleophile* (or pronucleophile) is normally a relatively acidic compound containing an O−H, S−H, or an N−H group with $pK_a \leq 15$, preferably below 11. Some common nucleophiles are carboxylic acids, phenols, imides, purine/pyrimidine bases, and related heterocycles, hydrazoic acid (HN_3), thiocarboxylic acids, thiols, fluorinated alcohols, and hydroxamates. Phosphoric/phosphonic acids can also be used. In place of HN_3, it is possible to employ diphenylphosphoryl azide (DPPA), trimethylsilyl azide, or zinc azide, which is far easier to handle. With suitable modification of the phosphine, if necessary, one can use even C−H-based nucleophiles such as malonate esters, β-diketones, β-keto esters, and triethylmethane tricarboxylate [$HC(CO_2Et)_3$, TEMT].

(iii) As can be expected, an intramolecular Mitsunobu reaction leading to lactones, lactams, cyclic ethers, and amines is possible. A large excess of Ph_3P-azodicarboxylate is utilized quite often in macrolactonization to obtain the products in decent yields. In many cases, addition of a base such as triethylamine could help in increasing the yield of the product.

(iv) In the presence of additional components such as acyl/alkyl halides or lithium/zinc halides, alcohols are converted to halides, with inversion of configuration. Use of additional CO_2 leads to carbamates

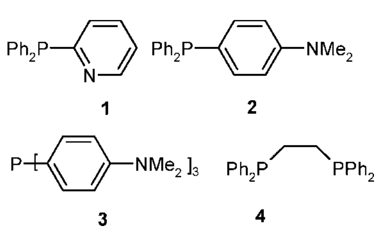
Scheme 1



while a combination of a primary amine along with CO_2 gives isocyanates.

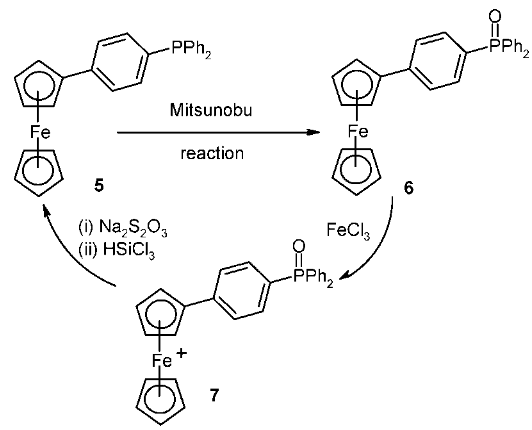
(v) Common solvents for the reaction are tetrahydrofuran (THF), toluene, benzene (*Caution*: *Benzene is a carcinogen and may be replaced by toluene wherever possible*.), dimethyl formamide (DMF), diethyl ether, acetonitrile, dichloromethane, and 1,4-dioxane. The first two solvents normally give better results. The reaction is generally conducted between 0 °C and 25 °C.

(vi) The preferred P^{III} component is triphenylphosphine (Ph_3P) or tributylphosphine (n-Bu_3P), both of which are quite cheap and commercially available. The triphenylphosphine oxide byproduct as well as unreacted Ph_3P are water-insoluble, and very often chromatography is required for the separation of the products. This is one of the major limitations in Mitsunobu chemistry. The phosphine Me_3P is volatile but a safety hazard. Although n-Bu_3P works well in many cases,[44] this phosphine is still not as popular as triphenylphosphine. An alternative is to use either diphenyl(2-pyridyl)phosphine (**1**) or (4-dimethylaminophenyl)diphenylphosphine (**2**) or tris-(4-dimethylaminophenyl)phosphine (**3**).[45−47] In such a case, the corresponding phosphine oxide can be removed by washing the reaction mixture with dilute hydrochloric acid. If the required product is fairly soluble in the chosen organic solvent, such as toluene or THF, a diphosphine such as 1,2-diphenylphosphinoethane (DPPE, **4**) may be a better choice, since the byproduct phosphine oxide is insoluble and hence can be removed by filtration.[48] The use of polymer supports, other phosphines, and fluorous reagents to alleviate some of the problems has been reviewed recently.[32,33,35] A brief survey of these aspects is also given in later sections.

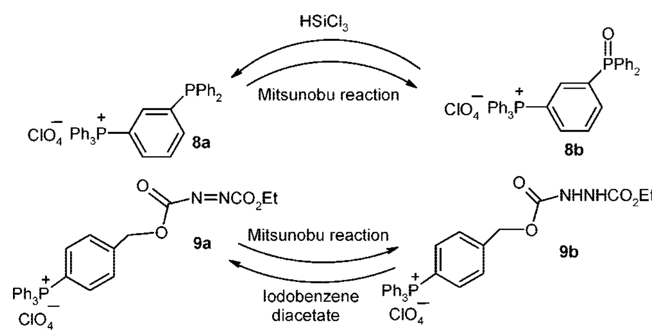


Another alternative to Ph_3P is the ferrocenyl-appended phosphine **5**.[49] Use of this compound, together with di-*tert*-butyl azodicarboxylate (DTBAD), could alleviate the problem of column chromatography. The ferrocenyl-appended phosphine oxide byproduct **6** can be oxidized at the iron center to the cation **7** (anion: chloride). The resulting species is rather insoluble in less polar media and, hence, can be separated from the required product. Di-*tert*-butyl azodicarboxylate (DTBAD) and the corresponding hydrazine byproduct are decomposed by treatment with aqueous hydrochloric acid. The cationic species **7** can be reverted back to **5** by reduction of the iron center (via $Na_2S_2O_3$), followed by treatment with $HSiCl_3$ (Scheme 2).

Scheme 2



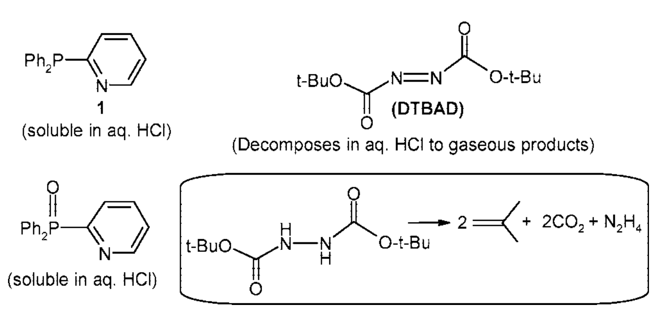
Scheme 3



By employing a phosphine or/and an azocarboxylate tagged with a phosphonium (salt) side chain, the reagents as well as the resulting byproducts can be made insoluble in a less polar solvent such as diethyl ether. A simple filtration will then remove the byproducts, alleviating the problem of tedious column chromatography. Thus, in the esterification reactions of 2-octanol and menthol using the redox system **8a**−**9a** (cf. Scheme 3) in ether medium, the phosphine oxide and the hydrazine byproducts are conveniently removed by filtration.[50−52] The phos-

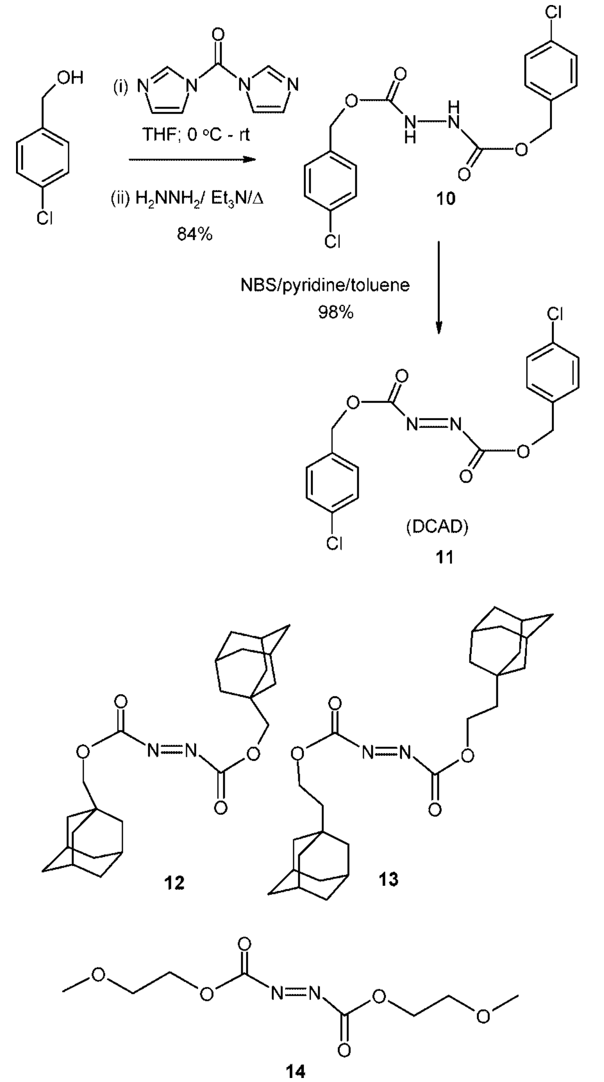
phine−phosphonium salt **8a** is prepared by starting with diphenyl(3-bromophenyl)phosphine, while the azocarboxylate−phosphonium salt **9a** is prepared by starting with 4-chlorophenylstilbene, 4-Cl-C_6H_4-C(H)=C(H)-C_6H_4-4-Cl. The phosphine oxide **8b** is reduced back to phosphine **8a** by trichlorosilane, while the hydrazine **9b** is oxidized to azocarboxylate **9a** by iodobenzene diacetate. What is important to note is that if the two phosphorus atoms are in the 1,4-position of the aromatic ring instead of 1,3- as in **8a**, reactions do not proceed that well.[50]

(vii) Both diisopropyl azodicarboxylate (DIAD) and diethyl azodicarboxylate (DEAD) can be used interchangeably in most cases [*Note*: *Azodicarboxylate esters are susceptible to explosion upon strong heating or impact. Hence, it is preferred that they are handled in solution. Wherever possible, smaller scale operations are recommended.*]. They are commercially available, but the former is cheaper. They can also be prepared by starting with hydrazine hydrate.[53−55] Only in a very few cases, DIAD is less effective.[56] Generally, the Ph_3P−DEAD/DIAD system is useful for acidic nucleophiles with pK_a < 11. For those having a pK_a > 11, more active coupling reagents such as 1,1′-(azodicarbonyl)dipiperidine [(*cycl*-C_5H_{10}N)C(O)-N=NC(O)(*cycl*-NC_5H_{10}), ADDP], 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione {[MeNCH_2CH_2NMe][C(O)-N=NC(O)], DHTD}, and *N*,*N*,*N*′,*N*′-tetramethyl azodicarboxamide [Me_2NC(O)-N=NC(O)NMe_2, TMAD] in combination with tributylphosphine (*n*-Bu_3P, TBP) or trimethylphosphine (Me_3P) have been developed.[26,34,57−64] The reagent DHTD can be prepared by starting with diphenyl azodicarboxylate and *N*,*N*′-dimethylethylene diamine.[61] In the reaction of dimethyl malonate with benzyl alcohol, while the use of Ph_3P−DEAD gave a negligible yield of *C*-alkylated product, a combination of *n*-Bu_3P with ADDP, TMAD, or DHTD afforded a much better yield (56%, 66%, or 75%, respectively).[60,61] Barring the cost, the combination of diphenyl(2-pyridyl)phosphine (**1**) and the acid labile DTBAD is very convenient because, upon treatment with aqueous HCl, the former (or its oxide) is removed while the latter is converted to gaseous byproducts.[47] The tagged reagents $Ph_2P(CH_2CH_2CO_2$-*t*-Bu) and *t*-BuO_2CCH_2NHC(O)N=NC(O)NHCH_2CO_2-*t*-Bu are other alternatives; the acid tag can be unmasked in subsequent steps.[65]



Modification of the organic group on the azodicarboxylate reagent for convenient handling is of some value. Thus di-4-chlorobenzyl azodicarboxylate

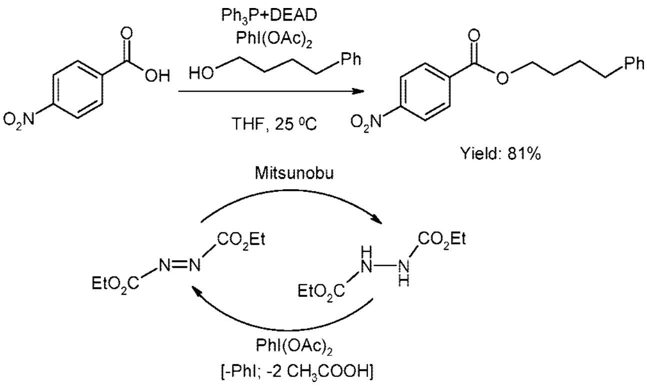
Scheme 4



(DCAD, **11**) has been conveniently prepared via hydrazine **10** starting with *p*-chlorobenzyl alcohol as shown in Scheme 4.[66] This stable orange crystalline compound can be stored at room temperature and is nearly as efficient as DEAD or DIAD in the reactions studied. Most of the byproduct hydrazine **10** formed in the Mitsunobu reaction can be precipitated from dichloromethane. The polarity of **10** is quite different from those arising from DIAD/DEAD which facilitates separation of the products more readily during chromatography. Another interesting approach by Curran and co-workers is noteworthy.[67] The azo compounds **12**, **13** and the corresponding hydrazine products have longer retention times in cyclodextrin-bonded silica gel compared to normal Mitsunobu hydrazine byproducts that facilitate ready separation/purification of the expected Mitsunobu products. Sugimura and Hagiya have introduced the new azocarboxylate **14** [di-2-methoxyethyl azodicarboxylate, DMEAD].[68] They point out that the highly polar and water soluble nature of **14** is an advantage and also that the preparation of **14** is easier than that of DEAD or DIAD.

(viii) Very often DEAD or DIAD is added (~5 min for the 1 mmol scale) to a solution of Ph_3P, followed

Scheme 5



by an alcohol and an acidic component (the orange-red color of DEAD/DIAD disappears immediately). The reverse addition of Ph_3P to the solution of the other three components as well as the use of a premixed solution of Ph_3P + DEAD/DIAD is also possible.

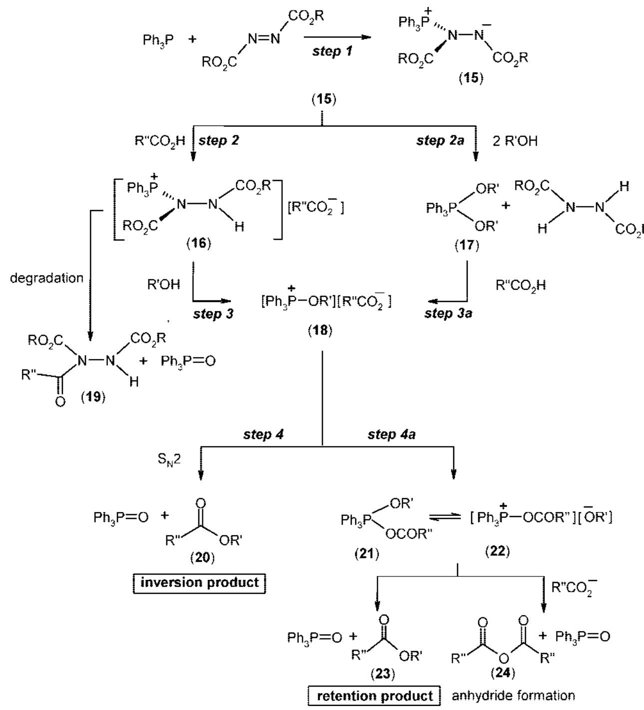
(ix) In lieu of using new types of reagents, we can devise methodologies to remove the byproducts. By washing the reaction mixture with a solution of 15 wt % hydrogen peroxide, followed by addition of aqueous sodium thiosulfite (to remove peroxide), all Ph_3P will be converted to the highly polar $Ph_3P(O)$ oxide, which can be filtered off through silica gel. In specific cases such as *N*-alkylation of *N*-hydroxyphthalimide with prenyl alcohol, this procedure was quite useful and provided the product in nearly 96% yield.[69] It was found that, during this brief exposure to hydrogen peroxide, the hydrazide from the DIAD did not get oxidized back to the precursor (i.e. DIAD) to any significant extent (^1H NMR). However, the authors have suggested precautions that will be handy, particularly if very large amounts of the reagents are used.

(x) It may be noted that, in the normal Mitsunobu reaction, the hydrazine byproduct is a waste. Therefore, if it can be reverted back to azodicarboxylate, a more useful protocol can be developed. This is essentially what Toy and co-workers have achieved recently by introducing an additional component, $PhI(OAc)_2$, that converted the hydrazine back to the DEAD (Scheme 5).[70] Only a catalytic amount of DEAD (0.1 mol equiv with respect to the alcohol) was used in these reactions. It may be noted that, in the oxidation with $PhI(OAc)_2$, acetic acid is a byproduct. As long as it does not interfere in the expected reaction, this methodology could work out to be a very useful one. Although the yields were slightly lower than the uncatalyzed reactions and secondary alcohols afforded poor results under these conditions, this "organocatalytic" idea is quite novel and needs further exploration in view of the fact that it avoids wastage of the expensive DEAD/DIAD.

2. Mechanism

Despite the fact that the Mitsunobu reaction is widely used in synthetic organic chemistry, the mechanistic details, particularly at the intermediate stages, are still a subject of debate and intensive studies.[41−43,71−103] A possible pathway

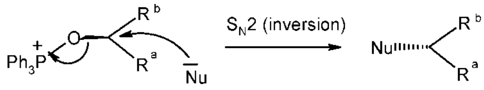
Scheme 6. Postulated Mechanism for the Mitsunobu Esterification



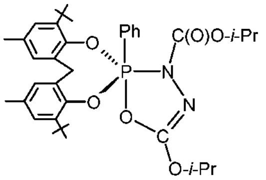
in the esterification process is shown in Scheme 6. The first step is the irreversible formation of the Morrison−Brunn−Huisgen (MBH) betaine **15**, whose identity has been established by multinuclear NMR [^{31}P NMR: δ 44.9 (R = Et), 44.2 (R = *i*-Pr), 42.6 (R = *tert*-Bu)][76] and ESI-MS.[87] In step 2, this betaine **15** deprotonates the carboxylic acid to form the ionic species **16**, which upon reacting with the alcohol forms the key alkoxyphosphonium salt **18** and the hydrazine $RO_2CNH\text{-}NHCO_2R$. Alternatively, betaine **15** can react first with the alcohol (depending on the order of addition) to lead to the pentacoordinate phosphorane **17**, as shown in step 2a; this phosphorane may also lead to the alkoxyphosphonium salt **18** upon reacting with the acid (step 3a). At this stage, degradation of **16** may take place to lead to **19** as well as the phosphine oxide $Ph_3P(O)$. The inversion product **20**, when a secondary alcohol is used, is formed in step 4. In cases where retention product **23** is observed, the intermediacy of the acylphosphonium salt **22**, which is in equilibrium with **18** and the phosphorane **21**, is invoked. Formation of the anhydride **24** via **22** is a complicating factor in some cases.

EPR spectroscopy shows that the betaine **15** may be formed via, or accompanied by, radical cations of type $(Ph_3P^+)\text{-}N(CO_2R)\text{-}N^{\bullet}\text{-}(CO_2R)$[89] or $(Ph_3P^+)\text{-}O\text{-}C(OR){=}N\text{-}N^{\bullet}\text{-}(CO_2R)$.[94] The intensity of the EPR signal varies as $n\text{-}Bu_3P < Ph_3P < (Me_2N)_3P$ in reactions with DIAD. This observation suggests that the nature of the intermediate in the Mitsunobu reaction could vary depending upon the P^{III} precursor. Indeed, the use of Ph_3P or $n\text{-}Bu_3P$ using a Mitsunobu protocol afforded different isomers of 2-oxazolidones from CO_2 and ethanolamines (section 8).[103] It is important to note that, by altering the electronic environment at the P^{III} precursor, intermediates other than **15** have been obtained in the first step of the reaction with DIAD/DEAD. These include the following: (a) pentacoordinate phosphoranes (e.g. **25**) formed by the [4+1] cycloaddition (with the nitrogen and a carbonyl oxygen of DIAD/DEAD attached to phosphorus) when the P^{III} precursor contains at least two oxygen atoms connected

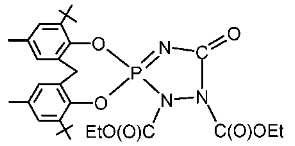
Scheme 7



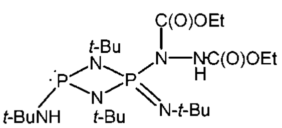
to phosphorus, (b) dipolar cycloaddition when a functional group such as −NCO is present on the phosphorus precursor (e.g. **26**), and (c) phosphinimines with a P(=N-*tert*-Bu)[N(CO_2R)-NH(CO_2R)] moiety (e.g. **27**−**28**) if phosphorus initially had a −NH-*tert*-Bu group.[100,101,104−107] The products **27**−**28** are the tautomeric forms of the expected betaine and, hence, give credence to the proposed first step in Scheme 6. Many such compounds are now well-characterized.[101,106] Some of the derivatives as obtained in parts (a)−(c) can take part in the Mitsunobu esterification,[101,102,108,109] leaving room to explore the viability of other P^{III} compounds for specific transformations.



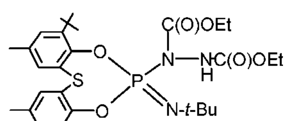
25 [δ(P) -51.7, X-ray]



26 [δ(P) 26.7, X-ray]



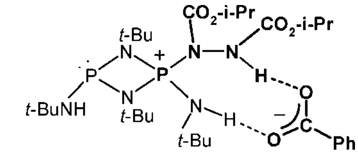
27 [δ(P) -28.7, 68.9; X-ray]



28 [δ(P, 298K) -56.3, X-ray] (four signals at low temperatures)

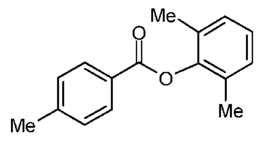
The order of addition of acid and alcohol to betaine **15** in the Mitsunobu esterification has a profound effect on the reaction pathway, implying potential duality of the mechanism.[79,83,95] The species {RO_2CN-(P^+Ph_3)-NH-CO_2R}-($R''CO_2^-$) (**16**) is formed from the reaction between the acid R″COOH and **15**.[40,79,81,85,89,90] The stability of this species may be enhanced by hydrogen bonding.[81] Crystallographic evidence for a protonated compound of type **16** has been recently provided, and many compounds of this type can be readily synthesized (e.g. **29**).[101,102] Partial degradation of **16** to **19** may also occur when a very weak acid (pK_a > 15) is used. Oxyphosphorane intermediates $Ph_3P(OR')_2$ (**17**) are formed by the reaction of **15** with alcohols.[76,78,80,110,111] Formation of a racemic phosphine oxide, when a chiral phosphine [e.g. (*cyc*-C_6H_{11})(1-naphthyl)(Me)P in place of Ph_3P] and excess alcohol are used, indicates the involvement of analogous pentacoordinate dialkoxyphosphorane.[95] Reaction of **16** with R′OH or **17** with R″CO_2H leads to the phosphonium-carboxylate salt [$Ph_3P^+(OR')$]($R''CO_2^-$) (**18**).[83,97] In most esterifications, attack of the carboxylate anion $R''CO_2^-$ at the alkoxy carbon in **18** is assumed for the formation of the configurationally inverted ester **20**. For the more general case wherein the nucleophile is Nu-H and alcohol is chiral (R^aR^bCHOH), the inversion process is shown in Scheme 7.

For a few examples in which retention of configuration (species **23**) is observed or when the acid anhydride (**24**) is the major product, intermediacy of the acyloxy phosphonium salt **22** is invoked.[41,77,84,90,92] In a recent study on the coupling



[**29**: δ(P) 1.1, 81.0 (**X-ray**)]

of substituted benzoic acids with various phenols that afforded aryl benzoates (e.g. **30**), Fitzjarrald and Pongdee have proposed the involvement of an acyloxy phosphonium intermediate (cf. **31**).[93] It may be noted that while in etherification reactions phenol is used as the nucleophile (see section 4), here it has taken the role of the alcohol (substrate).



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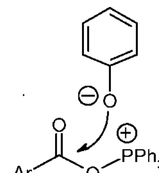


31

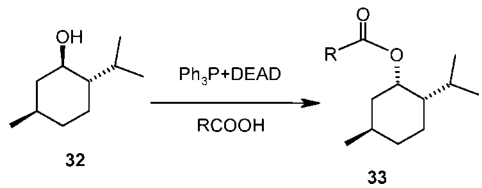
Recent theoretical calculations by Anders and co-workers show that the hypersurface of the Mitsunobu reaction is far more complex than is generally assumed, even for the simplest possible system (PH_3, MeO_2CN=NCO_2Me, MeOH, CH_3CO_2H).[97] Calculations also reveal that it is possible to divert the Mitsunobu procedure to a retention channel with judicious selection of experimental conditions, especially with regard to substituents at phosphorus.

3. Carboxylic Acids/Phosphorus-Based Acids as Nucleophiles: Esterification Including Macrolactonization

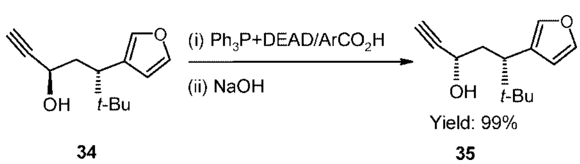
3.1. Esterification with Inversion

Alcohols react with carboxylic acids smoothly at room temperature (or lower) to afford the esters in good yields. When a chiral secondary alcohol is used, configurational inversion of alcohol occurs under mild and essentially neutral conditions. This is one of the “trump cards” of the Mitsunobu esterification route over many other methods. Hydrolysis of the product subsequent to esterification affords the inverted alcohol, generally in high enantiomeric purity. The pK_a of the usable acid must be below 13, preferably <11. The reaction is inherently sensitive to the steric environment of the alcohol. Primary alcohols, in general, react in preference to more sterically encumbered secondary alcohols. For successful esterification, a delicate balance is required such that the carboxylate anion is a strong enough base to initiate alcohol activation, but not such a strong nucleophile that it reacts with the cation in **16** (cf. Scheme 6) faster than the alcohol. It is likely that the acids of lower pK_a prefer the oxyphosphonium intermediate structure **18** over a phosphorane of type **17**.[84,85] Thus, to effect the inversion of configuration of chiral secondary alcohols, 4-nitrobenzoic acid (pK_a 3.41) or chloroacetic acid (pK_a 2.86) in a solvent such as THF or benzene (*Cautionary note*: *It is advisable to use toluene in place of benzene in view of the carcinogenic nature of the latter.*) is preferred.[40,90,112−114] This aspect was studied in detail for the esterification of (−)-menthol (**32**; Scheme 8). In case a crystalline product with inversion is

Scheme 8



Scheme 9

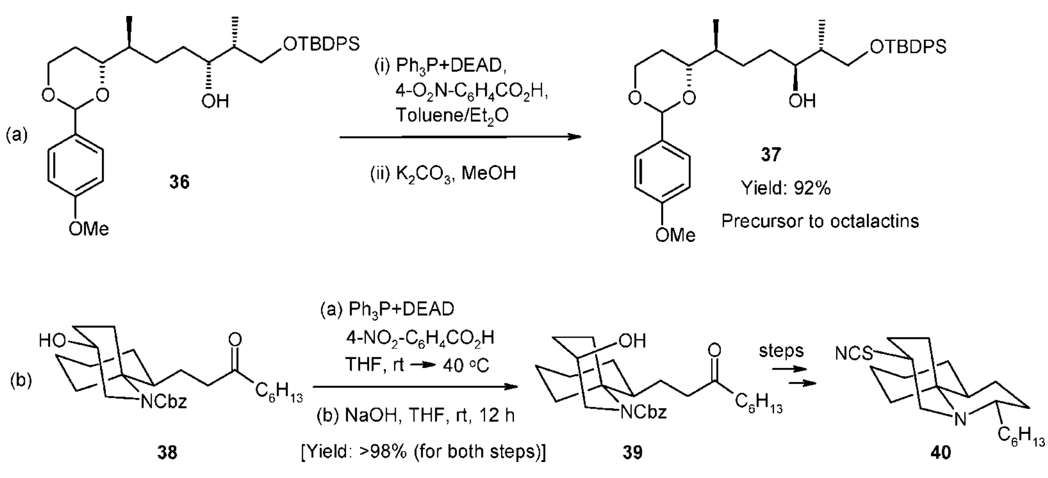


required, 3,5-dinitrobenzoic acid could be a good choice as the acidic partner. In place of substituted nitrobenzoic acids, picolinic acid is another option that can be considered. The advantage of using this acid is that the resulting esters can be cleaved under essentially neutral conditions using Cu $(OAc)_2$/methanol.[115] The (prenyloxymethyl)benzoic acid gives good yields of the inverted esters with secondary alcohols; the cleavage of this group later would require catalytic $Yb(OTf)_3$.[116] Use of 4-benzyloxybutyryl esters for which deprotection may be effected by Pd−C/H_2 may be yet another choice, although the yields in the Mitsunobu esterification were only moderate in the cases studied.[117] There is an example in which Zn(O-*p*-Ts)$_2$ is used instead of the pure acid for Mitsunobu inversion.[118]

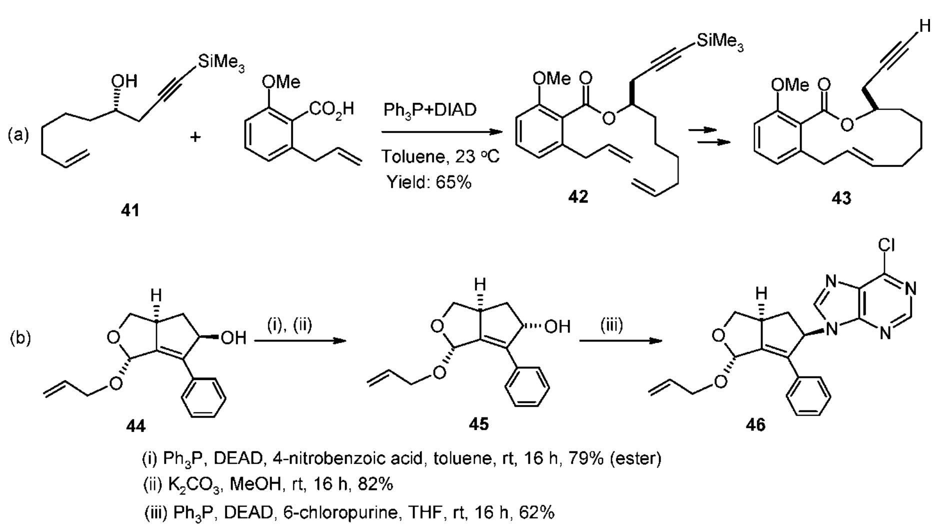
The utility of an inversion process is nicely illustrated in the total synthesis of (±)-ginkgolide B, where the undesired *anti* acetylenic alcohol **34** was efficiently converted to *syn*-**35** by the Mitsunobu protocol (Scheme 9).[119] In the esterification of sterically hindered 17-hydroxy steroids, it was found that a more acidic nucleophile provided a better yield of the inverted product.[120] 4-Nitrobenzoic acid was used as the preferred nucleophile to prepare the stereodefined precursor **37** in the synthesis of octalactins A and B (Scheme 10a).[121] The Mitsunobu reaction was one of the useful steps in the total synthesis of the marine alkaloid (±)-fasicularin (**40**), wherein the configuration at the secondary alcohol **38** was inverted to lead to the formation of **39** (Scheme 10b).[122] In the final step, an −OH group was converted to the required inverted thiocyanate compound **40** using the combination Ph_3P−DEAD/HSCN.

Compounds such as **42**, but with a bulkier protecting group [such as (*i*-Pr)$_3$Si in place of Me_3Si], are useful in ring closure metathesis leading to salicylihalamide.[123] Using the acetylenic alcohol **41** and a normal Mitsunobu protocol, compound **42** could be readily synthesized (Scheme 11a). A toluene solution of acid and DIAD was added to the solution of phosphine and alcohol using the stoichiometry 1:5:2.5:2.5 [alcohol/acid/phosphine/DIAD]. The product **42**, after con-

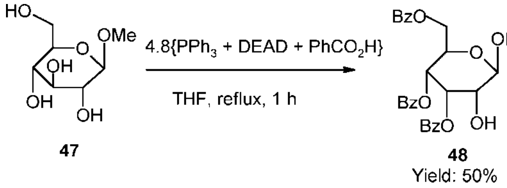
Scheme 10



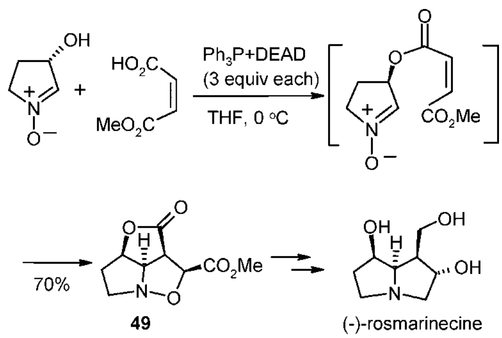
Scheme 11



Scheme 12



Scheme 13

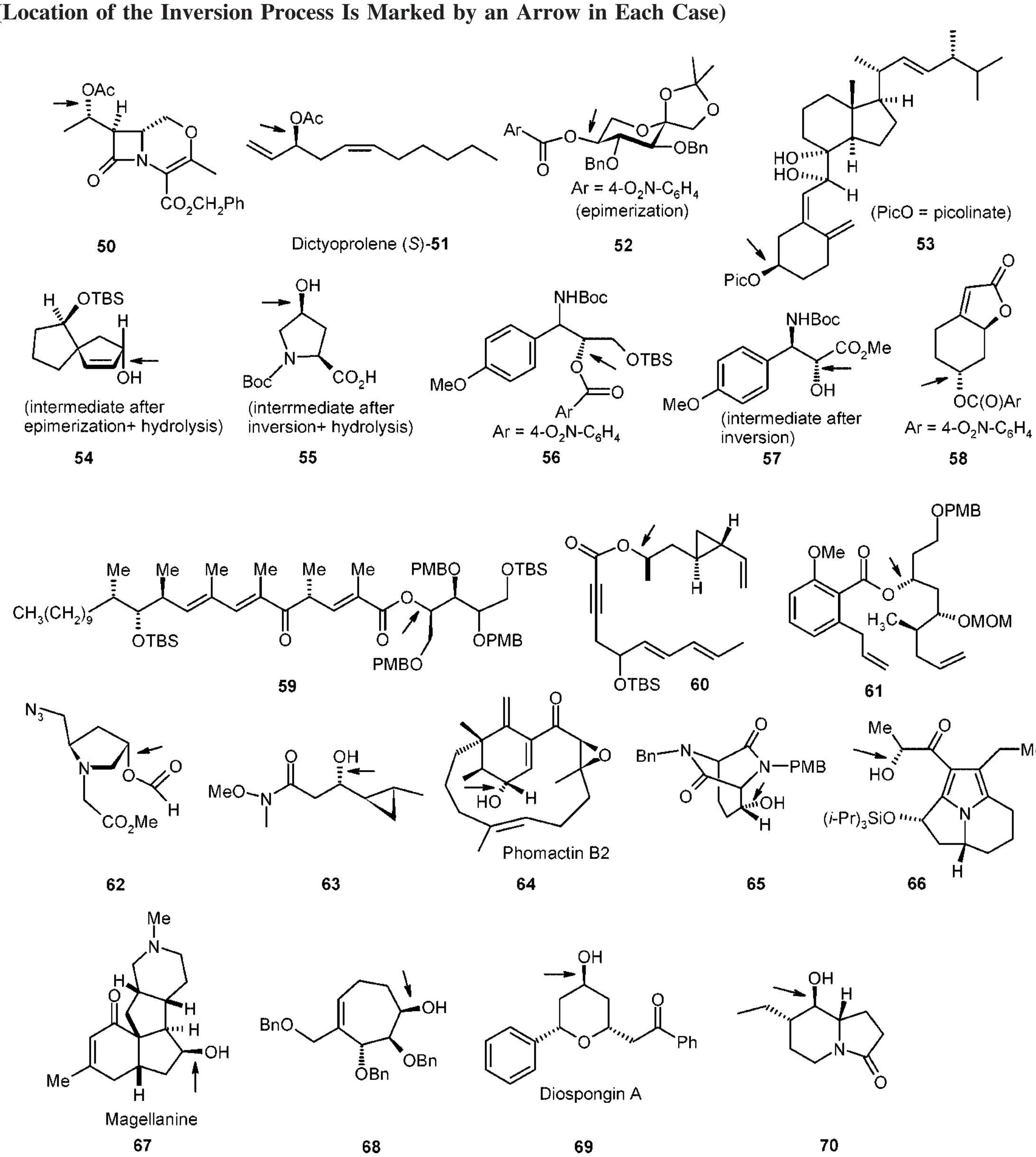


verting the $-SiMe_3$ group to $-Si(i\text{-}Pr)_3$, followed by ring closure via Grubbs' catalyst, led to **43**, which contained the required basic rings present in salicylihalamide. In the synthesis of carbocyclic nucleoside analogues, a Mitsunobu protocol can be effectively utilized for stereochemical inversion. The example given in Scheme 11b leading to the purine derivative **46** illustrates the manipulation of the configuration at the alcohol center by judicious choice of the nucleophile in different steps.[124]

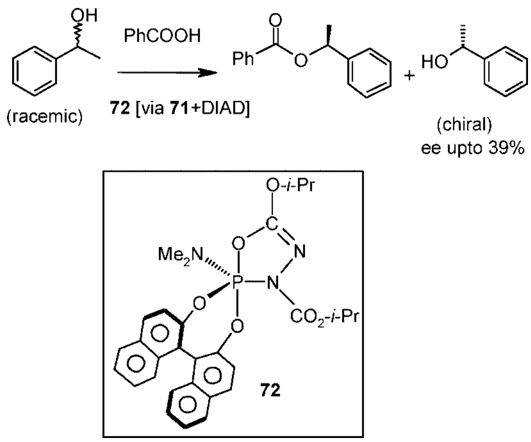
The Mitsunobu protocol has been successfully employed for esterification with inversion of methyl β-D-glucopyranoside **47**, which contains three secondary alcohol residues.[125] A 4.8-molar excess of Ph_3P−DEAD−benzoic acid was used to furnish four differently benzoylated methyl β-D-allopyranosides in a very good overall yield, with that of compound **48** being ~50% (Scheme 12). The results are significant in the sense that they give a better understanding of the reactivity of different −OH groups toward esterification in a polyol system.

A novel domino Mitsunobu−intramolecular nitrone cycloaddition process has been reported by Goti et al. (Scheme 13).[126] Here, the reaction of maleic acid monoester with the

Chart 1. (Location of the Inversion Process Is Marked by an Arrow in Each Case)



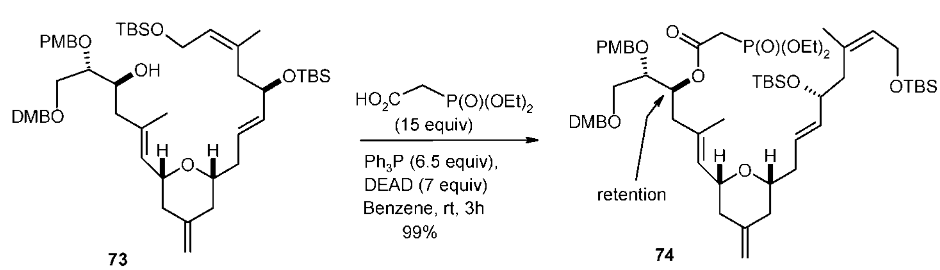
Scheme 14



hydroxy-substituted nitrone afforded an interesting cycloadduct **49** that must have come from the initially formed ester with inversion at the chiral center. The product **49** was later utilized for the synthesis of (−)-rosmarinecine, the necine base portion of many pyrrolizidine alkaloids.

In addition to the above, Mitsunobu inversion/epimerization is utilized in numerous diverse syntheses that include bicyclic lactams (e.g. **50**),[127] dictyoprolene (**51**),[128] D-fructose−L-sorbose interconversion (e.g. **52**),[129] intermediates for dihydroxyvitamin D_3 [e.g. **53** (from ref 130)],[130,131] (*S*)-epimeric carbaspironucleosides (e.g. **54**),[132] fluoroproline (e.g. **55**),[133] (*R*)-cytoxazone (e.g. **56** and **57**),[134,135] dihydroaquilegiolide (e.g. **58**),[136] khafrefungin **59**,[137] benzo-fused macrolactones (precursor to **60**),[138] salicylihalamide (e.g. **61** from ref 142),[113,139−143] azidomethyl-substituted pyrrolidine esters (e.g. **62**),[144] (−)-clavosolide B intermediate **63**,[145] phomactin B2 (**64**),[146] 6-benzyl-2-methoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane (**65**, this exhibited antitumor activity against lung cancer similar to cisplatin),[147] azafulvenium precursor (pyrroloindolizine) **66**,[148] magellanine **67**,[149] cycloheptenol **68**,[150] diospongin A (**69**),[151] and 7-ethyl-8-indolizidinol (**70**).[152] The structures of **50**−**70**, with the arrows indicating the position of inversion, are shown in Chart 1. It may be noted that, in place of the more common nucleophile 4-nitrobenzoic acid, picolinic acid or formic acid was employed for the synthesis of **53** and **55**, respectively.[130,133] For the conversion of 4-nitrobenzoate ester precursor to **57**, Et_3N/THF was used for hydrolysis during the workup.[135] Due to the large number of other applications involving similar inversion/epimerization, we only list them here; the structural drawings pertaining to these references are given in the Supporting Information (Table S1). These pertain to the synthesis of (i) pregnanone derivatives,[153] (ii) glucosphingolipids,[154] (iii) pyrrolidine-amide oligonucleotide mimics,[155] (iv) tubronic acid,[156] (v) enantiopure butanoates,[157] (vi) macroviracins,[158] (vii) reduced products of *cis*- and *trans*-hexahydronaphthalenones,[159] (viii) stereoinversion of *myo*-inositol into *scyllo*-inositol,[160] (ix) orthogonally-protected and unprotected depsipeptides such as L-Lys-D-Ala-D-Lac[161] and Boc-(*S*)-HOMeVal-(*R*)-Hmb,[162] (x) (2*S*,3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-2,3-isopropylidenedioxy-4-phenylbutanoate,[163] (xi) dihydroxycholesterol,[164] (xii) the acetate of the triol derived from jasminine,[165] (xiii) stereochemically inverted products of xylofuranosyl derivatives,[166] (xiv) 6-*epi*-aucubin,[167] (xv) hydroxyethylene dipeptide isosteres (e.g. L-682,679),[168] (xvi) orobanchol (a germination stimulant),[169] (xvii) long chain pentadeca-1,3,5,7,9,11,13,15-octols (16 diastereomers),[170] (xviii) mycalamide A (natural product),[171] (xix) murisolin (natural product),[172] (xx) leucascandrolide A (natural product with a sterically congested carbon),[173,174] (xxi) L-lyxose esters,[175] (xxii) cryptophycin (5-hydroxy acid subunit),[176] (xxiii) polycyclic carbohydrates,[177] (xxiv) protected aminooxyprolines,[178] (xxv) carbahexopyranose stereoisomers,[179] (xxvi) deoxynucleic guanidine (DNG) oligonucleotide,[180] (xxvii) D-hica, a component of kulokekahilide-2,[181] (xxviii) methylsulfonate esters,[182] (xxix) (4*R*,5*S*)- and (4*S*,5*R*)-muricatacins,[183] (xxx) trioxilins,[184] (xxxi) functionalized β-C-glycosyl aldehydes (a part of ambruticin),[185] (xxxii) pyrrolidinols,[186] (xxxiii) carbocyclic nucleosides,[187] (xxxiv) Δ^2-OPC-8:0 (a substituted cyclopentanone derivative),[188] (xxxv) fluorescence-labeled probes based on phyllanthurinolactone [in these cases, 4-dimethylaminophenyldiphenylphosphine (**2**) instead of Ph_3P worked better],[189] (xxxvi) (+)-cardiobutanolide,[190] (xxxvii) 3-amino-2,3,6-trideoxysugars,[191] (xxxviii) sesquiterpene lactones,[192] (xxxix) 3-methylcyclopentadecanol,[193] (xl) optically active β-methyl-γ-alkyl-γ-butyrolactone,[194] (xli) chiral P,N-ligands with a cyclohexane backbone,[195] (xlii) optically active aminobenzindanol,[196] (xliii) cyclopenta[*d*]pyridazinediol,[197] (xliv) 4-hydroxytetrahydropyranone,[198] (xlv) alkynic esters as precursors to chiral substituted phthalides,[199] (xlvi) tetracyclic lactones as structural analogues of kaurane diterpenoids,[200] (xlvii) pyrrolidine-*trans*-lactones,[201] (xlviii) sporiolide B,[202] (xlix) 1-β-*O*-glucoronide esters,[203] (l) *trans*-dihydrodiols,[204] (li) aigialomycin D,[205] (lii) butenolides (α,β-unsaturated lactones),[206] (liii) phospholipid diastereomers,[207] (liv) enantiomerically enriched aryl-alkyl carbinols [e.g. 1-indanol, 1-tetralol, 1-phenylethanol, 1-(1-naphthyl)ethanol],[208] (lv) the chlorohydrin precursor for NPS-2143 (calcilytic agent),[209] (lvi) (*S*)-4-benzyloxy-5,5-dimethoxypentanoic acid,[210] (lvii) (3*S*,4*R*)-1,1-difluoro-4-hydoxy-3-(palmitoylamino)-4-phenylbutylphosphonic acid (sphingomyelinase inhibitor),[211] (lviii) a tetracyclic diol precursor in the synthesis of cylindrospermopsin,[212] (lix) azidosphingosine,[213] (lx) a pseudoenantiomeric bisoxane fragment of phorboxazole A,[214] (lxi) 1-aminoalkyl-γ-lactones,[215] (lxii) C(1)−C(9) and C(12)−C(26) subunits of macrolide rhizoxin,[216] (lxiii) taxol precursors (a

Scheme 15

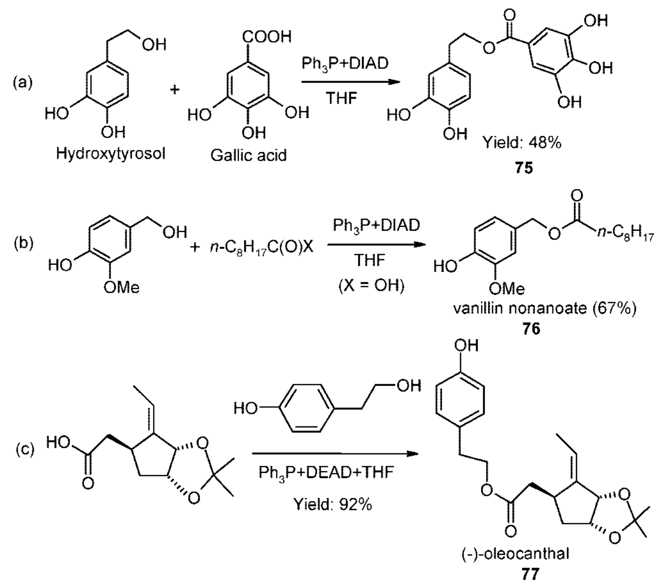


PMB = *p*-methoxybenzyl; DMB = dimethoxybenzyl; TBS = *tert*-butyldimethylsilyl

bicyclo[9.3.1]pentadecatriene derivative),[217] (lxiv) 2,3,5,6-tetrasubstituted tetrahydropyrans,[218] (lxv) *N*-Boc-β-methylphenylalanines,[219] (lxvi) *cis*-2-amino-1-indanol,[220] (lxvii) 4-amino-1,2,3-cyclopentanetriols,[221] (lxviii) segment C of tautomycin,[222] (lxix) the C(3)−C(13) segment of the macrolide rhizoxin,[223] (lxx) macrosphelide A/B,[224,225] (lxxi) bengamide B,[226] (lxxii) chiral substituted cyclopentenols,[227] (lxxiii) *N*-Cbz-protected 6-aminotalose and 6-aminogulose,[228] (lxxiv) (−)-lasubine II,[229] (lxxv) L-lyxose dibenzyl dithioacetal from D-ribose dibenzyl dithioacetal,[230] (lxxvi) enantiomers of 1-phenylethan-1,2-diol,[231] (lxxvii) 3-*O*-dimethoxytrityl-2(*S*)-(*N*-thymin-1-ylacetyl)-amino-1(*R*)-phenyl-1,3-propanediol,[232] (lxxviii) tropane alkaloids,[233] (lxxix) macrosphelides C and F,[234] (lxxx) the hydroxyl- and aldehyde-substituted cyclohexene part of the guanacastepene skeleton,[235] (lxxxi) 4-deacetoxyagosterol A,[236] (lxxxii) configuration confirmation (not total synthesis) of 6-epikericembrenolide A (1*S*,2*S*,6*R*),[237] (lxxxiii) modified 1β-methyl carbapenem antibiotic S-4661,[238] (lxxxiv) vitamin D_3 A ring precursor diols[239] and chiral cyclohexenols (analogues of dihydroxyvitamin-D_3 A ring synthons),[240,241] (lxxxv) 8-(phenylsulfonyl)de-A,B-cholestane precursors to hydroxyvitamin D_3,[242] (lxxxvi) bullatacin,[243] (lxxxvii) 2′-deoxy-4′-thio-1′-purine nucleosides,[244] (lxxxviii) the aplasmomycin tetrahydrofuran ring,[245] (lxxxix) D-isomannide,[246] (xc) *trans*-2,3-dihydroxy-1,2-dihydrobenzenes,[247] (xci) 7-hydroxy-5-dodecanolides,[248] (xcii) C^{10} esters of dihydroartemisinin,[249] (xciii) amphidinolide A (presumed structure),[250] (xciv) 17α-dihydroequilenin (a steroid),[251] (xcv) *cis*-methyl-3-hydroxy-2-pyrrolidone-5-carboxylates,[252] (xcvi) tetrahydrolipostatin,[253] (xcvii) cyclohexylnorstatine,[254] (xcviii) trilobacin,[255] (xcix) *trans*-(2*R*,3*S*)-2-hydroxymethyl-3-hydroxypyrrolidine,[256] (c) *syn*-α-hydroxy-β-amino acids,[257] (ci) optically active 1,2-diols,[258] (cii) protected 3-hydroxy-4-cyclohexenylcarbinol,[259] (ciii) an intermediate for the β-adrenergic receptor antagonist MY336 (results obtained in the esterification were utilized),[260] (civ) 3,4-epoxybutane-1,2-dio1,[261] (cv) 7-deoxyxestobergsterol A (a pentacyclic steroid),[262] (cvi) (−)-hastanecine,[263,264] (cvii) (+)-asperlin,[265] (cviii) an enantiomer of lubeluzole,[266] (cix) 8-*O*-4′-neolignans,[267] (cx) (−)-andrachcinidine,[268] (cxi) (*S*)-timolol,[269] (cxii) the cytotoxic agent (−)-macrolactin A,[270] (cxiii) the C^4 epimer of 7-oxa-phomopsolide E,[271] (cxiv) a precursor to amphidinolide H1,[272] (cxv) panclicins A−E (pancreatic lipase inhibitors),[273] (cxvi) 17α-estradiol derivatives,[274] (cxvii) (+)-muscarine iodide,[275] (cxviii) 3,5-dideoxy-5-*C*-branched-chain hexulopyranose derivatives,[276] (cxix) the L-enantiomer of trifluridine, an antiherpetic drug approved by the FDA for topical applications,[277] (cxx) unsaturated aminopyranosides,[278] (cxxi) (+)-broussonetine C,[279] (cxxii) *trans*-4-N^3-benzoylthymin-1-yl-2-(Boc)aminomethyl pyrrolidine,[280] (cxxiii) (*R*)-3-iodocyclohexenyl acetate,[281] (cxxiv) the acetate of chiral dihydropyranol,[282] (cxxv) cyclic ADP-carbocyclic xylose,[283] (cxxvi) (−)-3-hydroxybaikiain,[284] and (cxxvii) an epimer of 5α-cholestan-3α-ol.[285]

It is of some interest to see whether kinetic resolution of secondary alcohols can be effected or not by a Mitsunobu protocol. In the reaction using 0.5 mol equiv each of Ph_3P, DEAD, and (1*S*)-(+)-ketopinic acid with 1 mol of racemic (±)-PhMeCHOH, the unreacted alcohol could be obtained in yields of 44% with an *ee* of ∼90%.[286] It was also possible to use the pentacoordinate derivative **72** obtained by reacting 1,1′-bi-2-naphthoxy-based P^{III} compound (+)-(1,1′-$C_{20}H_{12}O_2$)-$P(NMe_2)$ (**71**) with DIAD to effect kinetic resolution as shown by Kellogg and co-workers (Scheme 14).[108] However,

Scheme 16



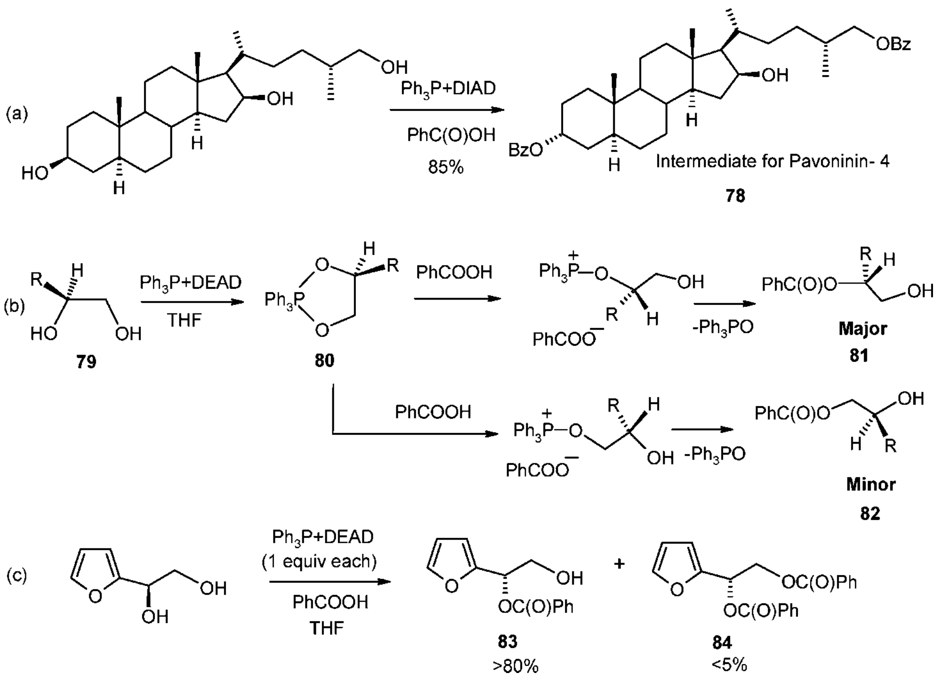
the enantiomeric excess (*ee*) was only moderate (up to 39%) and the yields were not very high. It may be noted that this reaction took place via a pentacoordinate phosphorus intermediate rather than a betaine analogous to **15**. Use of the phthalimide route [Ph_3P−DEAD, phthalimide, and racemic alcohol] also gave moderate *ee* of the resolved alcohols.[109]

Although the Mitsunobu reaction is conducted typically at low temperatures, it has now been established that the controlled microwave heating minimized the time required. It has been noted that while the conventional protocol at room temperature was sluggish, essentially complete esterification of (*S*)-sulcatol to the (*R*)-acetate using ∼2 equiv of the reagents could be accomplished within 5 min at 180 °C under sealed-vessel microwave conditions.[287] An excellent review on this as well as *N*-alkylation (in general, on microwave-assisted synthesis) is available.[288]

3.2. Esterification with Retention (in the Intermolecular Mitsunobu Reaction)

In intermolecular Mitsunobu esterification, if the alcohol is sterically hindered, retention of configuration may be favored. In the total synthesis of (+)-zampanolide reported by Smith and co-workers, retention of configuration leading to product **74** was encountered in an intermediate step (Scheme 15).[289] Two possible reasons were considered. First was the failure of the Morrisson−Brunn−Huisgen intermediate to activate the alcohol because of steric congestion. The reaction would then proceed with the acyloxyphosphonium intermediate. The second possibility was the formation of an oxonium intermediate followed by ring opening by the carboxylate. This was not favored in view of the regioselectivity observed in the reaction. It is important to note that the investigators had to saturate the reaction medium with a large excess of the carboxylic acid as well as the reagents to effect the reaction. When they used the normal procedure of premixing acid and alcohol followed by addition of Ph_3P−DEAD, incomplete consumption of the starting material **73** was noticed even after prolonged stirring at room temperature. When they tried to perform the reaction at 40−50 °C, only an unexpected dehydration side product with an internal double bond was obtained almost exclusively. In reactions using allyl alcohols also, a fairly high percentage

Scheme 17



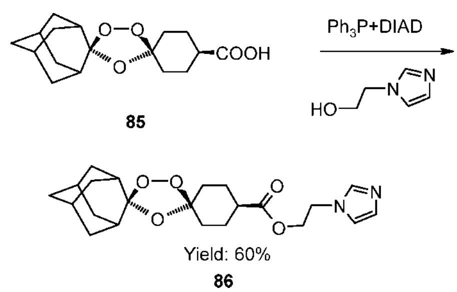
of retention product is usually obtained;[290] several earlier reports also have revealed such a feature.[291−293] The observation of retention is attributed to deviations from the normal mechanistic pathways involving S_N2' or S_N1 processes or to the participation of neighboring groups. While preparing isodideoxythionucleosides, Jeong et al. observed minor retention products in esterification (as well as azidation) and ascribed it to the participation of sulfur of the nucleoside skeleton.[294,295] Retention of configuration was also reported recently by Qing and co-workers in the synthesis of fluorinated nucleosides.[296]

3.3. Competitive Esterification

Since the Mitsunobu reaction effectively differentiates between alcoholic and phenolic hydroxyls in esterification reactions, it provides a broadly applicable entry into various phenolics and polyphenolics (e.g. **75**) of biomedical and nutritional relevance (Scheme 16a).[297] In the synthesis of vanillin nonanoate **76** (Scheme 16b), other routes [X = Cl using pyridine and X = OH using DCC/DMAP (cat.), DEPC/TEA, or $Yb(OTf)_3$ (cat.), THF] gave poor yields or a mixture of products. Discrimination between alcoholic and phenolic hydroxyls has also been recently utilized in the total synthesis of (−)-oleocanthal (**77**), a naturally occurring nonsteroidal, anti-inflammatory and antioxidant agent (Scheme 16c).[298]

In cases where two secondary alcoholic groups are available, it can be expected that the sterically less hindered site is the one that will preferentially take part in esterification with inversion. Such a distinction has been utilized in the synthesis of the shark repellent pavoninin-4 recently (Scheme 17a).[299] However, this need not be the case with 1,2-diols. Unsymmetrical 1,2-diols (e.g. 1,2-propanediol and 1-phenyl-1,2-ethanediol) underwent a highly chemoselective monobenzoylation with Ph_3P−DEAD/benzoic acid, affording both *kinetically and thermodynamically* least stable secondary benzoate (Scheme 17b).[83,300] The 1,3,2-λ^5-dioxaphospholane species **80** was the key intermediate; in its conversion to the oxyphosphonium salt, the proton transfer from the acid occurred predominantly at the least hindered site, leading to

Scheme 18

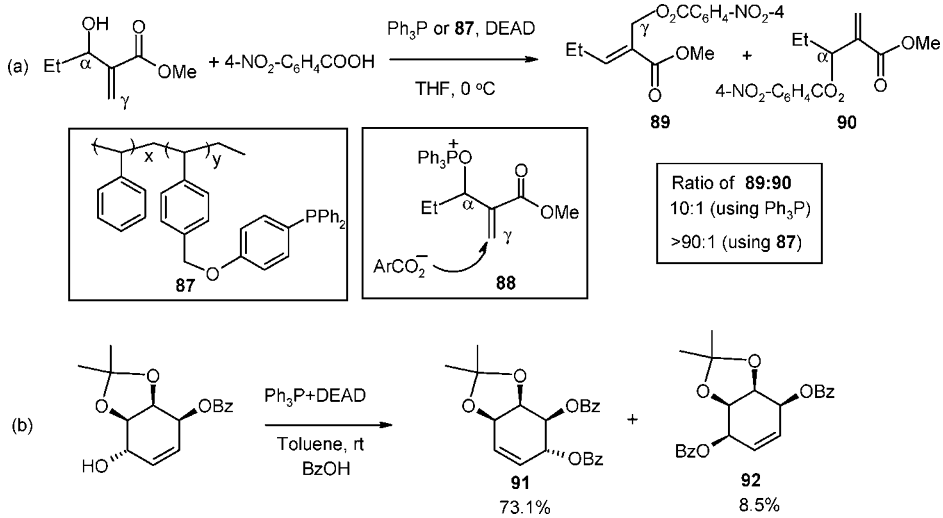


secondary benzoate **81** as the major product. This result is important to be noted whenever one is using a 1,2-diol in the Mitsunobu reaction. Similar selectivity has also been observed by Voelter and co-workers.[301] In an intermediate step in the total synthesis of *R*-(−)-argentilactone, they obtained 80% of the *secondary* monobenzoate **83** with <5% of the dibenzoate **84** when 1 mol equiv of Ph_3P−DEAD was used (Scheme 17c). One more example of this type has been reported recently by Wang and Yue in connection with the synthesis of (*R*)-(−)-dihydrokavain by starting with (*S*)-4-phenyl-1,2-butanediol (*S*)-$PhCH_2CH(OH)CH_2OH$.[302] In this case, the authors found it more convenient to prepare the di-4-nitrobenzoate ester and then hydrolyze it to get the inverted diol (*R*)-$PhCH_2CH(OH)CH_2OH$ in high yield and excellent *ee* (98%).

The ozonide-acid **85** reacts with 1-(2-hydroxyethyl)imidazole to form the ozonide imidazole ester **86** (Scheme 18) in decent yield; similarly phenyl ethers also are synthesized.[303] This reaction illustrates that the ozonide functionality does not interfere with triphenylphosphine.

In contrast to the normal alcohols, Baylis−Hillman adducts (allylic alcohols)[304] behave differently. Both the α and γ adducts are formed, with the latter predominating (Scheme 19a).[305−307] The yields of the γ adducts can be maximized by using non-cross-linked polystyrene-based triphenylphosphine **87**.[306] After forming the oxyphosphonium salt (**88**), the carboxylate anion attacks the olefinic γ-carbon rather than the normally expected α-carbon leading to the *E*-isomer of

Scheme 19



Scheme 20

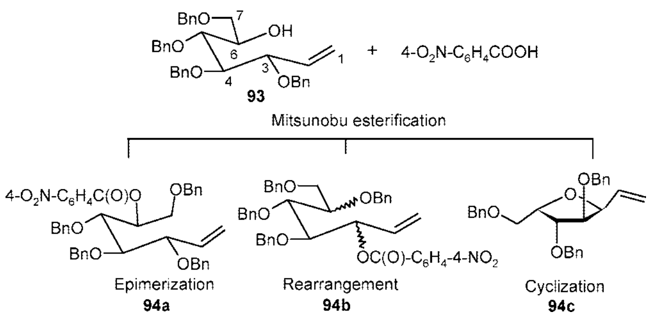


Table 1. Product Distribution in the Mitsunobu Esterification of 93 (cf. Scheme 20)[a]

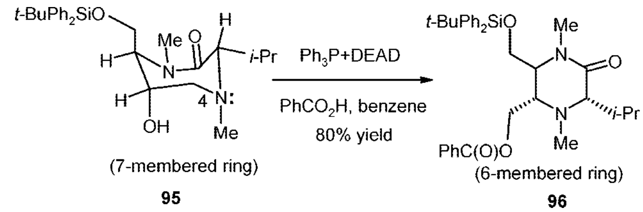
					product ratio	
mole ratio					**94a**	**94b**
Ph_3P	acid	DEAD	Et_3N	solvent		
4	4	4		THF	1	5[b]
2	2	2	5	THF	2	1
2	10	2	25	THF	1	2
2	2	2	5	toluene	4	1
2	10	2	25	toluene	1	1

[a] Data taken from ref 310. [b] The authors observed minor cyclization product **94c** also.

89. A stereo- and regioselective rearrangement was also observed by Chung and co-workers while attempting to esterify a conduritol (an allylic alcohol) derivative (Scheme 19b).[308,309] The reaction proceeded predominantly with both inversion and allylic rearrangement; a likely pathway for the formation of **91** has also been suggested by the authors.

The Mitsunobu reaction on the glucose derivative (3*S*,4*R*,5*R*,6*R*)-3,4,5,7-tetrabenzyloxy-6-hydroxy-1-heptene (**93**) yielded an unexpected major rearranged product (Scheme 20), as reported by Persky and Albeck.[310] The product distribution varied with the stoichiometry of the reagents as well as the solvent used. Thus, by suitably modifying the ratios of the reactants and solvents, the authors could obtain a 4:1 ratio of the products **94a/94b**. Possible mechanistic pathways are also discussed in the paper. Because these results are instructive for any future work, the data are shown in Table 1. Similar epimerization in other reactions leading to selectively labeled D-fructose and D-fructose phosphate analogues is also reported by the same authors.[311]

Scheme 21



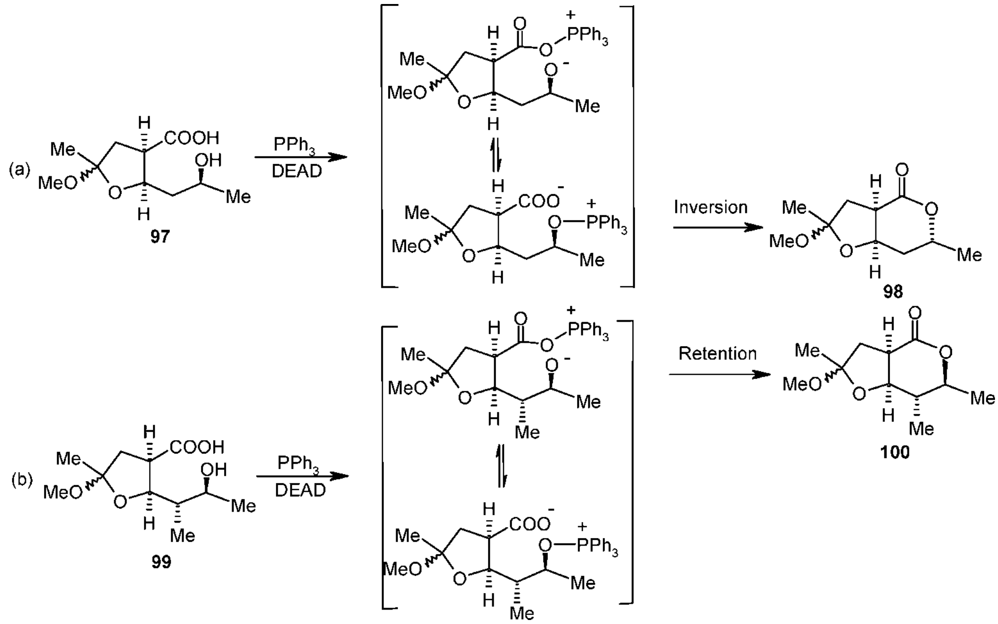
In an attempted epimerization of 6-hydroxy-1,4-diazepan-2-one (**95**) by a normal Mitsunobu protocol, Knapp et al. found ring contraction to 1,4-piperazine-2-one (**96**), although esterification did occur (Scheme 21).[312] A possible pathway involving one of the nitrogen lone pairs of electrons [N^4 in the scheme] was put forth by the authors to rationalize this result. Stereoselective transformations (along with esterification) of polyhydroxyazepanes to piperidine or pyrrolidine derivatives were also reported by Lohray et al. earlier.[313]

3.4. Lactonization/Macrolactonization

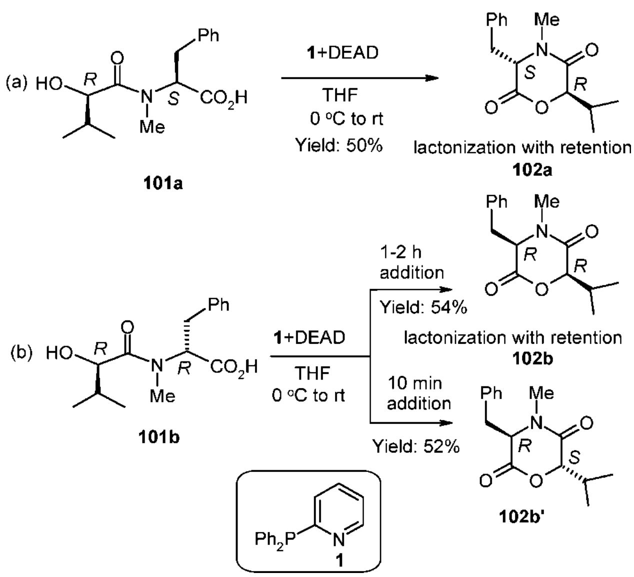
An intramolecular esterification will lead to lactonization, and the Mitsunobu protocol has long been known to be one of the viable methods to effect this.[12,314−320] Although inversion of configuration takes place during normal Mitsunobu esterification most often, retention is observed during lactonization of the hindered alcohol **99** (Scheme 22), very likely through the intermediacy of an acyloxyphosphonium salt followed by acyl transfer to the alcohol.[41,321] These results reported by DeShong and co-workers are of paramount importance in assigning the stereochemistry during macrolactonization involving natural product syntheses. Fleming and Ghosh had also observed retention of configuration during lactonization leading to a five-membered ring.[322] Involvement of a carbocation intermediate was invoked to explain this observation.

For the preparation of *S*,*S*- and *R*,*R*-configured morpholine-2,5-diones **102a**, when the hydroxy acid **101a** was treated with Ph_3P−DEAD in THF, it was difficult to purify the products due to persistence of Ph_3PO and the hydrazine. This problem was overcome by using diphenyl(2-pyridyl)phosphine (**1**), which could be removed in the workup by an aqueous acid wash (*cf.* Scheme 23a).[323] The isolated compounds were the products of Mitsunobu cyclization with *retention* of configuration. However, in the case of **101b**,

Scheme 22



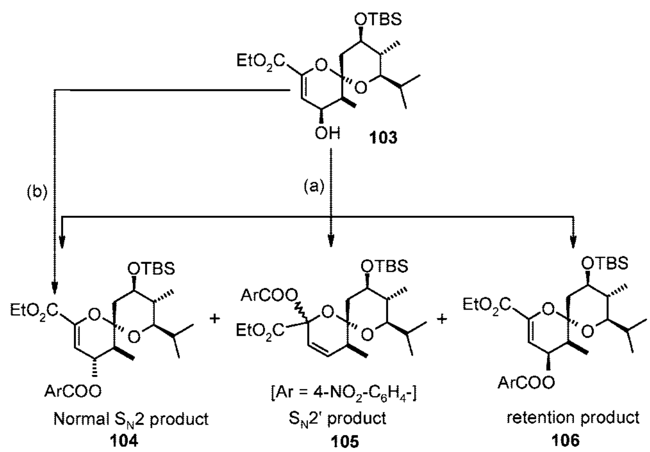
Scheme 23



the configuration of the product was dependent on the addition time. Slow addition (1−2 h) of the hydroxy acid to the premixed solution of Ph_3P + DEAD resulted in **102b**, while fast addition (10 min) afforded **102b′** (Scheme 23b). These studies were done in connection with the total synthesis of bassiatin and its stereoisomers. The authors have pointed out that this was the first example of Mitsunobu cyclization with a different stereochemical outcome depending on the rate of addition. This paper also summarizes some of the earlier results with regard to retention/inversion in the lactonization process.

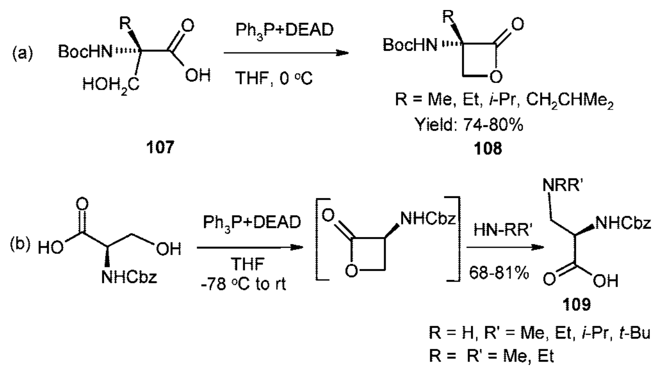
In the synthesis of spiroketals **104**−**106** from **103**, Lopez et al. have found that a less polar solvent mixture can avoid the interference due to retention as well as other byproducts by using benzene−hexane (2:1) medium in place of THF (Scheme 24).[324] Cyclization of *N*-Boc-α-alkylserines leading to 2-oxetanones **108** was efficiently carried out by cyclization of *N*-Boc-α-alkylserines **107** using a Mitsunobu protocol (Scheme 25a).[56] Here, deprotection of the amine by CF_3COOH in the presence of *p*-toluenesulfonic acid afforded

Scheme 24



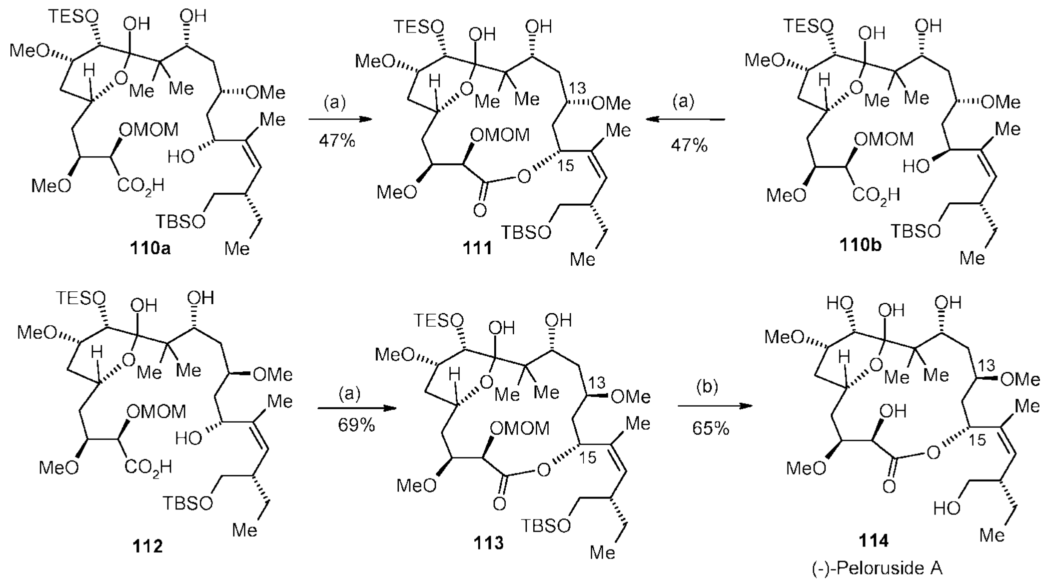
(a) Ph_3P, DEAD, 4-O_2N-$C_6H_4CO_2H$, **THF**
(b) Ph_3P, DEAD, 4-O_2N-$C_6H_4CO_2H$, **C_6H_6-hexane** (better yield of inverted product)

Scheme 25



the *p*-toluenesulfonate salts of optically active 3-amino-3-alkyl-2-oxetanes. These were then coupled with amino acids followed by oxetane ring opening by appropriate thiols in the presence of Cs_2CO_3 to lead to peptidomimics. An analogous lactonization has been used in the synthesis of enantioenterobactin.[325] Another useful alternative is to open the four-membered lactone ring (obtained via the Mitsunobu protocol) with an amine to give various modified amino acids

Scheme 26



(a) Ph_3P+DIAD/THF; (b) 4N HCl/THF

TES = triethylsilyl; MOM = methoxymethyl; TBS = *tert*-butyldimethylsilyl

as shown by Moura and Pinto (Scheme 25b).[326] Mohapatra et al. have used Mitsunobu lactonization to generate a spirobicyclic β-lactone-γ-lactam that is present in oxazolomycin.[327] A γ-lactone intermediate with a five-membered ring required in the total synthesis of pyranicin, a cytotoxic acetogenin, was prepared in excellent yield via Mitsunobu lactonization by Takahashi et al.[328] In the preparation of 1-deoxy-D-galactohomonojirimycin reported by Achmatowicz and Hegedus also, a five-membered lactone was involved in an intermediate step. Both Mitsunobu and Mukaiyama procedures worked well in this case.[329] A bicyclic tetronate that is a part of the core structure in the antibiotic abyssomicin-C was prepared by Maier and co-workers via Mitsunobu transannular lactonization.[330] Polymer-supported triphenyl phosphine along with DIAD was utilized recently in a lactonization step by Burke and co-workers in the synthesis of thrombaxane B_2, since use of Ph_3P itself posed separation problems.[331]

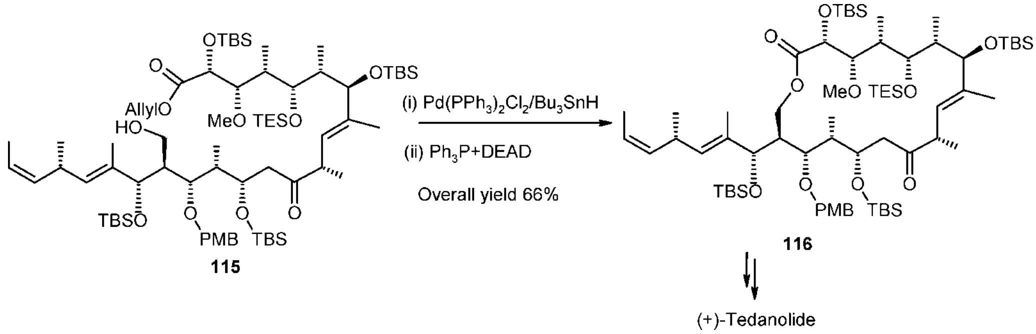
Macrolactonization

Creation of large lactone rings (macrolactonization) is a synthetic challenge. Perhaps because of the mild reaction conditions, the Mitsunobu protocol is quite popular in this area and is utilized very frequently in natural product syntheses. Earlier reports on the macrolactonization route relate to (i) verrucarin A,[332] (ii) the griseoviridin core (9-membered macrocycle),[333−335] (iii) (+)-milbemycin β_3,[336,337] (iv) suspensolide,[338,339] (v) latrunculins A and B,[340−344] (vi) (+)-gloeosporone,[345−347] (vii) (+)-brefeldin C,[348] (viii) 19-epi-avermectin B_1,[349] (ix) cyclodepsipeptides,[350−353] (x) erythromycin derivatives,[354,355] (xi) cyclothialinide,[356] (xii) lasiodiplodin,[357] (xiii) antifungal dilactones UK-2A and UK-3A,[358,359] and (xiv) (±)-patulolide C.[360] In the synthesis of zearalenone dimethyl diether, polymer-supported alkyl diazocarboxylate afforded a better yield (42%) compared to the classical route (8%).[361] Bracher and Krauss have reported a simple Mitsunobu route to the saturated analogue, (±) Zearalanone, which contains two intact phenolic −OH groups.[362] The yield in the cyclization step was 42%. A similar macrocycle was also prepared by Krauss et al. by macrolactonization.[363] A solid as well as solution phase synthesis (based on Wang resin) of two 19-membered ring containing macrolactones via the hydroxy acids has been reported by Gragnon et al.[364]

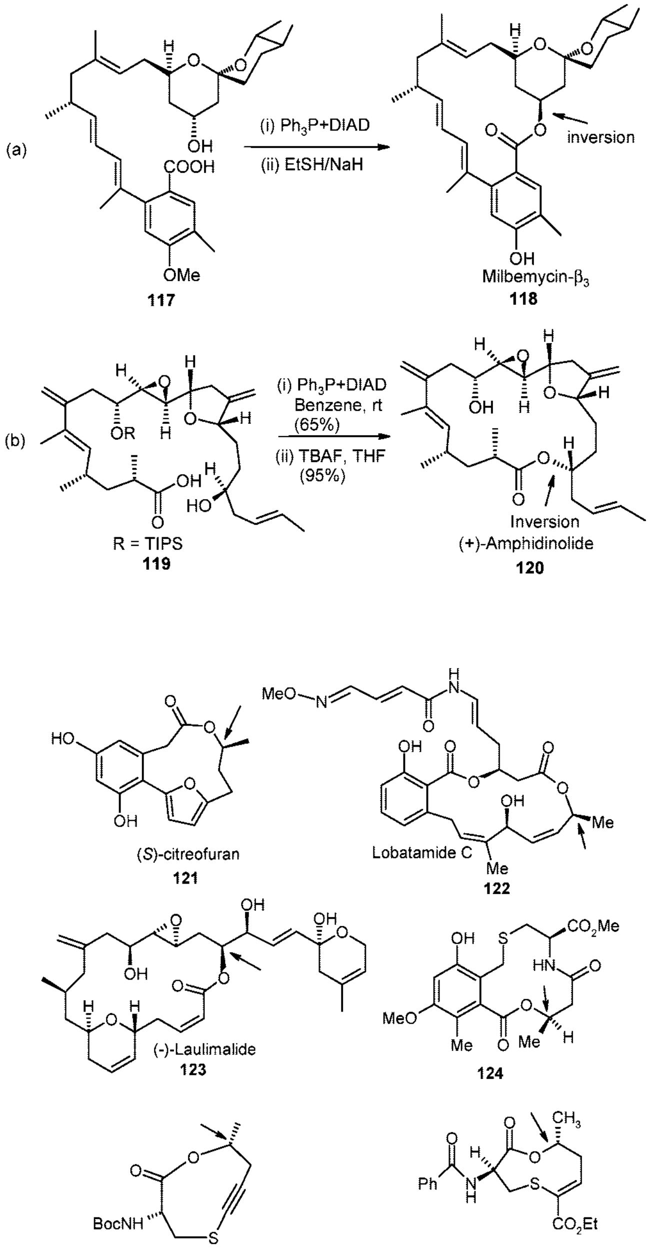
Mitsunobu lactonization was utilized by De Brabander and co-workers in the synthesis of (−)-**114**, the enantiomer of the naturally occurring (+)-peloruside, a marine metabolite (Scheme 26).[365] More importantly, while preparing its protected C^{13} epimer **111**, an interesting observation was made. By starting with either **110a** or the isomeric **110b**, the authors ended up with the same macrocyclic compound **111**. They rationalized this result on the basis of geometrical/conformational constraints that could have precluded the formation of C^{15} epimeric lactones and enforced the cyclization of substrate **110a** via an acyloxyphosphonium intermediate (retention) and **110b** via the alkoxyphosphonium intermediate (inversion), thus providing a nice illustration of a configuration dependent mechanistic switch. The other two unprotected hydroxyl groups do not seem to have interfered in this lactonization. Macrolactonization involving primary alcohols does not have this problem of stereochemistry. A recent example of this type is involved in the synthesis of (+)-tedanolide (Scheme 27).[366] Considering the fact that an 18-membered macrocycle **116** is formed, a decent yield of ~66% (including a preceding deprotection of allyl ester) in the Mitsunobu cyclization is noteworthy. This yield was higher than that obtained by other routes such as the Keck−Boden protocol or Yamaguchi esterification.

Several members of the family of structurally complex milbemycins have shown significant activity against agricultural pests as well as parasites, with low toxicity to plants. In recent work on the synthesis of one of these members (**118**), Li and O'Doherty utilized the Mitsunobu reaction in two important steps, one involving etherification and the other incorporating a macrolactonization; the latter is shown in Scheme 28a.[367] The NaSEt used in the last step was to remove the methyl protecting group. It may be noted that, in this case, an inversion of configuration at the secondary alcohol site is observed. The yield in the Mitsunobu step was 79%. In the synthesis of several other macrocycles that include (−)-dactylolide[368] and (−)-spongidepsin,[369] inversion

Scheme 27



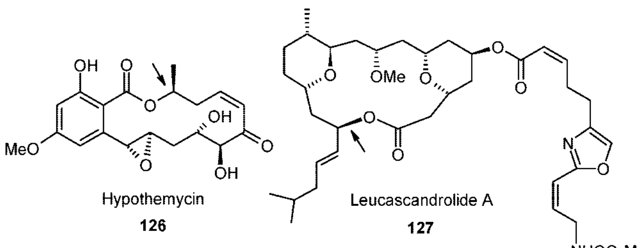
Scheme 28



of configuration at the secondary alcohol site was effected by Mitsunobu esterification. In the preparation of (+)-amphidinolide **120**, the antipode of the natural antitumor macrolide, the macrolactonization took place by inversion of configuration at the secondary alcoholic carbon site (Scheme 28b).[370] The structure of compound **120** has been established by single crystal X-ray diffraction studies. Lactonization with inversion of configuration at the chiral center has also been observed in the synthesis of (i) the naturally occurring macrocycle (S)-citreofuran **121** [using Ph_3P−DEAD/toluene] reported by Bracher and Schulte,[371] (ii) the potent antitumor macrolide lobatamide C (**122**) [Ph_3P (10 equiv)/DIAD (10 equiv)/THF] reported by Porco et al.,[372−374](iii) the cell growth inhibitor (−)-laulimalide **123** reported by Paterson et al.[375,376] as well as Crimmins et al.,[377] and (iv) the marine metabolite xestodecalactone A reported by Danishefsky and co-workers.[378] In the lactonization leading to the DNA gyrase inhibitor (cyclothialidine analogue) **124**[379] again, inversion was the pathway; approximately 1:1.3 mol equiv of the substrate to reagents in toluene was used to obtain reasonable yields (53%) of the cyclized product. Analogous core structures with different ring sizes have been prepared by Hebeisen and co-workers.[380] Inversion at the chiral alcohol center was utilized in the construction of the 9-membered thiolactone core (e.g. **125a**) of griseoviridin under dilute conditions (0.014 M) in toluene−THF medium.[381] In the synthesis of the same core with different substituents (**125b**; yield 68%) reported by Marcantoni et al., use of (2-pyridyl)PPh_2 and DTBAD alleviated the problem of tedious chromatography.[382] The authors have pointed out the crucial importance of adding the precursor hydroxyl acid very slowly, which might have avoided high stationary concentrations of the substrate. The corresponding methyl ester had been prepared earlier by Meyers and Amos by a traditional Mitsunobu reaction using Ph_3P−DEAD.[333] In a later paper, Meyers and co-workers have prepared the lactone with the same skeleton but as an allyl (in place of methyl or ethyl) ester that was obtained in 50−70% yields;[383] this was an intermediate in their synthesis of (−)-griseoviridin.

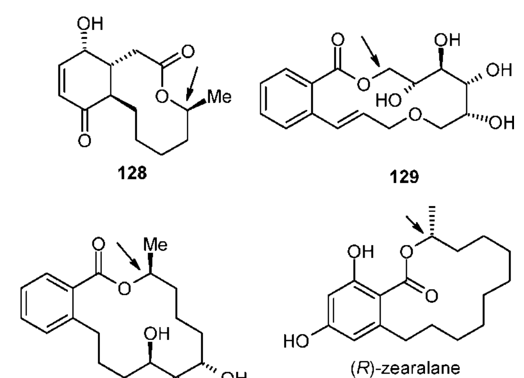
The 14-membered ring containing macrolides required for the synthesis of hypothemycin **126** were prepared more efficiently via a Mitsunobu macrolactonization (64−70%, inversion at the secondary alcohol chiral center) than via an intramolecular Suzuki coupling, by maintaining a concentration of 0.007−0.01 M of the precursor in toluene.[384] For the macrolactonization in the synthesis of leucascandrolide A (**127**), Wipf and Reeves added the required hydroxyl acid via syringe to a premixed Ph_3P (25 equiv)−DIAD (20 equiv) solution in THF at 0 °C to obtain a yield of 58% of the protected intermediate lactone. Only the inversion pathway was observed here.[385] Paterson and Tudge also used an excess of Ph_3P−DEAD (~6 equiv to 1 equiv of the hydroxyl acid) to obtain a decent yield of ~50% at the lactonization step while preparing this compound.[386] In another paper, for the macrolactonization step in the synthesis of (+)-leucascandrolide A, the same authors could get a 65% yield. In the

penultimate step, a Mitsunobu inversion (81% yield) was effected on a chiral secondary alcohol center.[387]



Hypothemycin **126** Leucascandrolide A **127**

A convergent stereoselective synthesis of the macrolactone ring of the bacterial DNA primase inhibitor Sch 642305 (**128**) was established using the Mitsunobu cyclization with inversion of configuration; 1:5 mol equiv of the substrate to the reagents was utilized.[388] Mitsunobu cyclization was also employed for (i) the synthesis of polyhydroxylated oxamacrolide **129** (97% yield) wherein only a primary alcoholic group was involved in the cyclization step,[389] (ii) the construction of a 14-membered ring (73% yield) of the spiromacrolide retipolide (present in North American mushrooms),[390] and (iii) an intermediate stage while preparing the benzolactone **130** (78% yield), a model for the naturally occurring queenslandon.[391] In the synthesis of one of the enantiomers of zearalane [(R)-**131**], Mitsunobu lactonization with inversion was a key step. About 8 mol equiv of the reagents per substrate was utilized to obtain a 50% yield during cyclization.[392]



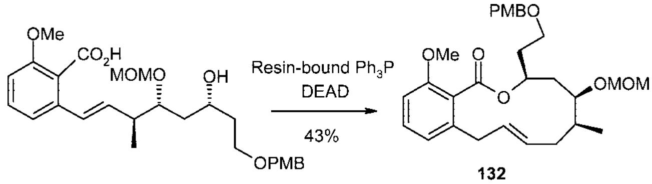
128 **129** **130** (*R*)-**131**

High dilution conditions, in general, should favor formation of cyclic products. In this context, polymer-supported phosphines/azocarboxylates which give rather low concentrations of the reactants, in addition to the fact that the products can be removed by filtration, may offer advantages over the traditional Ph_3P−DEAD system. Resin-bound triphenylphosphine in conjunction with DEAD was found to be more effective (yield 43%) compared to resin-bound DEAD along with free Ph_3P in the ring closure leading to lactone **132** (Scheme 29), an intermediate in the synthesis of salicylihalamides A and B.[393] Actually, there was no reaction in the latter case. Use of DIAD in place of DEAD reduced the yields to ca. 25%. The resulting compound is a 12-membered macrocycle. In a later work, the same group has reported the total synthesis of salicylihalamides A and B that involved (i) Suzuki cross-coupling and intramolecular Mitsunobu cyclization as well as (ii) Mitsunobu esterification and ring-closing metathesis.[143] Two other syntheses involving macrolactonization are those of (a) combretastatin D-4, which inhibits cell proliferation of colon carcinoma cells reported by Nishiyama and co-workers,[394] and (b) macrocyclic glycopeptides reported by Wong and his co-workers.[395]

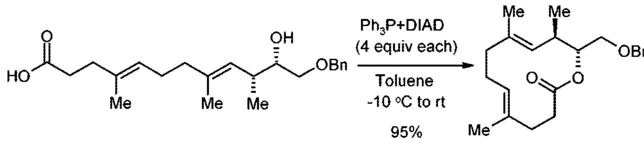
Although we have discussed success stories of Mitsunobu macrolactonization above, there are cases wherein difficulties have surfaced. For example, in the total synthesis of the antibiotic lonomycin A that was reported by Evans and co-workers (Scheme 30), use of DEAD/THF/25 °C resulted only in the DEAD substrate acylation (85%) but not the required macrocyclic intermediate **133**.[396] Changing the solvent to benzene afforded **133** in a yield of only 47%. The problem was solved by the use of hindered DIAD in conjunction with a less polar solvent such as toluene, which gave the best yields (95%); a 1:4 mole ratio of the substrate to reagents was utilized. In another study on the synthesis of the natural product (−)-spinosyn A, Frank and Roush observed that although macrolactonization from **134** to **135** in THF solvent occurred, the hydrazide N-alkylated product **136** was also obtained in significant amounts (Scheme 31). Use of DIAD (48% yield of **135**) in place of DEAD also did not help much in this case.[397] Nicolaou and co-workers have recently explored different approaches for the construction of the macrocycle present in palmerolide isomers. Despite the fact that the Mitsunobu route afforded the expected macrolactone, side products that contained the diethyl azodicarboxylate residue also had formed.[398]

It was mentioned above (cf. Scheme 19) that the Baylis−Hillman alcohols, which are allylic in nature, lead to both α and γ esters and thus behave differently from normal alcohols. Even in the synthesis of macrolactonization, use of allyl alcohols is not straightforward, as pointed out by Campagne and co-workers.[37] Rychnovsky and Hwang

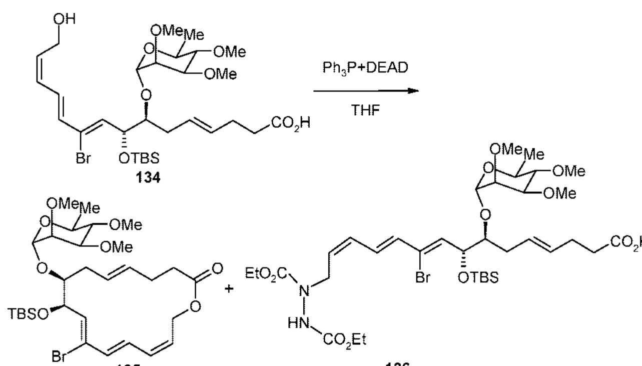
Scheme 29



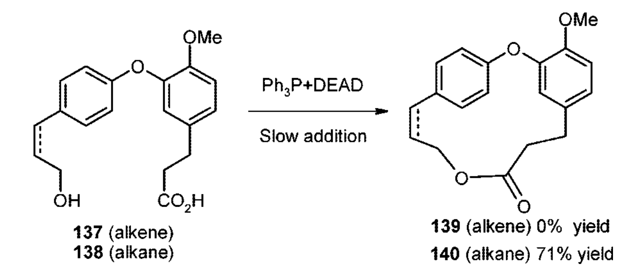
Scheme 30



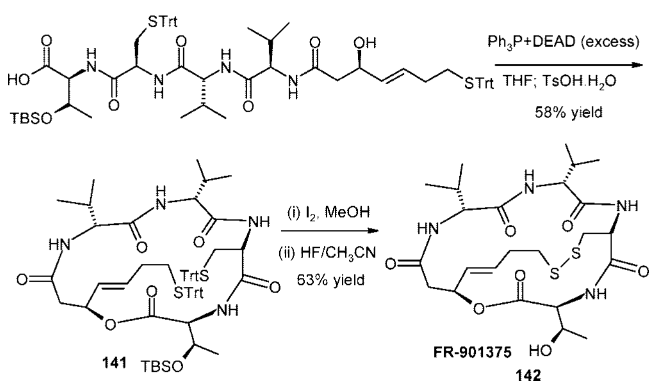
Scheme 31



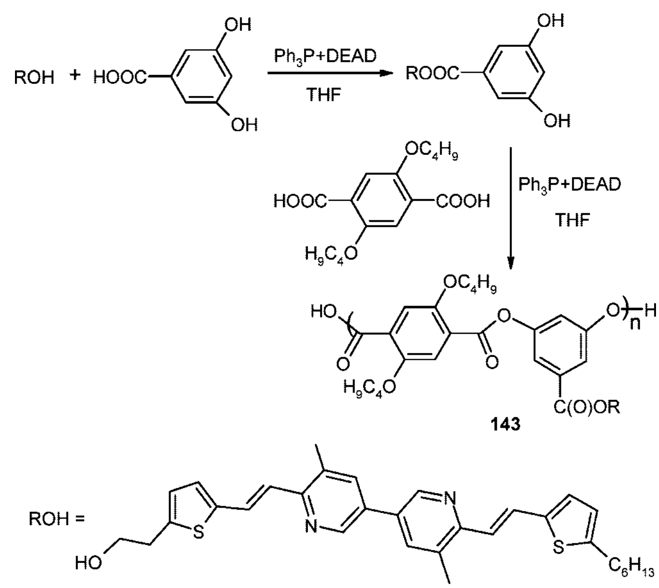
Scheme 32



Scheme 33



Scheme 34



used both allylic **137** and its corresponding saturated substrate (**138**) and found that only the saturated substrate underwent smooth macrolactonization to lead to **140** (Scheme 32). They rationalized the results owing to a competing S_N1 side reaction because of conjugation to an electron-rich aromatic ring in the case of an allylic substrate, and they have used this methodology in the synthesis of the natural product combretastatin D1.[399] Couladouros et al. obtained an excellent yield (91%) in the macrolactonization step by slow addition of the saturated *seco*-hydroxy acid (7 h) and maintaining a concentration of <2 mM.[400−402] Simon and co-workers noted that addition of *p*-toluenesulfonic acid and an excess (>20 fold) of the reagents prevented the side reactions of the allylic alcohol substrate in the synthesis of cyclodepsipeptides.[353] A similar approach was adapted by Chen et al. for the synthesis of **141**, a precursor for the natural product depsipeptide FR-901375 (**142**) (Scheme 33).[403]

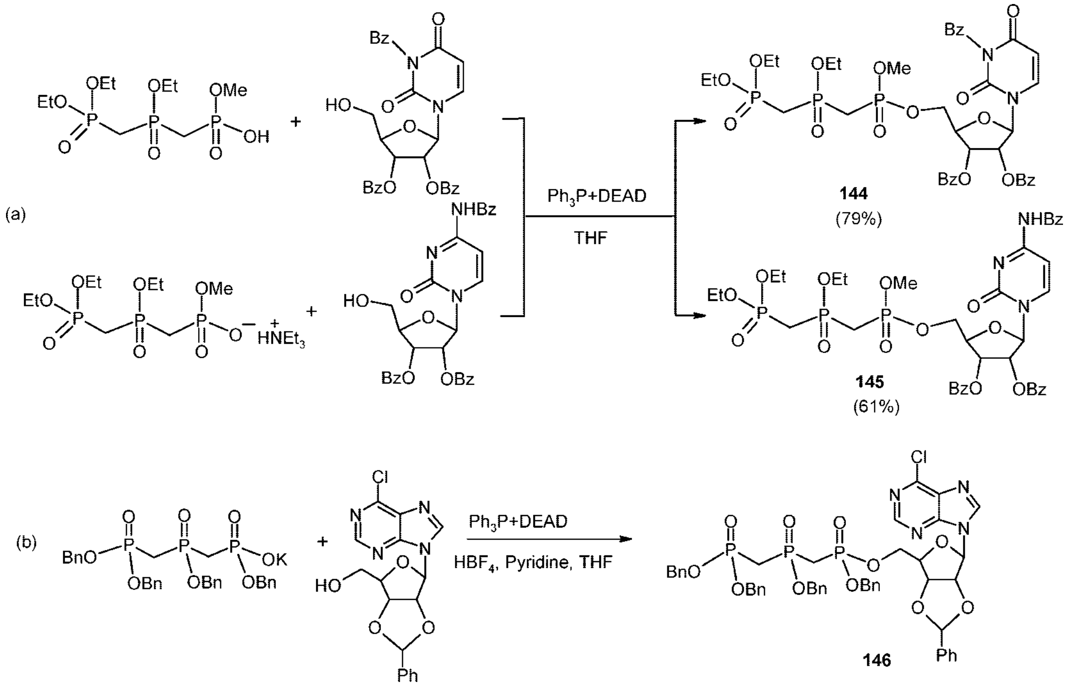
3.5. Other Esterification Reactions Including Those of Phosphates/Phosphonates

Use of a primary or a saturated achiral alcoholic substrate generally does not pose a problem in the Mitsunobu process, and hence, only a list of compounds wherein it is used is provided here. These include (i) photoresponsive esters with an azobenzene group, using the reaction of the mesogenic alcohols with fumaric acid or maleic acid,[404] (ii) cyclohexyl nitronic ester by starting with cyclohexanol,[405] (iii) polar functional PPV derivatives with ester groups for sensor applications,[406] (iv) capsular polysaccharides,[407] (v) acetylenic esters of 2,3-dibromomaleic acid[408] and isophthalate esters[409] as precursors for dendrimers, (vi) enfumafungin,[410] (vii) buprestin A and B,[411] (viii) cinnamyl monoglyceride,[412] (ix) *β*-acyl glucuronides,[413−415] (x) ^{17}O-enriched esters of carbohydrates with PhC(O)^{17}OH,[416] (xi) bromoacetylation of Wang resin,[417] (xii) (±)-6-myoporol,[418] (xiii) multiple porphyrin arrays through ester linkages,[419] (xiv) 3,5-hexadienyl acrylates,[420] (xv) mono- and di-esters of sucrose with long chain carboxylic acids,[421] (xvi) (*S*)-(−)-camphanic acid esters of (hydroxymethyl)pyrroles,[422] (xvii) *syn*, *syn*-bicyclo[3.3.0]octyl-2-benzoate,[423] (xviii) an esterification step in the synthesis of *syn*-enol ethers,[424] (xix) glass forming liquid crystals,[425] (xx) conjugated reactive mesogen 2-methyl-1,4-bis[2-(4-acryloylpropyloxyphenyl)ethenyl]benzene,[426] (xxi) 6,6′-di-*O*-*p*-nitrobenzoyl-2,3,4,3′,4′-penta-*O*-benzyl-1′-methoxymethylsucrose,[427] (xxii) poly(triacetylene) oligomers with ester linkages,[428] (xxiii) *β*-anomers of bile acid 24-acyl glucuronides,[429,430] (xxiv) geodiamolide A (an 18-membered cytotoxic depsipeptide from marine sponges),[431] (xxv) 5′-*O*-acyl derivatives of nucleosides,[432,433] (xxvi) the acetate of (*R*)-1-indanol,[434] (xxvii) side chain copolymers containing liquid crystalline and photoactive chromophores,[435] (xxviii) dimethyl-3-((1*Z*)-propenyl)cyclopropanecarboxylic acid methyl ester,[436] (xxix) oligothiophene containing photorefractive material with NLO chromophore,[437] and (xxx) 4-flurobenzyl 4-(4-nitrophenyl)butyrate.[438] The structural drawings pertaining to these references are given in the Supporting Information (Table S2).

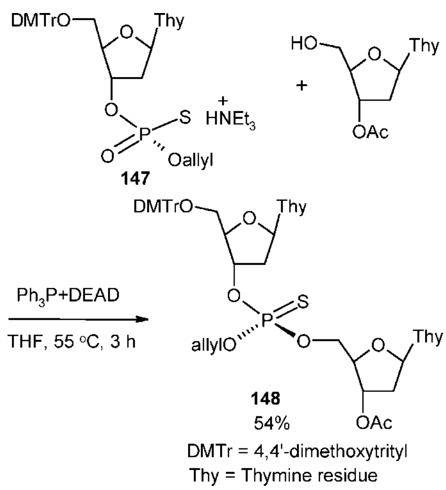
Generally, the phenolic −OH group participates as an acidic component in the Mitsunobu reaction. Apart from the report of Fitzjarrald and Pongdee cited above,[93] esterification of phenols was employed by Attias and co-workers in the synthesis of polyester-based low molecular weight copolymer **143** [$M_n = 5.3 \times 10^3$, $M_w = 6.3 \times 10^3$, $T_g = 75$ °C], incorporating the fluorescent center for application in PLEDs (Scheme 34).[439] The resulting polymer had properties similar to those obtained by using the normal acid chloride route.

Organophosphates/phosphonates and sulfates can also undergo Mitsunobu esterification.[15,440−451] Nonhydrolyzable methylene bridged polyphosphate analogues are useful as probes for and inhibitors of enzymes and other proteins that bind or hydrolyze polyphosphates. Mitsunobu coupling of the phosphonic acid with the nucleosides can be a convenient route to such compounds. Recently, Taylor and co-workers have utilized this method to obtain bismethylene triphosphate analogues.[452,453] While the synthesis of **144** from the precursor acid smoothly proceeded to afford 79% yield, the authors had to use the triethylammonium salt to get a good yield in the case of **145** (Scheme 35a).[452] This result is consistent with earlier observations on the beneficial effects of the addition of Et_3N/pyridine in such reactions. Previously, Salaski and Maag as well as Imamura and Hashimoto had

Scheme 35



Scheme 36

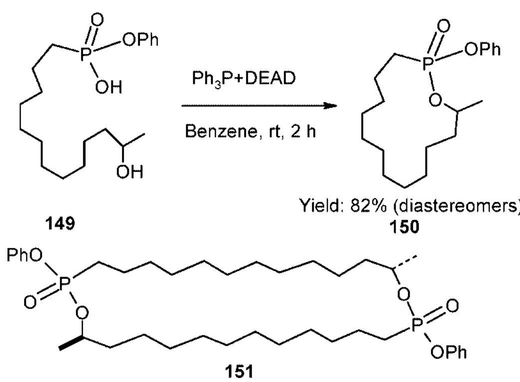


also used alkylammonium salts for the phosphonate esterification in the synthesis of nucleoside-appended phosphonates.[454,455] Lay and co-workers have made extensive use of the Mitsunobu protocol in their synthesis of phosphonoesters. In place of the phosphonic acid, they have also used the corresponding triethylamine salt during the esterification with the 6-OH moiety of a mannosaminyl residue.[456,457] Phosphonate esters of type **146** have been prepared before by a similar route (Scheme 35b).[458] Pyridine was used in this reaction to preserve the full integrity of the acid sensitive moieties.

A thiophosphate salt is expected to have the P=O unit intact, but when its ester is prepared, this is the oxygen to which the alcoholic residue gets connected. Thus, the salt **147** reacted with 3′-*O*-acetylthymidine under Mitsunobu conditions to give the dinucleotide **148** (Scheme 36).[459] In this reaction, it has been claimed that the phosphorus configuration is controlled. When a free thiophosphate is used, *S*-alkylation could also occur.[460]

Macrocycles can also be generated by using phosphonates. An example of this is shown in Scheme 37, wherein, apart

Scheme 37



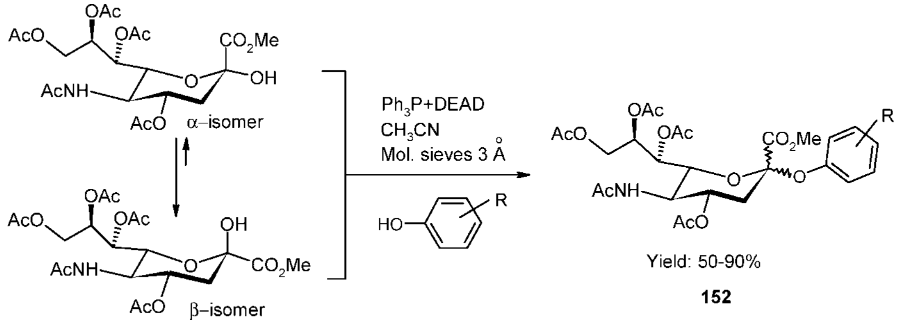
from the 14-membered phosphacycle **150**, a 28-membered diphospha-heterocycle **151** is also isolated in small quantities starting with the acid **149**.[461]

It is possible to prepare phosphite esters $(MeO)_2P(OR)$ from the phosphites such as $(MeO)_2P(O)H$ and Ph_3P−DIAD in toluene.[462] The reaction probably occurs *via* $(MeO)_2P$-$[N(CO_2$-*i*-Pr$)NH(CO_2$-*i*-Pr$)]$. Interestingly, the compound $(MeO)_2P(OPh)$ [slow reaction] can also be obtained by this route; we may note that, in several other reactions such as etherification, phenol takes the role of the nucleophile. Another interesting application of the Mitsunobu reaction involves $Ph_3P\cdot HBF_4$ as the nucleophilic source in reactions with alcohols to obtain the phosphonium salts $[Ph_3PR]^+[BF_4]^-$.[463] This system has been utilized for the synthesis of *N*-(acyl)-triphenylphosphonio- and *N*-(acyl)dimethoxyphosphoryl- glycinates.[464,465]

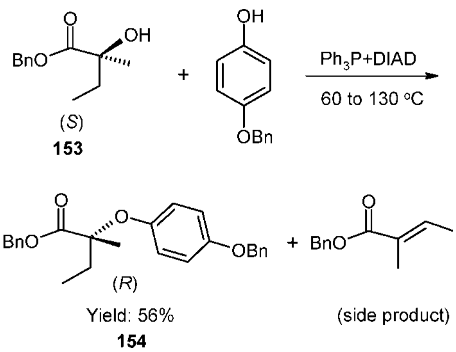
4. Phenols and Alcohols as Nucleophiles: Ether Formation

Phenols, and alcohols with strongly electron withdrawing groups attached to the carbon, can act as nucleophiles in the Mitsunobu coupling. If the substrate is a diol, intramolecular dehydration can also occur even though both −OH groups are alcoholic. These reactions will lead to cyclic or acyclic

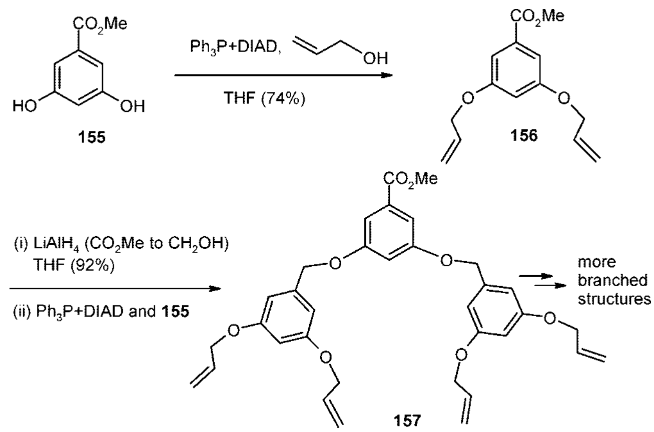
Scheme 38



Scheme 39



Scheme 40



ethers, depending on whether the reaction is intra- or intermolecular. Inversion of configuration in general may be expected if the substrate is a chiral secondary alcohol, although there are a few cases in which retention is observed.[466] We shall first discuss those in which acyclic ethers are formed, followed by the ones that give cyclic products. Later on, we shall also briefly allude to special cases wherein NHC(O) to N=C(OH) tautomerization precedes ether formation.

4.1. Etherification without Cyclization

Aryl α-sialosides (e.g. **152**) that are often used as chromogenic substrates for detecting and quantifying sialidase activity are readily synthesized along with their *β* diastereomers *via* Mitsunobu etherification by the reaction of carbohydrate substrates with the weakly acidic phenols. The best stereoselectivity is observed with 2-naphthol (α/*β* 74:26) (Scheme 38).[467]

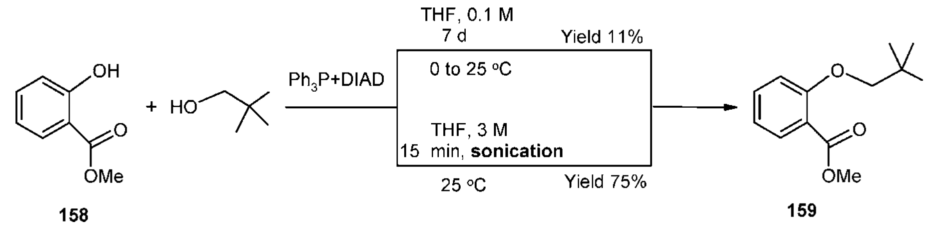
Configurational inversion of (*R*)-3-chloro-1-phenyl-1-propanol (a secondary alcohol) in etherification with 2-bromophenol takes place readily.[468,469] The resulting compounds are useful in the synthesis of biologically active chromans. Chiral secondary alcohols undergo Mitsunobu etherification with inversion in their reaction with substituted 3-pyridinols by using the n-Bu_3P−TMAD combination.[470] A rare example in which a tertiary alcohol takes part in the etherification is that of the reaction of chiral (*S*)-**153** with a phenol (Scheme 39) at *elevated* temperatures to afford the desired ether **154** in moderate yields with inversion of configuration.[43]

Sequential allylation of a dihydric phenol using a Mitsunobu protocol can lead to dendrimeric structures. A nice example of such a situation is the allyl ether system **155** → **156** → **157** ⟶ shown in Scheme 40.[471] Compound **157** upon reduction followed by etherification with the phenol **155** led to more branched species. In such later steps, the Mitsunobu protocol was found to be superior to Williamson's etherification route. Species **157** and its subsequent dendritic products have potential in molecularly imprinted dendrimers (MIDs). A similar strategy, with **155** as the phenolic precursor, has been employed by Luscombe et al. recently in the high yield synthesis of perfluorinated dendrons with thiol residues that may find application in generating self-assembled monolayers (SAMs) for attachment to a gold surface via the thiol.[472] For the synthesis of dendrons, protected 3,5-bis(hydroxymethyl)phenols can also be coupled with 3,5-bis(methoxycarbonyl)phenols.[473] An analogous iterative two-step protocol involving Mitsunobu coupling and carbonyl reduction has been utilized for the synthesis of a library of 84 ether oligomers.[474] In reactions of guanidinium mimetics and *N*-substituted 5-hydroxyindoles to prepare compounds that antagonize integrin−ligand interactions, a Mitsunobu etherification protocol is employed.[475]

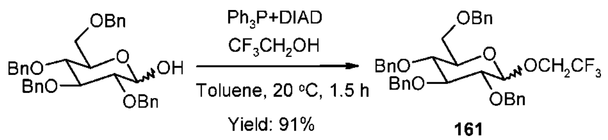
The Mitsunobu reaction is extensively used for the preparation of alkyl-aryl ethers under mild conditions. However, the reaction becomes slow in the case of sterically hindered substrates. In the reaction of phenols with alcohols, where either or both are sterically hindered, carried out at high concentrations combined with sonication, a vast increase in product formation (e.g. **159**) rate is achieved (Scheme 41).[476]

As mentioned above, if sufficiently electronegative groups are provided at the α-carbon of an alcohol so that the pK_a becomes low, such an alcohol can behave as a nucleophile in the Mitsunobu reaction. It is then possible to couple it with other alcohols. For example, $(F_3C)_3COH$ [nucleophile] can be coupled with $C_nF_{2n+1}CH_2CH_2CH_2OH$, leading to the formation of fluorophilic ether $(F_3C)_3COCH_2CH_2CH_2C_nF_{2n+1}$ (**160**).[477] Similar ethers have been prepared by using perfluoro-*tert*-butanol by the same research group.[478] The products were isolated using fluorous extraction, fluorous solid−organic liquid filtration, or steam-distillation. Hexafluoroacetone hemihydrate reacts with the fluoroalcohols

Scheme 41



Scheme 42



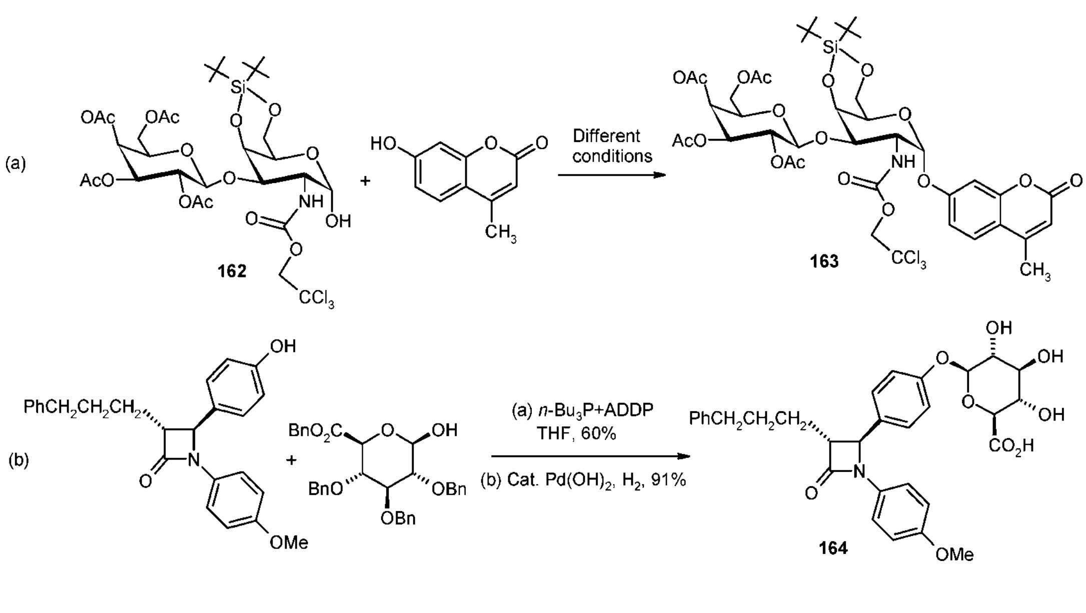
$C_nF_{2n+1}(CH_2)_3OH$ [n = 4, 6, 8, 10] using $Ph_3P-DEAD$ in ether solution to lead to the ketals $[(CF_3)_2C(O(CH_2)_3-C_nF_{2n+1})_2]$.[479] Fluorophilic ethers with the formula $ArC(CF_3)_2O(CH_2)_m(CF_2)_nF$ ($m = 1, n = 1, 7; m = 3, n = 8$) were obtained in high yields, by reacting 2-aryl-1,1,1,3,3,3-hexafluoropropanols with 3-perfluorooctylpropanol using the $Ph_3P-DEAD/PhCF_3$ system.[480] Mitsunobu etherification offers the best possible synthetic route to fluoroalkyl and fluoroaryl glycosides (e.g. **161**) from primary, secondary, and tertiary fluoroalkyl alcohols (pK_a 9−12) and pentafluorophenol (cf. Scheme 42);[481] similar ethers derived from normal alcohols have also been reported before.[482] The reaction proceeds under comparatively mild conditions, most often in isolated yields of above 70%. Other similar applications include the synthesis of (a) oligonucleotides containing a hexafluoroacetone ketal internucleotide linkage,[483] (b) perfluorinated ethers as oils/amphiles,[484] (c) fluoroalkyl ethers of dihydroartemisinin,[485] and (d) perfluoro-*tert*-butyl ethers.[486]

The steric factor imposed by the di-*tert*-butylsilylene protection can alter the stereochemical outcome in the etherification reactions. Thus, Ando and co-workers reacted the silyl protected hemiacetal **162** with 4-methylumbelliferone using various combinations of phosphines and azodicarboxylates (Scheme 43a).[487] The best result (yield 80%) was obtained using $Ph_3P-DEAD$ and 8 equiv of 4-methylumbelliferone at the reflux temperature of toluene. Both the silyl and *N*-2,2,2-trichloroethoxycarbonyl (Troc)-protection influenced the observed retention of stereochemistry at the alcohol site. The resulting compound was useful for the final synthesis of 4-methylumbelliferyl (4-MU) T-antigen. In another study, by etherification using umbelliferone, a geiparvarin analogue with a fluorinated segment has been synthesized by Amato and Calas.[488] The Mitsunobu glycosylation using lactam-substituted phenols and protected sugars led to the glucuronides in good yield after subsequent deprotection.[489] Here, the combination n-Bu_3P/ADDP was utilized to effect the reaction (cf. **164**, Scheme 43b). However, similar reactions utilizing many other substituents in place of the $Ph(CH_2)_3$- moiety on the lactam ring were not successful.[490]

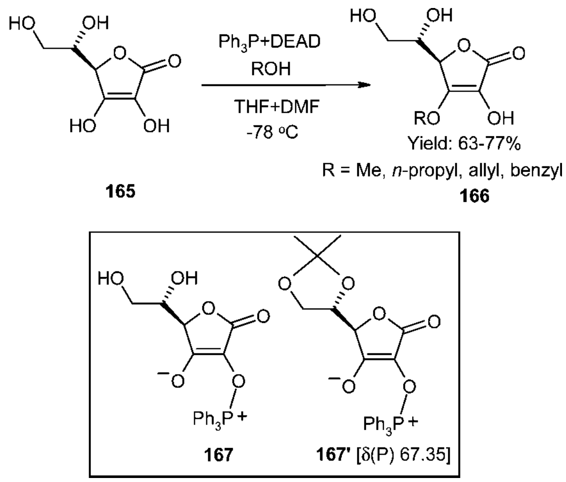
Alkylation of L-ascorbic acid (**165**) with primary alcohols preferentially takes place on the 3-OH group to lead to ethers **166**.[491] An intermediate of type **167** is invoked for the observed reaction (Scheme 44). Details on further steps are not clear, however. Interestingly, after protection of the other two hydroxyls, compound **167′** could be isolated (assignment of the structure is based on ^1H, ^{13}C, and ^{31}P NMR). A similar alkylation at the 3-hydroxy position of L-ascorbic acid is also reported by Déléris and co-workers.[492] This route avoided the unwanted alkoxide alkylation (Williamson's procedure). In analogous chemistry, reaction of codeine and 2-bromophenol led cleanly to the etherification with inversion and without any interference from the allylic double bond of codeine.[493]

Etherification of 4-hydroxycoumarin with alcohols (e.g. isopropyl alcohol) in the presence of high-intensity ultrasound reduced the time required from 5 h (conventional method) to 1 h and gave better yields.[494] This modification perhaps needs more studies for general applicability.

Scheme 43

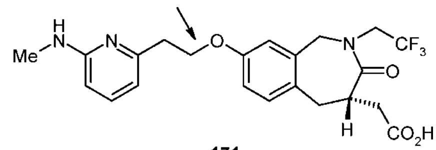


Scheme 44



A report by Wang and Gutsche on calixarenes is also interesting. Here, the authors observed both *O*-alkylation and *C*-alkylation on the calixarene (Scheme 45).[495] For the alcohol R^1R^2CHOH, the mono- and bis-*O*-alkylated products **168−169** were obtained when R^1 = Ph and R^2 = H. While R^1 = 4-O_2N−C_6H_4 and R^2 = H led only to mono-*O*-alkylated product, for R^1 = 4-O_2N−C_6H_4 and R^2 = CH=CH_2, essentially *C*-alkylated product **170** was isolated. Thus, it appears that, for the less reactive alcohol, the likelihood of *C*-alkylation is greater, with the reactivity being determined by both steric and electronic factors. A plausible rationalization for the unusual *C*-alkylation is also suggested in the same paper. In another study, by using proximal bistriflate substitution, Hattori and co-workers could achieve an *anti*-selective dialkylation of thiacalixarenes.[496] In addition, they have also prepared *syn-O,O″*-bis(2-aminoethyl)-*p-tert*-butylthiacalix[4]arenes by starting with thiacalixarene and *N*-(2-hydroxyethyl)phthalimide.[497]

The benzazepin **171** (SB-273005) is a known vitronectin receptor antagonist. In the scale-up operations to produce multi-kilogram quantities of **171**, Wallace et al. found that the Mitsunobu protocol was a better approach than Williamson's etherification.[498] Although the phosphine oxide was difficult to remove completely by column chromatography, a subsequent work-up procedure that included a saponification step gave the desired compound **171** in 99% purity and 66% yield over two steps without recourse to chromatography. The authors noted that even though Mitsunobu chemistry is environmentally unfriendly, is atom uneconomical, and poses problems in purification, it worked better.

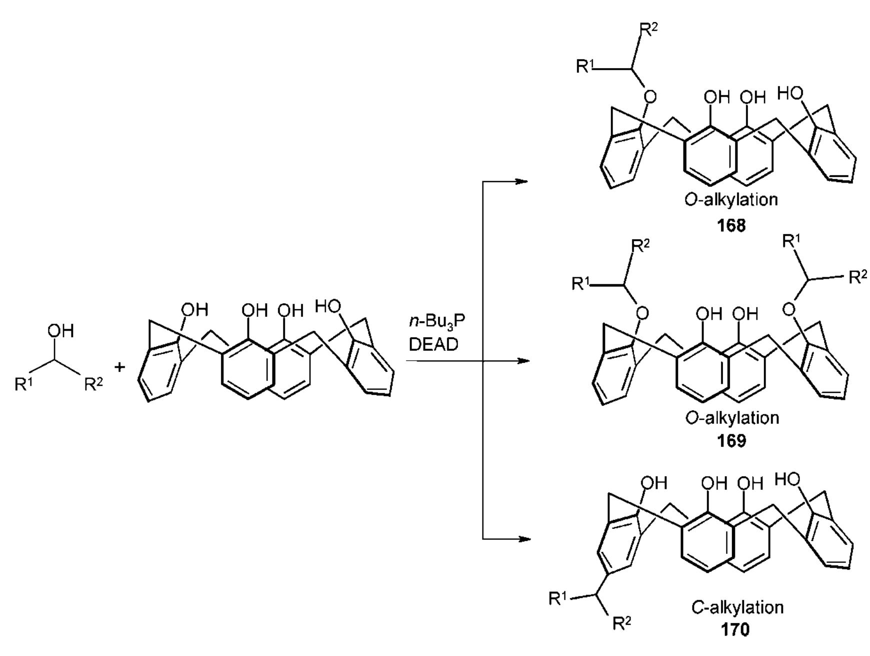


171

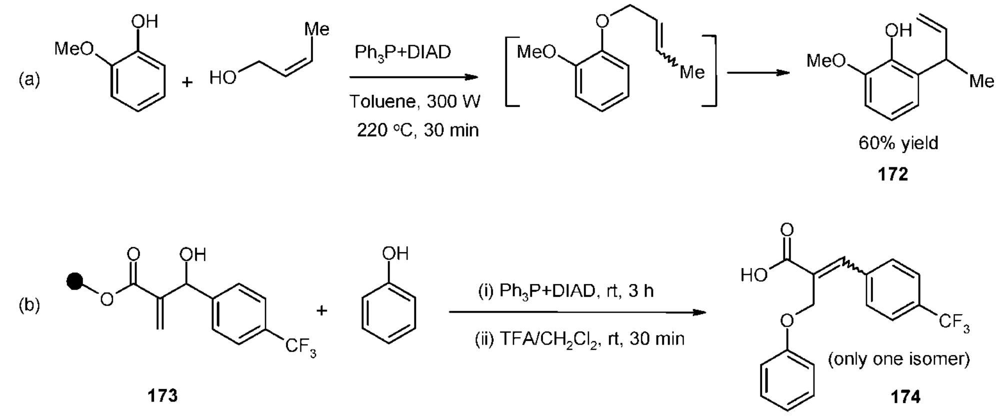
The somewhat unusual behavior of Baylis−Hillman (allyl) alcohols was discussed above. An interesting microwave-assisted combined Mitsunobu etherification−Claisen rearrangement of allylic alcohols is reported by Jacob and Moody.[499] An example (**172**) from their studies is given in Scheme 46a. These results were later utilized for the synthesis of primin natural products and unusual nitrogen containing 3-alkyl-1,4-benzoquinones.[500] Such rearrangements have also been reported in the reaction of 4-hydroxycoumarin with prenyl alcohol; buchapine was thus obtained from 4-hydroxyquinolone and dimethylallyl alcohol.[501] A similar rearrangement in the etherification using allylic alcohols was reported by Wan et al. in their studies on epi-gallocatechin gallate (EGCG) analogues as proteasome inhibitors.[502] Similar but polymer bound species **173** underwent reaction with phenol, leading to an S_N1'-reaction product (89% yield), which could later be hydrolyzed to the acid **174** by TFA/CH_2Cl_2 (Scheme 46b). NMR analysis using NOE experiments suggested the formation of only one isomeric ether in which the aryl and the ether groups were on the same side.[503]

Use of polymer-supported substrates/reagents in the synthesis of small molecules constitutes an important modification in the Mitsunobu etherification process (see section 9 also). Selective alkylation of pharmaceutically important ethers derived from 6,7-dihydroxyquinazoline (e.g. **175**) via polystyrene-supported phosphine [PS-PPh_3] and DTBAD has

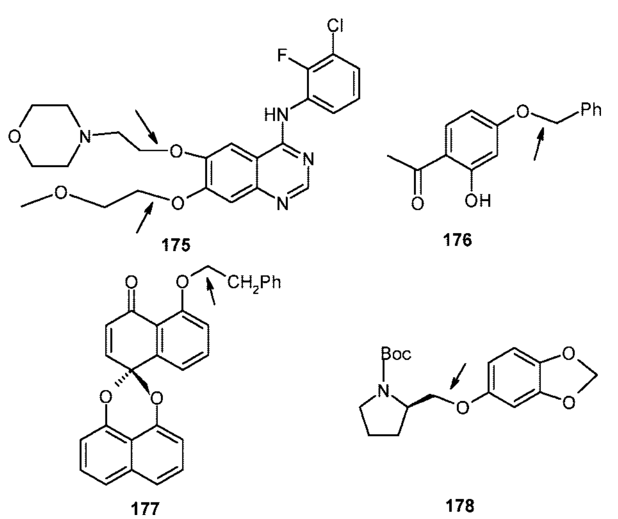
Scheme 45



Scheme 46



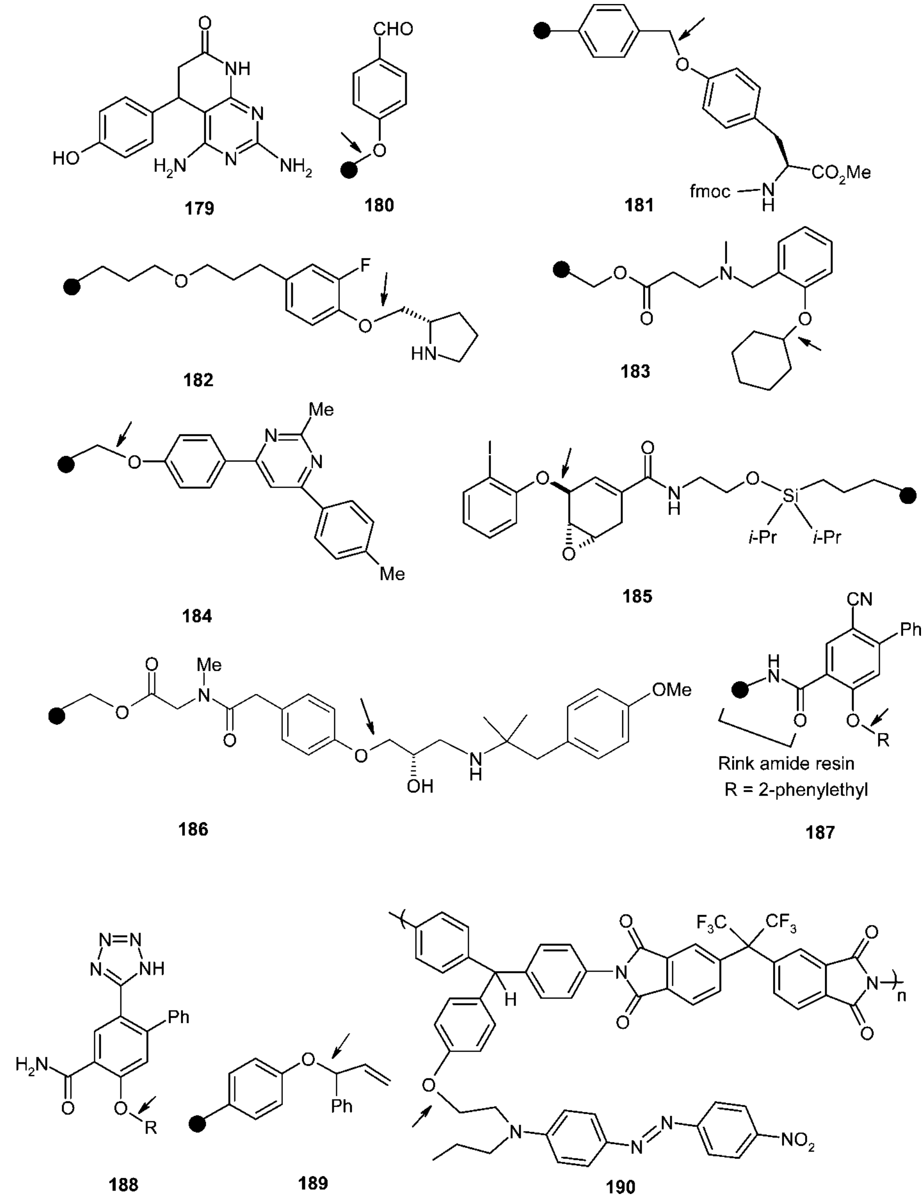
been reported by Harris and co-workers.[504] There was no interference from competitive *N*-alkylation, and the yields were very good with no contamination from the homo-dialkylated product. Gentles et al. have developed an automated Mitsunobu protocol using PS-PPh_3 along with DTBAD that is useful for etherification.[505] Primary alcohols reacted with not much difficulty, while in the case of secondary alcohols double addition of DTBAD with the overall stoichiometry of phenol/PS-PPh_3/DTBAD/alcohol maintained at 1:4.4:3.2:2.5 significantly improved the yield. Tunoori et al. also have earlier shown the utility of PS-PPh_3 in ether (e.g. **176**) formation;[506] only the sterically unhindered phenolic −OH reacted in this case. Three other examples of the use of PS-PPh_3 include diverse aryl alkyl ethers,[507] palmarumycin analogues (e.g. **177**),[508] and ethers derived from *N*-protected amino alcohols (e.g. **178**).[509] In the second example, use of PS-PPh_3 greatly facilitated purification while, in the last one, the presence of an added base such as triethylamine in the reaction medium was beneficial.



Mitsunobu etherification can be performed on polymers with appropriate functional groups to lead to new polymers for further applications or small target molecules after delinking the polymer backbone. Azobenzene-modified cellulose polymers have been successfully synthesized through linking of 4-cyanophenylazophenol to natural cellulose of ultrahigh molecular weight by Mitsunobu coupling (Ph_3P−DEAD in DMF).[510] Dendritic resins with an efficiency comparable to that of tentagel (polystyrene−PEG) resin have been used in the synthesis of aryl-alkyl ethers.[511] Here, resin bound phenols were used as the acidic substrates. Using an fmoc-protected PL-Rink resin as the solid support for phenols, a 4500 member library of tyrphostin ethers was obtained by Player and co-workers.[512] The same group has also developed a procedure for solid-phase synthesis of ethers starting from *N*(fmoc),*O*(THP)-protected *cis*-hydroxyproline derivatives and 2-(3,5-dimethoxy-4-formylphenoxy) ethoxymethyl polystyrene (FDMP).[513] Other related applications include synthesis of (i) 2-substituted 4-aminopyrido[2,3-*d*]pyrimidines (**179**) using etherified Wang resin (**180**),[514] (ii) tyrosine containing cyclic peptides using fmoc protected resin (**181**),[515] (iii) functionalized phenolic amino acids,[516] (iv) tellurium bound polymer with an ether linkage,[517] (v) polymer-supported chiral amines (e.g. **182**) with ether linkages,[518] (vi) non-PEG derived polyether resins,[519] (vii) resin-bound aryl-cyclohexyl ethers (e.g. **183**),[520] (viii) amphiphilic poly(para-phenylene)s,[521] (ix) germanium-based linker (aryl-alkyl ether) for solid phase synthesis of pyrazoles,[522] (x) polymer-bound alkyl-bromophenyl ethers for nickel-catalyzed couplings,[523] (xi) ethers derived from OH-terminal Wang resin and hydroxybenzenesulfonate esters,[524] (xii) 2/4-hydroxyl acetophenone linked Wang resin useful for the synthesis of 2,4,6-trisubstituted pyrimidines (e.g. **184**),[525] (xiii) polymer-bound seleno-alkyl-aryl ethers,[526] (xiv) oxindole-quinazolines with a side-chain ether linkage,[527] (xv) 4-alkoxyacetophenones,[528] (xvi) Shikimic acid-based aryl-allyl ethers (**185**),[529] (xvii) 6-arylpyridazin-3(*2H*)-one precursors,[530] (xviii) tentagel-supported peptide containing disperse red residue,[531] (xix) aryloxypropanolamines (e.g. **186**),[532] (xx) 5-substituted oxazoles via (5-hydroxymethyl)oxazoles,[533] (xxi) luminescent polymers of distyrylbenzenes with oligo-(ethylene glycol) spacers,[534] (xxii) precursors to biphenyl tetrazoles (**187**, **188**),[535] (xxiii) dendritic macromolecules,[536] and (xxiv) aryl-allyl (e.g. **189**) and aryl-alkyl ethers.[537−540] There are also applications related to the synthesis of NLO active polymers (e.g. **190**) containing disperse red 1 (DR1)[541] or other suitable chromophores.[542−549] Compounds **179**−**190** are shown in Chart 2; others are given as Supporting Information (Table S3). For the Mitsunobu step in the preparation of **188**, 5 equiv each of Ph_3P, DIAD, and the alcohol were employed in DMF solvent medium.

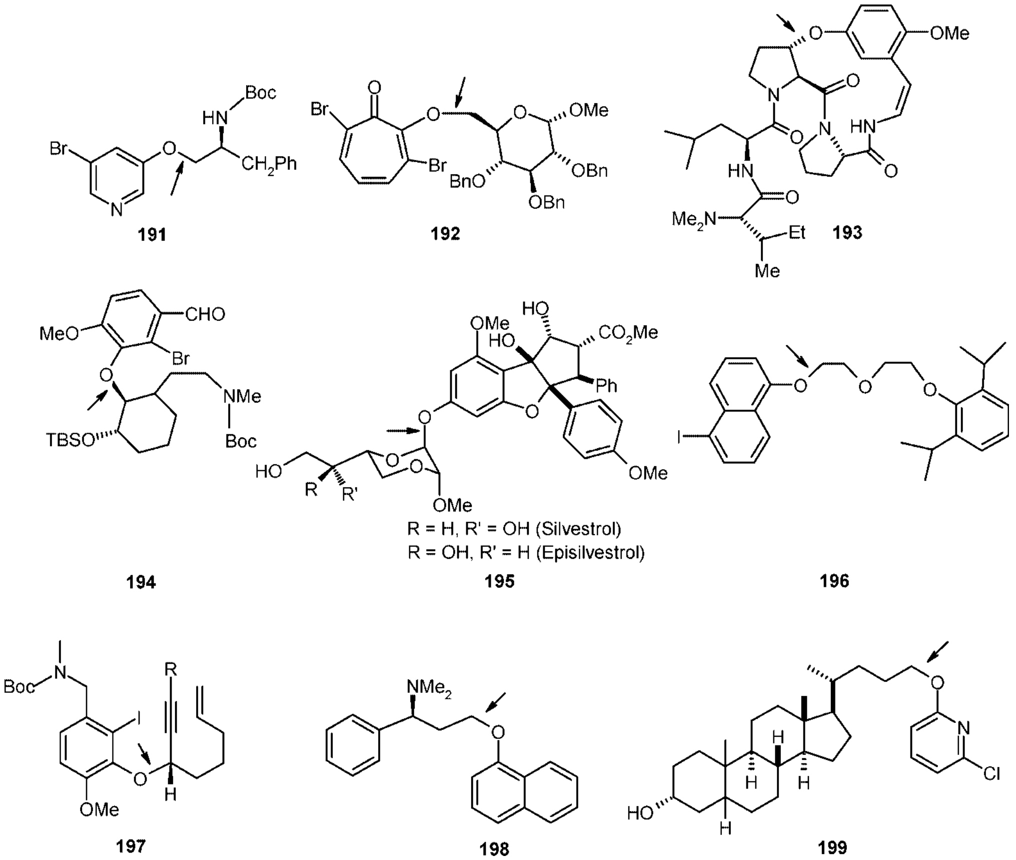
In view of the multitude of other reports on normal Mitsunobu etherification, only a consolidated list is provided here. These include the synthesis of (i) aryl-alkyl, propargylic, cinnamyl, benzyl, and allylic ethers,[550−588] (ii) substituted benzofurans[589] and benzopyrans[590] with ether linkages, (iii) indolyl, imidazolyl, indazole-pyridyl [protein kinase-B

Chart 2



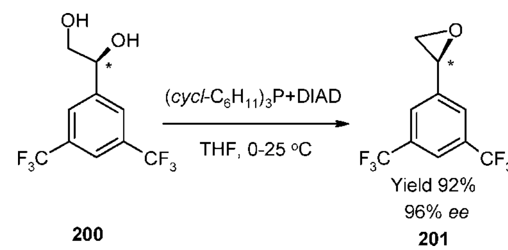
(Akt) inhibitors (**191**)], and other *N*-heterocyclic-alkyl/aryl and aryl/*sec*-alkyl ethers,[591−594] (iv) tropolonyl ethers of saccharides (**192**),[595] (v) side chain modified riboside phosphoramidites,[596] (vi) lupiwighteone,[597] (vii) dianhydrohexitole-based benzamidines,[598] (viii) (4*S*)-phenoxy-(*S*)-proline,[599] (ix) the carbamate protected Cdc42 inhibitor secramine A,[600] (x) constrained arylpiperidines,[601] (xi) repinotan [a 2-(aminomethyl)chroman derivative, a potent 5-hydroxytryptamine antagonist],[602] (xii) BILN 2061 (a protease inhibitor),[603] (xiii) ziziphine N [**193**, an antiplasmodial agent],[604] (xiv) O^6-alkyl derivatives of triacyl-2′-deoxyguanosines,[605] (xv) ferrocene-modified artificial ditopic nucleobase receptors,[606] (xvi) 2′-*O*-benzyladenosine,[607] (xvii) CMI-977 [a 5-lipoxygenase (5-LO) inhibitor],[608] (xviii) 3′-*O*-(carboxyalkyl)fluorescein labels,[609] (xix) cored dendrimers with a 1,3,5-trisubstituted benzene moiety,[610] (xx) chiral ferroelectric thiobenzoates,[611] (xxi) the codeine precursor allyl ether **194**,[612] (xxii) amino-/guanidino-G-clamp PNA monomers,[613] (xxiii) the neolignans rhaphidecursinol A and virolongin B,[614] (xxiv) virologins,[615] (xxv) 5,8-bicyclic γ-alkylidenebutenolides,[616] (xxvi) hydroxy-substituted rosiglitazone derivatives,[617] (xxvii) prodrugs derived from the reaction of hydroxymethylimides (saccharin, benzotriazole, etc.) with substituted phenols,[618] (xxviii) (−)-episilvestrol and (−)-silvestrol (**195**),[619] (xxix) optically pure cyclopenta[*b*]benzofurans,[620] (xxx) ferrocenyl units linked to perfluoroethers,[621] (xxxi) a functionally rigid rotaxane precursor (**196**),[622] (xxxii) 3-aryloxymethylindolequinones,[623] (xxxiii) xanthohumol and isoxanthohumol,[624] (xxxiv) precursor **197** for the alkaloid (−)-galanthamine (a drug to treat Alzheimer's disease),[625] (xxxv) epicalyxin F,[626] (xxxvi) phosphinated dendrimers,[627] (xxxvii) 3-{4-(2-aminoethoxy)-phenyl}propanoic acid derivatives,[628] (xxxviii) 3-(2,5-dihydro-1*H*-pyrrol-2-ylmethoxy)pyridines (analogues of epibatidine and tebanicline),[629] (xxxix) nonbasic quinolone GnRH antagonists via 4-hydroxyquinolone,[630] (xl) dibromotyrosine alkaloids,[631] (xli) ethers from methyl vanillate-aliphatic diols (yield was better than that of Williamson's synthesis),[632] (xlii) fluorenylaminoserine-acridine conjugates (sonication was used),[633] (xliii) 5′-ethers derived from 2′-deoxyuridine,[634] (xliv) dendrimers with tridentate pyridylthioether coordination sites,[635] (xlv) (+)-(*S*)-dapoxetine (**198**),[636] (xlvi) highly functionalized *cis*-decalins via ethers derived from protected hydroquinones and dienols,[637] (xlvii) histamine H3-receptor antagonists possessing a 4-(3-(phenoxy)propyl)-1*H*-imidazole

Chart 3



structure,[638] (xlviii) oligophenylenevinylene derivatives with long alkyl chains and a carboxylic acid that show liquid crystalline phases,[639] (xlix) succinate-derived hydroxamic acids incorporating a macrocyclic ring as inhibitors of matrix metalloproteinases,[640] (l) mono(6-chloropyridin-2-yloxy-)cholane (**199**),[641] (li) optically pure (*R*,*R*)-1,1′:5′,1′′-ternaphthalene-2,2′,6′,2′′-tetraol,[642] (lii) photoaffinity-labeled 3-(4-alkoxyphenyl)-3-trifluoromethyldiazirine derivatives,[643] (liii) (−)-gallocatechin,[644] (liv) neoisopinocampheyl-aryl ethers,[645] (lv) azobenzene-modified cellulose (azocellulose),[646−648] (lvi) mono-*O*-alkylated BINOL derivatives,[649,650] (lvii) (*R*)-5′,6′-benzo-6-methoxy-2,2′-biphenol,[651] (lviii) (*R*)-l-(4-trifluoromethylphenoxy)-1-phenyl-3-butene,[652] (lix) calixarene-sugars,[653] (lx) (*R*)-(+)-*O*-coumarinyllactic acid,[654] (lxi) C_2 symmetric 2,6-diarylalkyloxybenzaldehydes,[655] (lxii) *N*-alkylated 5- and 6-alkoxy-l,2,3,4-tetrahydroisoquinolines,[656] (lxiii) chiral perfluoroalkyl-substituted hexahydrofuro[2,3-*b*]pyran derivatives,[657] (lxiv) photo-cross-linkable polyimide-based polymers with a decyl alcohol residue,[658] (lxv) bicyclic peptidomimetic inhibitors,[659] (lxvi) naphthyl *O*-glycoside,[660] (lxvii) 2′-benzyl-substituted 6-chloropurine 3′-*O*-benzoylriboside,[661] (lxviii) isoflavanones,[662] (lxix) C^5-substituted imidazolines,[663] (lxx) duloxetine,[664] (lxxi) 4-substituted α-tolylgalactosides,[665] (lxxii) benzoxazole containing thiazolidinediones,[666] (lxxiii) chiral ferrocene-labeled tyrosine PNA monomer,[667] (lxxiv) ether derived from poly(4-vinyl phenol) (P4VP), and poly(ethylene glycol)methyl ether (MPEG) for lithium battery electrolyte applications,[668] (lxxv) erythro 8-*O*-4′-neolignans,[669] (lxxvi) chiral liquid crystalline 3,6-disubstituted cyclohex-2-enones/azafluorenones/thiadiazoles,[670−672] (lxxvii) α,ω-bis(4-cyanobiphenyl-4′-yloxy)alkanes,[673] (lxxviii) ferroelectric liquid crystals bearing a chiral pyrrolidine-type ring,[674] (lxxix) 2-alkoxyethoxy-substituted nematic crystals,[675] (lxxx) chiral liquid crystals based on 2-amino-1,3,4-thiadiazoles,[676] (lxxxi) liquid crystals based on 4-arylbutyric acid [aryl = 2′,3′-difluoro-4′-(2-(*E*-4-pentylcyclohexyl)ethyl)-biphenyl-1-yl],[677] (lxxxii) aryloxy-alkylpyridines,[678] and (lxxxiii) chiral liquid crystalline materials.[679] Chart 3 shows the structures of **191**−**199**; the rest are given in the Supporting Information (Table S4).

Scheme 47

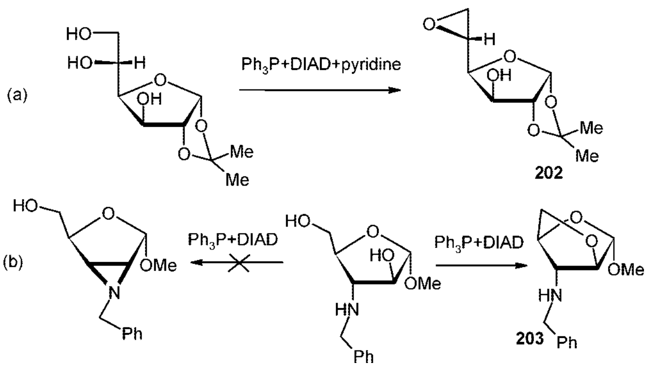


4.2. Etherification with Cyclization

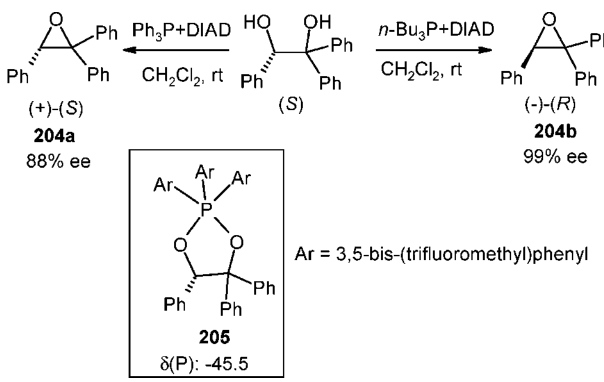
Mitsunobu cyclodehydration of 1,2-diols readily leads to the epoxides.[680−682] Although the nucleophilic site is most often not acidic, the cyclization takes place readily, leading to the formation of the three-membered ring. Thus, optically active phenethane-1,2-diol (e.g. **200**) led to the stereoselective formation (up to 99%) of styrene oxide (e.g. **201**) in substrates lacking electron donating substituents (Scheme 47).[681] A combination of tricyclohexylphosphine and DIAD in THF gave the best results. Remarkably, use of Ph_3P produced more *inversion* whereas tricyclohexylphosphine resulted in *retention*.

In the reaction shown in Scheme 48a, although many possibilities exist, only the epoxide **202** is formed preferen-

Scheme 48



Scheme 49



tially. In reaction b, shown in Scheme 48, only **203** with the formation of a furan ring, and not an aziridine, is formed. These results are quite useful when one intends to use a multifunctional substrate in Mitsunobu coupling.[683] The epoxide, 1,6-di-*O*-benzoyl-2,5:3,4-dianhydro-*d*-talitol is also readily obtained from its mannitol precursor.[684] Other examples wherein epoxide formation via a Mitsunobu protocol is effected include several anhydro-carbohydrate derivatives[685,686] and substituted porphyrins.[687] In the esterification of sucrose also, Molinier et al. have provided unequivocal evidence for the formation of anhydro-derivatives, albeit as minor products.[272]

In an elegant study, Verdaguer and co-workers have recently shown that Mitsunobu cyclodehydration is very effective in transforming triaryl-1,2-ethanediols stereospecifically into their corresponding chiral nonracemic epoxides.[688] More importantly, depending on the phosphine used, the two enantiomers of the final epoxides (**204a** and **b**) are formed in high enantiomeric excess (Scheme 49). Here, use of an electron-rich phosphine such as n-Bu_3P provided the corresponding epoxide with inversion of configuration, while the use of Ph_3P led to retention. This result may be contrasted with that shown in Scheme 47. The configuration of the products was also dependent on the aryl groups of the 1,2-diols. The authors were also able to isolate the pentacoordinate intermediate **205**, which, over a period of a month, decomposed in dichloromethane solution at room temperature to give **204a** with 79% ee. On the basis of this, a mechanistic pathway, involving pentacoordinate species of type **205** that converted into different intermediate alkoxyphosphonium salts prior to epoxide formation, is proposed.

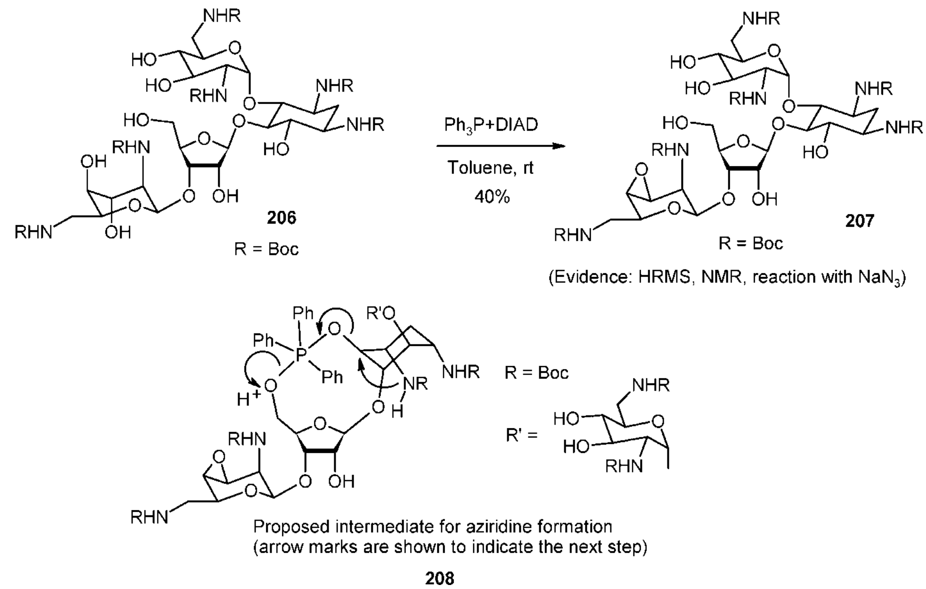
When a multifunctional substrate such as *N*-Boc neomycin B was utilized in the Mitsunobu reaction with N^3-benzoyl thymine, it was reported that a product with double-intramolecular ring closure leading to an aziridine ring and a four-membered *N*-heterocyclic ring were formed in 78% yield.[689] The thymine nucleophile did not react. However, Jenkins, Houston, and their co-workers, based on their more recent studies on the reaction of hexa-*N*-Boc neomycin B **206** with 4-nitrobenzoic acid, suggested that epoxide (**207**) formation is much more likely than aziridine or azetidine formation, which has literature precedence.[690,691] A full account of the aforementioned work is now published.[692] The epoxide was formed under carefully controlled conditions (Scheme 50), but subsequently under more forcing conditions, aziridine ring formation also took place. Interestingly, involvement of an intermediate of type **208** was proposed for formation of the aziridine ring. This aziridine formation could be blocked by protecting the primary alcoholic group of the ribosyl ring (as a 4-nitrobenzoate ester) in the precursor.

The work by Barrero also gives more insight into the different possibilities that exist in reactions using 1,2-diols. Although epoxides (e.g. **209**) are formed in many cases (Scheme 51a), if the intermediate pentacoordinate phosphorane is sufficiently stabilized, it can be isolated as the major product (e.g. **210**, Scheme 51b). If one were to use 1,1-disubstituted 1,2-diols such as **211**, carbonyl compounds (e.g. **212**) are formed by dehydration (Scheme 51c).[693] Similarly, 1,1,2-trisubstituted 1,2-diols yield ketones. Synthesis of compound **210** has also been reported previously in an earlier work.[694] Even in the case of **213**, dehydration led to the ketones sesquiterpene **214** and isocaryolan-9-one **215**.[695]

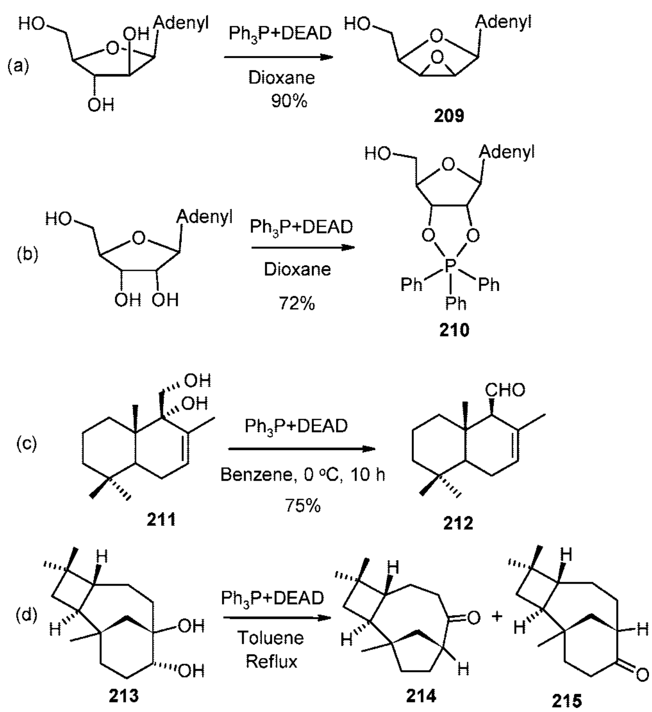
A common method for the synthesis of oxetanes (e.g. **217**) is the intramolecular dehydration of 1,3-diols of type **216**. A Mitsunobu-type procedure using zinc *N*,*N*-dimethyldithiacarbamate [$(Me_2NCS_2)_2Zn$, Ziram@] as an additive worked very well for their stereoselective synthesis (Scheme 52).[696] The amount of the byproduct, substituted tetrahydrofuran **218**, could be minimized by using toluene as the reaction medium in the presence of 2 mol equiv of Ziram@. A ^{31}P NMR investigation suggested the intermediacy of the phosphorane **219**. Similar ring closure is feasible in xylofuranoside chemistry also.[697] Cirelli et al. were also successful in generating the oxetane ring present in thromboxane A_2 from the precursor 1,3-diol-2-bromo-2,6-dideoxy-4-*O*-methyl-α/*β*-D-altropyranose.[698]

In the synthesis of excitatory amino acid analogue **220**, an intramolecular etherification of sterically cumbersome substrate leading to a furan skeleton was accessed using the Mitsunobu reaction (Scheme 53a).[699] Such a ring closure by dehydration leading to a furan system should be quite general and is used in the synthesis of several *C*-nucleosides. Thus, Guianvarćh et al. have reported a stereoselelctive synthesis of heterocyclic (indole, imidazole, benzimidazole, and 6-iodobenzimidazole) *C*-nucleosides.[700,701] Imanishi and co-workers have also utilized a similar strategy to obtain *C*-nucleosides.[702] In selected instances, they have used n-Bu_3P−TMAD/benzene in place of Ph_3P−DEAD/THF for better results. In each case, one of the anomers was obtained exclusively or as a predominant product. Kurihara and co-workers have studied the Mitsunobu cyclization of **221**, which was obtained by starting with L-glutamic acid, and prepared a 1:1 mixture of (*trans*+*cis*)-cyclization product **222** in 97% yield (Scheme 53b).[703−705] These investigations were directed toward the synthesis of new histamine derivatives. Similar furan ring construction (using n-Bu_3P−TMAD) in the synthesis of *C*-aryl nucleotides has been reported by Wengel and co-workers.[706] Other examples of intramolecular

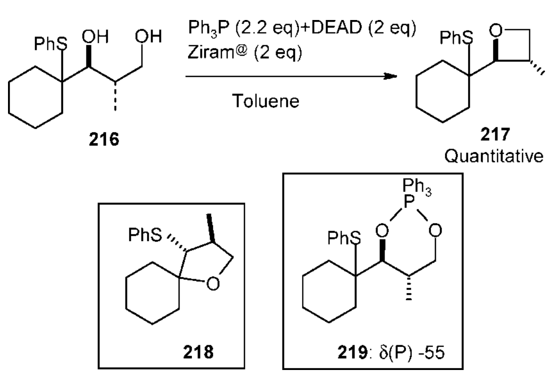
Scheme 50



Scheme 51

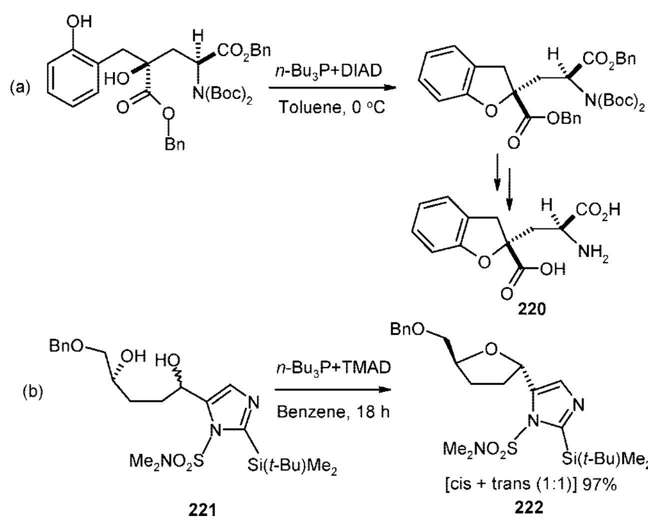


Scheme 52



etherification leading to a five-membered ring involve (i) 3′-β-*C*-branched anhydromannitol nucleosides,[707] (ii) epoxy-

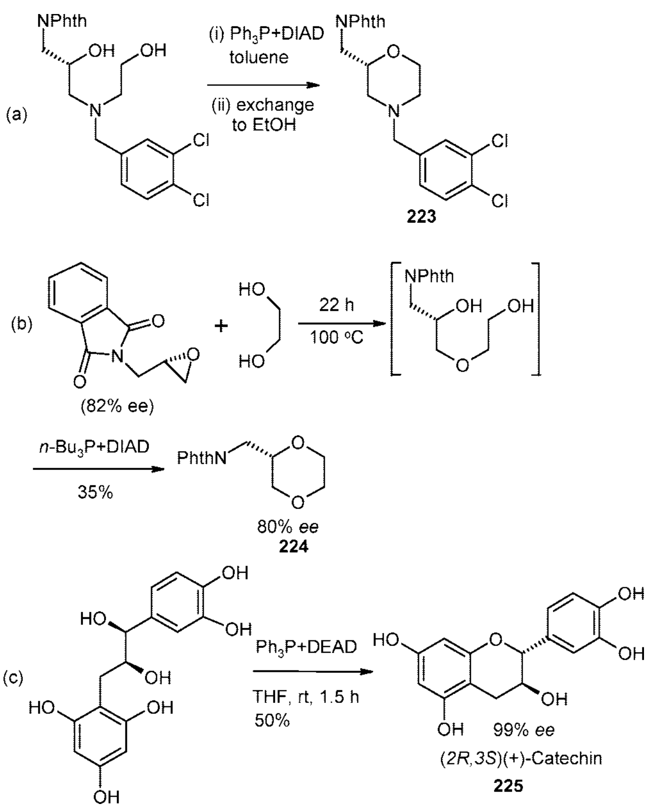
Scheme 53



phenylmorphans,[708] (iii) flavone *C*-glycosides,[709] (iv) [(2*R*,3*R*)-3-aminotetrahydrofuran-2-yl]imidazole,[710] (v) (α-D-xylofuranosyl)imidazoles,[711] (vi) indole/thiazole-appended *C*-nucleosides,[712] (vii) isonucleosides,[713] (viii) furan-3,4-dicarboxylic acid,[714] (ix) cycloalkenobenzofurans,[715] (x) 3-aryl-2,3-dihydrobenzofurans,[716] (xi) fluorescent 3-aminobiphenyl-*C*-nucleosides,[717] (xii) 2-amino-5-(2-deoxy-β-D-ribofuranosyl)pyridine,[718] (xiii) β-ribofuranosides,[719] (xiv) pharmaceutically interesting chiral tetrahydrofurans,[720] (xv) 4(5)-(β-D-ribofuranosyl)imidazole,[721] (xvi) 8-oxa-3-azabicyclo[3.2.1]-octane-6,7-diol,[722] and (xvii) 3′-β-*C*-branched anhydrohexitol nucleosides.[723] The structural drawings corresponding to these references are given in the Supporting Information (Table S5).

A ready access to chiral substituted morpholines and dioxanes (e.g. **223**−**224**) is achieved by diol cyclization as shown in Scheme 54 (a and b).[724] In the synthesis of **224**, to alleviate the problem arising from oligomerization, the authors used dilute (0.1 M) conditions. Enantiomerically pure arylmorpholin-2-ylethanols have also been prepared earlier by a similar route.[725] Jew et al. employed Mitsunobu cyclization for preparing (2*R*,3*S*)-(+)-catechin **225** (Scheme 54c), a member of the category of 3-flavanols.[726] It may be

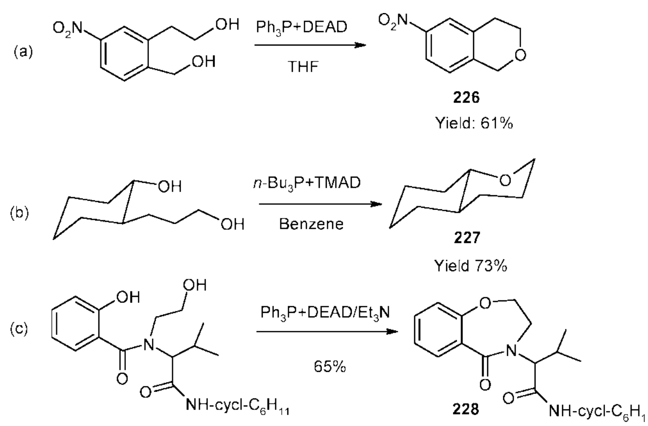
Scheme 54



noted that a five-membered ring also might have formed in this reaction. The same saturated six-membered ring in flavanone (both enantiomers), 2-methylchromanone,[727] and 3-hydroxyflavanones[728] was also constructed using the Mitsunobu etherification protocol. This type of chroman ring is fairly easily synthesized if suitable OH groups are available at the 1,5-positions.[729] Hodgetts has also utilized the Mitsunobu protocol for the cyclization step leading to the saturated ring in the asymmetric synthesis of (*S*)-2,6-dimethylchroman-4-one[730] and other 2-substituted chroman-4-ones, including (−)-pinostrobin.[731] The author has pointed out that the specific rotation of the synthetic (*S*)-2,6-dimethylchroman-4-one was higher than that for the natural product. The intermediates 2-methyl- and 2,3-dimethylchromanones required for (+)-calanolide A, an anti-HIV agent, were prepared by a Mitsunobu intramolecular cyclization.[732−734] Other applications leading to six-membered heterocycles involve (i) heliquinomycinone reported by Danishefsky and co-workers,[735] (ii) functionalized steroid-like molecules reported by Yus and co-workers,[736] and (iii) the structural elucidation of capituloside reported by Zhou and co-workers.[737]

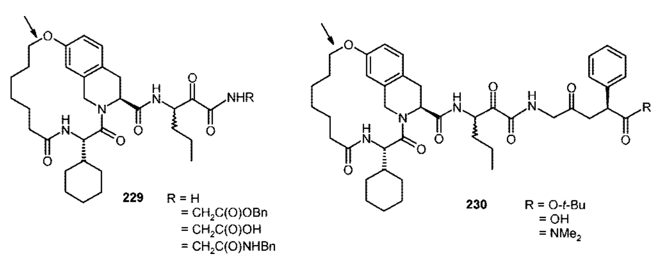
The electron-poor benzopyran **226** could be obtained via intramolecular cyclization using a Mitsunobu protocol (Scheme 55a).[738] This reaction showed that intramolecular ether formation could be readily achieved in an inactivated system also. Another example that led to the fused ring system **227**, utilizing TMAD that enhanced the reactivity of these nucleophiles, is shown in Scheme 55b.[62] This paper also dealt with a variety of other heterocycles generated via Mitsunobu cyclization. The δ-*altro*-2,6-dihydroxy-hexonolactones underwent efficient Mitsunobu dehydration by ring closure of the C^2-OH onto C^6 to lead to tetrahydropyrans (bicyclic lactones).[739] Reduced phenoxazines that contain a six-membered ring have also been prepared by Mitsunobu

Scheme 55



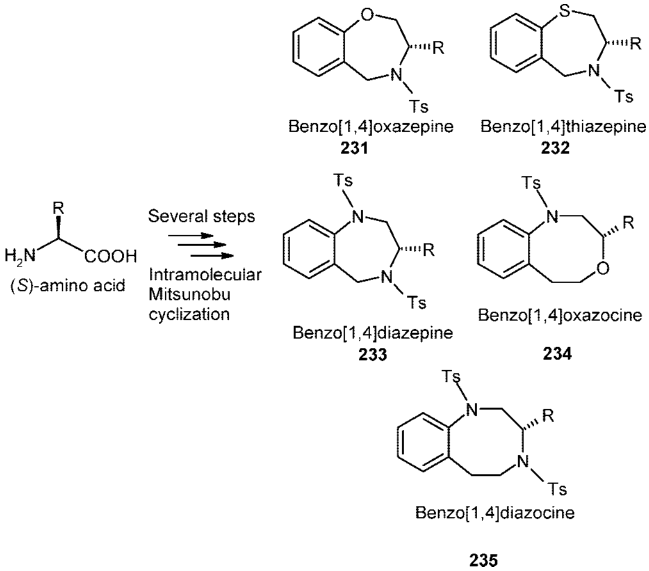
etherification.[740] In the etherification of protected polyhydroxy pyrrolidines bearing a CH_2OH connected to the carbon adjacent to the nitrogen of the ring, in addition to the expected ethers, ring enlargement to piperidines also took place, as shown by Dondoni et al.[741] Intramolecular etherification leading to the formation of dihydrobenzo[*f*][1,4]oxazepin-5-one (**228**), which contains a seven-membered ring, is also reported (Scheme 55c).[742] The amide functionality did not appear to adversely affect the reaction, and the best results were achieved by using DEAD in the presence of triethylamine (~65% yield). An analogous route is adapted by the same research group to prepare many other tetrahydrobenzo[1,4]diazepinones.[743] Oxepane/oxepin derivatives,[744−746] including the naturally occurring radulanin E, were synthesized similarly.[746] Dehydration leading to the construction of the seven-membered oxygen heterocycle in dihydro-6,13-dioxabenzo[3,4]cycloheptanaphthalene was also accomplished readily via etherification, despite the presence of two additional phenolic −OH groups in the precursor.[747]

In the synthesis of hepatitis C virus (HCV) protease inhibitors **229**−**230** that are potent therapeutic agents, the macrocyclization was accomplished by a Mitsunobu protocol using Ph_3P−ADDP.[748] Although an NHC(O) group was present in the precursor, the reaction took place preferentially with phenolic −OH, and the yield for the cyclization step was quite good (66%). Arasappan et al. have synthesized 4-hydroxyproline derived macrocycles that showed HCV NS3 serine protease inhibitory activity.[749,750] Novel proline-based 16- and 17-membered macrocycles have been prepared by Chen et al. via intramolecular etherification using the combination Ph_3P−ADDP.[751] The authors stated that bubbling the reaction solution with argon gas helped in obtaining a better yield. Such a macrocyclization leading to a 17-membered macrocycle has been used later by the same research group for the synthesis of potent inhibitors of the hepatitis C virus.[752]

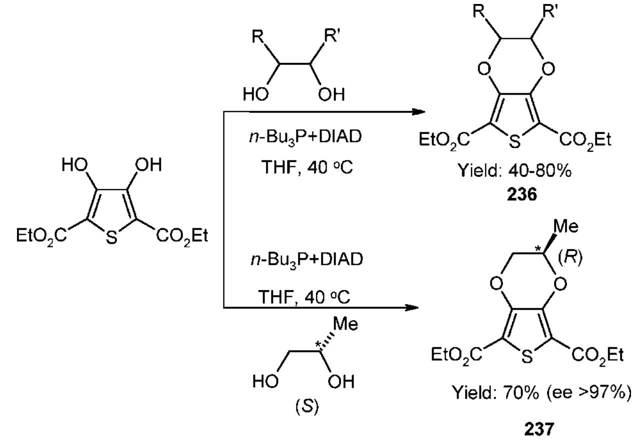


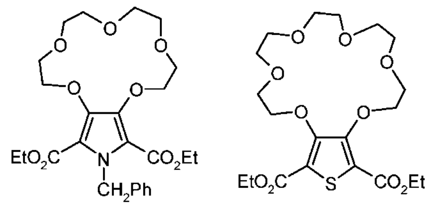
Naturally occurring *S*-amino acids have been employed as chiral synthons for enantiomerically pure benzannulated

Scheme 56



Scheme 57





238 239

oxazepine, diazepine, thiazepine, oxazocine, and diazocine compounds (e.g. **231−235**; Scheme 56).[753] Both inter- and intramolecular Mitsunobu reactions have been used to construct these heterocycles. Either *N*-alkylation or ether formation was used in the cyclization process with the normal reagent system of Ph_3P−DEAD in THF (0 °C to room temperature) to obtain yields of >63%. The authors have stated that this was the first example where the Mitsunobu approach was utilized for the construction of *S*-amino acid-based seven- and eight-membered ring systems.

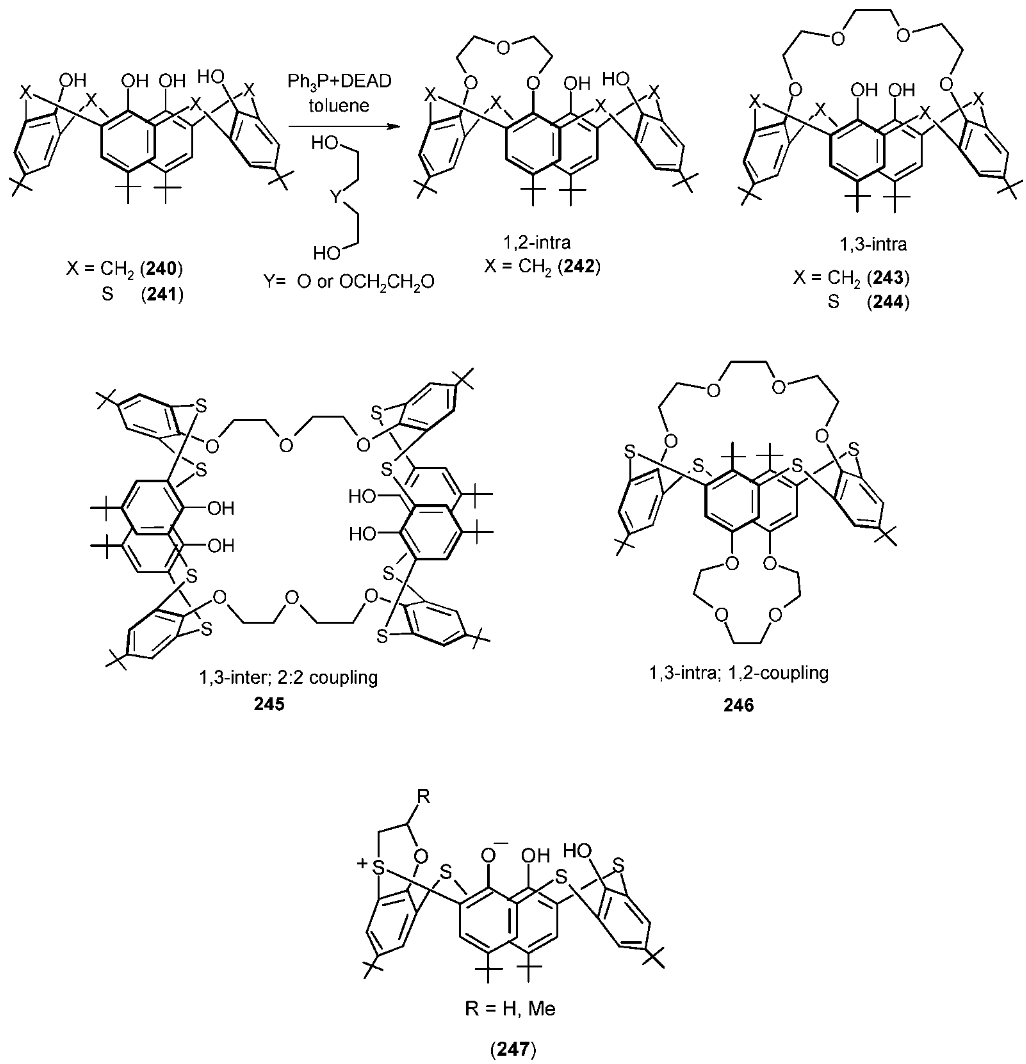
The monomer for poly(3,4-ethylenedioxythiophene) (PEDOT), a widely used antistatic coating in photographic films and an electrode material for solid electrolyte capacitors, is substituted 3,4-ethylenedioxythiophene (EDOT). Both achiral (**236**) and chiral (**237**) monomers were readily synthesized by using a Mitsunobu protocol (Scheme 57); the yields were moderate to good, except in the case of 1,2-cyclohexane diol.[754] Cyclization was effected by intermolecular dehydration. Use of a chiral glycol led to an inverted product. Reynolds and co-workers have reported compounds of type **236** as well as those derived from 1,3-diols (that lead to seven membered rings) in place of 1,2-diols. The yields were in the range 60−95%.[755] Qing and co-workers have also prepared compounds of the type **236** with R = H and R′ = -CH_2-*n*-C_6F_{13}; after the removal of the carboxylate group, they obtained the corresponding poly(ethylenedioxythiophene).[756] Analogous pyrrole derivatives and crown ethers based on such thiophene/pyrrole skeletons (e.g. **238−239**; for applications to sensory electroactive polymers) have been synthesized by a similar route.[757,758]

Selective ring closures of *p-tert*-butylcalix[4]arene (**240**) and *p-tert*-butylthiacalix[4]arene (**241**) with diols have been effected using a Mitsunobu protocol in very short reaction times.[759] The 1:1, 2:2, and 1:2 couplings, leading to **242−246**, were observed depending upon the type of glycol used (Scheme 58). It was also shown that the sterically less hindered 1,3-phenolic positions were more prone to alkylation and the corresponding 1,3-diethers were readily formed by using simple alcohols.[760] This observation was later used to obtain ethers with long chain chloro and bromo alcohols.[761] The resulting mono- and diethers with residual −Cl or −Br functionalities were needed for the generation of macrocycles. Following the same approach, synthesis of macrocycles containing 1,1′-bi-2-napthoxy derivatives could be accomplished. The thiacalixarene **241** underwent an unusual reaction with 1,2-diols in the presence of Ph_3P−DEAD, and the structure **247** was assigned to the product.[762] The same principles were extended to the preparation of (i) oligoethylene glycol analogues composed of O, S, and N atoms in the chain[763] and (ii) macrocyclic ethers containing two calixarene units.[764] Chiral macrocycles capped by carboxamide bridges were also synthesized by chemoselective intramolecular ring closure on the phenolic OH groups of *p-tert*-butylthiacalix[4]arene-1,3-bis(*N*-hydroxyalkylamides) under Mitsunobu conditions recently.[765] Bartsch and co-workers have also reported calixarene-crown ethers that were prepared using a Mitsunobu route and used later for competitive metal ion extraction.[766]

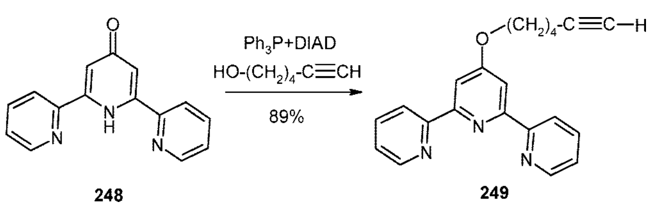
4.3. *O*-Alkylation (Ether Formation) via an NHC(O) to N=C(OH) Proton Shift

When there is an NH−C(O) group in the molecule, Mitsunobu coupling using such a compound as a nucleophile often leads to *O*-alkylation, effectively via the N=C(OH) tautomeric form. Thus, in the Mitsunobu coupling of 2,6-di(pyridin-2-yl)pyridin-4(1H)-one (**248**), ether formation instead of *N*-alkylation was the preferred pathway, as shown by Hovinen (Scheme 59).[767] This method has been utilized to obtain **249** with a terminal alkyne unit. In all cases, the reaction was completed in a few hours at room temperature. In the glycosylation of the 8-oxo-purine nucleoside 2′,3′,5′-tri-*O*-acetyl-6-*N*-trityl-8-oxoadenosine with 2,3,4,6-tetra-*O*-benzylmannopyranose, Sugimura and co-workers have obtained the *O*-alkylated product in excellent yield.[768] In the Mitsunobu reaction of *N*-(2-hydroxyethyl)ureas PhNHC(O)NRC(R′R″)CH_2OH using Ph_3P−DEAD, a mixture of *O*- and *N*-alkylation products or a single isomer was obtained, depending on the substrates.[769] *O*-Alkylation via a NH−C(O) to N=C(OH) tautomeric shift was used by Maruyama and

Scheme 58



Scheme 59

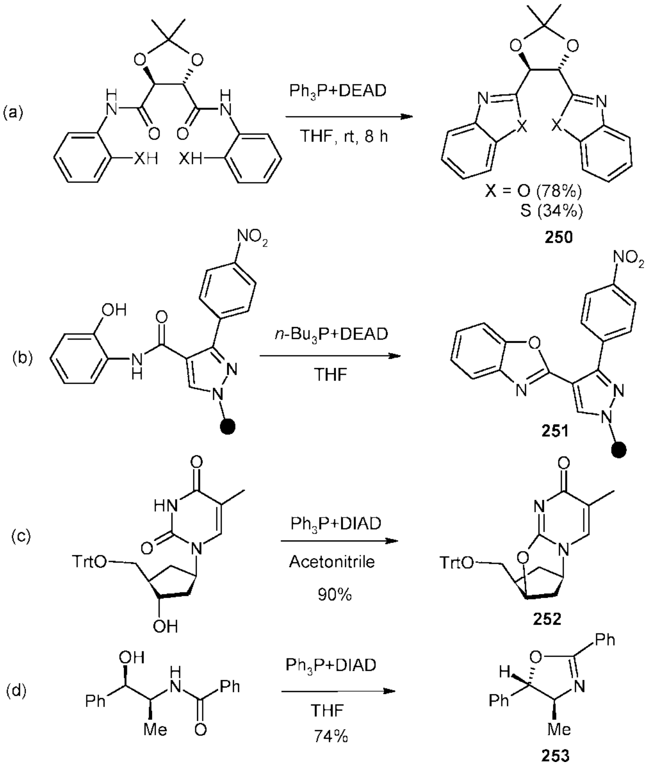


co-workers to obtain a uric acid derivative.[770] However, an exocyclic NHC(O)CH_3 group connected to guanosine underwent only *N*-alkylation leading to N^2-alkylguanosine.[771] In the synthesis of pteridine$-N^8-$nucleosides, Pfleiderer and co-workers utilized an *O*-alkylation in an intermediate step for protection of an amide functionality.[772]

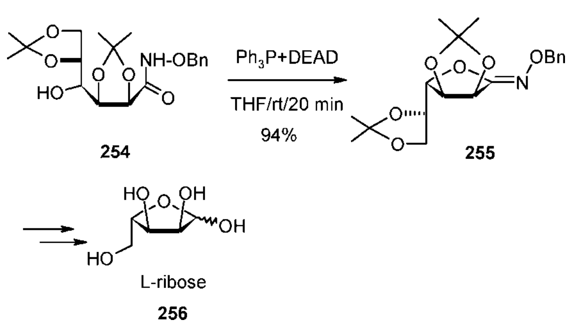
An interesting case of *O*(*S*)-alkylation with cyclization involved bisbenzoxazoles and bisbenzothiazoles of type **250** (Scheme 60a).[773] Here also, an NH to OH tautomerization is required prior to cyclization and crude dihydroxyaryl diimides could be used directly. A possible mechanism involving the phenolate salt of $[(EtO_2C)HN-N(CO_2Et)-PPh_3]^+$ was also proposed by the authors. Another interesting case entails a highly effective route for the synthesis of polymer-bound 2-(3-aryl-1H-pyrazol-4-yl)-1,3-benzoxazole **251** but by using a stepwise solid phase path with Mitsunobu cyclization as the key step (Scheme 60b).[774] Here, the *n*-Bu_3P-DEAD reagent system was employed. The reaction did not go to completion when Ph_3P was used instead of *n*-Bu_3P. An earlier report by Wang and Haske also involved an analogous solid phase synthesis.[775] A similar intramolecular etherification afforded interesting carbocyclic nucleosides such as **252** (Scheme 60c);[776] the derivative with a PMB group in place of triphenylmethyl (Trt) is also known.[777] Oxazoline formation by this route appears to be facile, and many useful ligands for transition metals and an intermediate for norpseudoephedrine (**253**, Scheme 60d) have been synthesized.[778,779] An unwanted oxazoline formation was noted by Jackson and Zhang in the course of their studies on the carbacephem antibiotic loracarbef.[780] In the reactions of saccharins, Woodward and co-workers observed *O*-alkylation with alcohols using a Mitsunobu protocol, while that using alkyl halide and a base afforded *N*-alkylated derivatives.[781] Upon Mitsunobu etherification conditions, β-hydroxy amides gave oxazines (*O*-alkylation), while β-hydroxy thioamides gave either thiazines (*S*-alkylation) or pyrrolidines (*N*-alkylation) depending on the substituents present in the precursors.[782]

D-Mannono-1,4-lactone was efficiently converted into L-ribose **256**, in which a key step was the cyclization of γ-hydroxyalkoxamate **254** (Scheme 61).[783] The *O*-alkylation product was obtained in 94% yield with none of the *N*-alkylation product detected in the cyclization process. Using D-glycono-1,5-lactones, L-pyranoses were obtained

Scheme 60



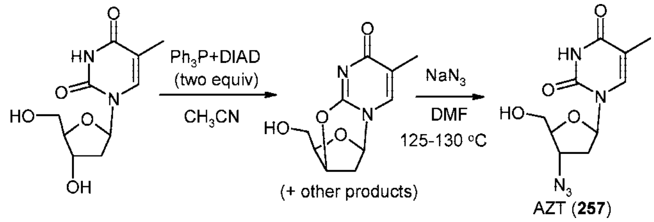
Scheme 61



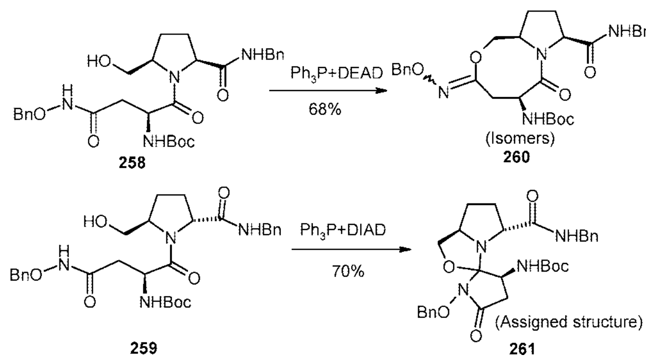
similarly. Here, depending on the stereochemistry of the substituents, *N*-alkylation was observed in a few cases with *O*-alkylated product still predominating.[783,784] *O*-Alkylation on purine bases was also employed in the synthesis of protected O^6-deoxyguanosine derivatives via NHC(O) to N=C(OH) tautomerization.[785] Similarly, 9,N^2-diacetylguanine reacted with 2-(*p*-nitrophenyl)-ethanol to give the *O*-alkylated compound N^2-acetyl-O^6-(2-(*p*-nitrophenyl)ethyl)guanine.[786] For O^6-protection in the synthesis of N^2-benzyl[2-^{15}N]guanosine[787] and 2,8-disubstituted guanosine derivatives also,[788] a similar etherification with 2-(4-nitrophenyl)ethanol has been utilized.

Azidothymidine (AZT)/Zidovudine (ZDV)/Retrovir/Retrovis (**257**) is a drug approved for treatment of HIV. Balagopala and co-workers have described a high yield route to this compound using a Mitsunobu protocol (Scheme 62).[789] In the first step, Mitsunobu dehydration converted thymidine into 2,3′-anhydrothymidine, which upon heating with NaN_3 gave AZT in an overall yield of 62%. It is interesting to note that the configuration at the secondary alcohol site was retained after azidation. A similar chemistry has been utilized by Marquez et al. for the synthesis of many AZT analogues.[790] In another study, Christopher Wilds et al. have synthesized oligonucleotides containing an alkyl interstrand

Scheme 62



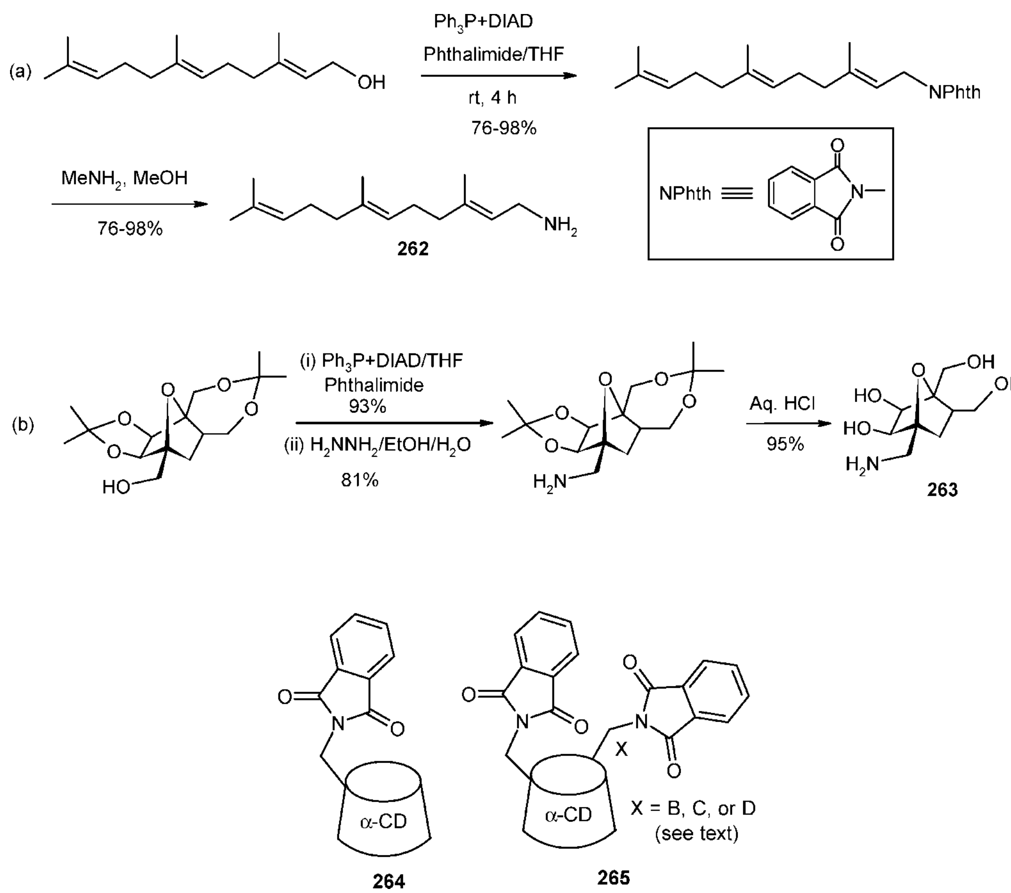
Scheme 63



cross-link between the two O^6 atoms of deoxyguanosine by using a Mitsunobu protocol, where the coupling probably occurred via a NHC(O) to N=C(OH) tautomerization.[791]

In the synthesis of 1-sulfonyl-1,4-diazepan-5-ones, Banfi et al. encountered an interesting difference in reactivity between the *cis*- and *trans*-isomers of substituted pyrrolidines **258**−**259** (Scheme 63).[792] While the *cis*-isomer gave the *O*-cyclized eight-membered ring containing product **260**, the *trans*-derivative gave a different product **261**, in which cyclization led to a fused spirocyclic five-membered ring system. The yields were quite good in both the cases. The two types of proton shifts [NH−C(O) to N=C−(OH) and CH−C(O) to C=C(OH)] coupled with different orientations of the reactive functional groups might have contributed to this difference. These results also show that different amidic groups can interfere with the expected course of the Mitsunobu reaction. In the reaction of 3-methyl-4H-[1,2,4]-oxadiazol-5-one, although both *N*- and *O*-alkylation occurred, the authors noted that alkylation was selective for the allylic when compared to alkyl sites of the alcohol substrates.[793] In the synthesis of many isoquinoline/isoquinolinone-based prodrugs, Threadgill and co-workers used both *O*-alkylation and ring *N*-alkylation.[794] Isoquinolin-1-ones[795] and 3-methyl-1-phenyl-2-pyrazolin-5-ones[796] underwent predominantly *O*-alkylation with benzyl alcohol under Mitsunobu conditions. Sulfahydantoins reacted with hydroxyl acids (e.g. ethyl (*S*)-lactate) to lead to *O*-substituted compounds rather than the expected *N*-alkylated ones. Here also NH−C(O) to N=C(OH) tautomerization might have occurred prior to *O*-alkylation.[797] In an earlier study by Overman and Zipp, it was noted that $[PhC(O)]_2NH$ underwent Mitsunobu *O*-alkylation with allylic alcohols [e.g., PhCH=CH−C(Me)(OH)] to afford allylic *N*-(benzoyl)benzimidates.[798] N^3-Benzoyl thymine gave more of the *O*-alkylated product while the primary base thymine itself underwent predominantly *N*-alkylation with 2-(tetrahydropyran-2′-yloxymethyl)hexahydropyrrolo[1,2]isoxazol-4-ol in the Ph_3P−DEAD/dioxane system.[799] *O*-Alkylation after tautomerization was also employed in the preparation of isoxanthopterin N^8-(2′-deoxy-*β*-D-ribonucleosides by Lehbauer and Pfleiderer.[800] Synthesis of nucleoside-based solid supports, in which the nucleosides are anchored onto the resin

Scheme 64



through the base, has been reported by Di Fabio and co-workers.[801] The authors were able to obtain high yields of the products using the normal reagents Ph_3P−DEAD in THF−CH_2Cl_2 medium.

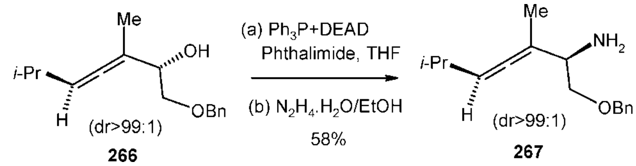
5. Amines, Amides (Including Nucleobases), or Azides as Nucleophiles

The utility of the Mitsunobu reaction in the conversion of alcohols to amines using acidic imide derivatives as nucleophiles is well-known.[15] Phthalimides and related compounds in which an NH is connected to an electronegative group (e.g. *o*-nitrobenzenesulfonyl) can readily take part in *N*-alkylation. In place of phthalimide, one can use nucleobases. Suitably protected amino acid moieties also contain activated NH moieties that readily undergo Mitsunobu alkylation, thus expanding the scope of this reaction enormously. Finally, HN_3 or any of its alternative sources, such as trimethylsilyl azide, diphenylphosphoryl azide (DPPA), and zinc(II) azide, do take part in this reaction. Since the resulting phthalimides or azide functionalities can be conveniently transformed into amines or heterocycles, the Mitsunobu protocol is useful in various organic syntheses. These aspects are discussed below.

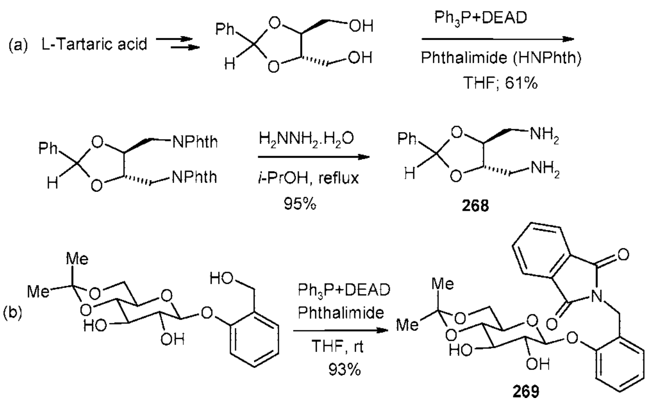
5.1. *N*-Alkylation Using Phthalimide and Related Imides

Allylic amines can be prepared by the reaction of corresponding allylic alcohols with phthalimide under Mitsunobu conditions followed by treatment with methylamine. Deprotection using methylamine rather than hydrazine hydrate would alleviate the problem of allylic rearrangement and destruction of sensitive functionalities, besides providing very mild reaction conditions, high yields, and high isomeric purity. This procedure was used for the preparation of farnesyl amine **262**, a potent *in vitro* inhibitor of *ras* prenyl transferase and synthetic precursor to several squalene synthase inhibitors (Scheme 64a).[802] Buser and Vasella have utilized phthalimide for the synthesis of 7-oxanorbornanyl amino alcohols (e.g. **263**). For the removal of the phthalimide residue later, they used hydrazine (Scheme 64b).[803] The yields were pretty good. Gotor and co-workers obtained orthogonally protected *cis*- and *trans*-indane-1,3-diamines in high yields using the phthalimide route.[804] The inversion process (>99% *ee*) in this reaction was corroborated by a combination of NMR spectroscopy and molecular modeling. Linares et al. reported that although the phthalimido group could be readily introduced at the 5″-position of ribostamycin, a similar reaction was not possible on neomycin B, wherein a competitive bicyclization process involving other functional groups occurred.[805] Deguin and co-workers were able to introduce more than one NH_2 group using a phthalimide protocol in the conversion of aucubin into aminoside antibiotic analogues, diamino-dideoxyaucubin and triamino-trideoxyaucubin.[806] They had earlier prepared polyfunctionalized tetrahydro-1H-cyclopenta[*c*]furan glucosides also by starting with aucubin.[807] Yuan, Fujita, and co-workers have been successful in the conversion of two adjacent primary face −OH groups of α-cyclodextrin (α-CD) to phthalimide derivatives.[808] The monosubstituted derivative **264** was obtained in 41% yield using a 3.3:1.8:2.4:1 molar ratio of phthalimide, DEAD, Ph_3P, and α-cyclodextrin with DMF as a solvent at room temperature. A mixture of three bis-isomers of **265** (A, B, C) and the mono compound (yields of 22%, 9.5%, 4.6%, and 13%, respectively) were obtained

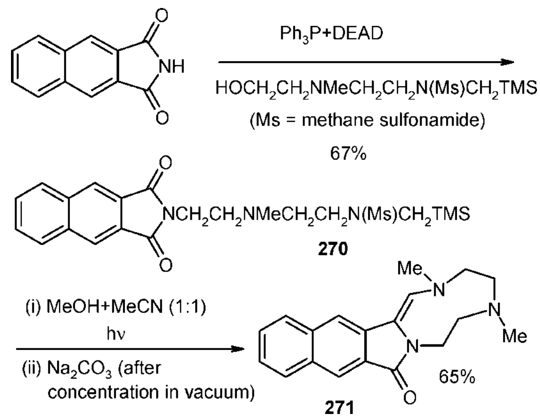
Scheme 65



Scheme 66



Scheme 67



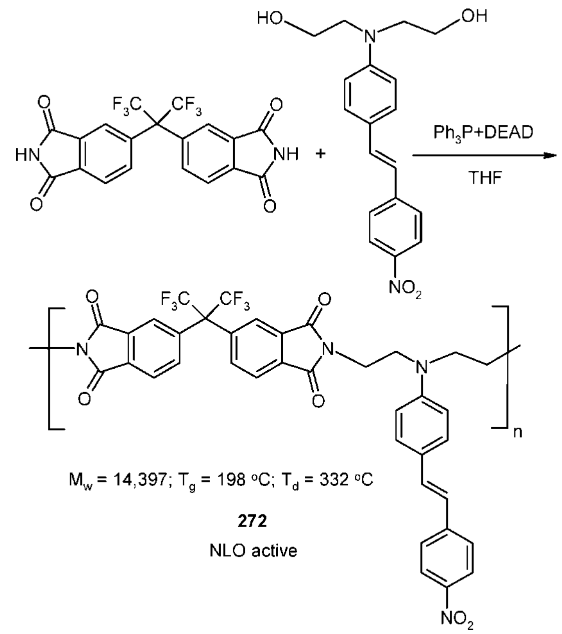
using a 7:4.6:4:1 stoichiometry of the same reagents. All these intermediates could be successfully converted to the amino compounds by hydrazinolysis. Another recent report, by Pirondini et al., involved phthalimide mediated conversion of −OH to NH_2 (and then to hydrochloride) at the lower rim of tolylpyridine-bridged cavitands for use as water-soluble molecular receptors.[809] In a reaction reported by Morita and Krause, the allenyl alcohol **266** was converted to the α-aminoallene **267** in good yield with complete inversion as depicted in Scheme 65.[810,811] *N*-Alkylation of nitrophthalimide using DEAD incorporated nanoporous magnesium aluminometasilicate tablets has been reported recently. In this process, however, the phosphine reagent has not been specified.[812] A phthalimide analogue supported on aminomethyl polystyrene resin has been prepared and used for the solid phase synthesis of 5′-amino-5′-deoxy-N^6-benzyladenosine by Aronov and Gelb.[813]

An elegant use of Mitsunobu *N*-alkylation for the synthesis of chiral synthons has been developed by Grycko et al.[814] For example, the chiral diamine **268** was obtained by starting with L-tartaric acid, as shown in Scheme 66a. The utility of this precursor for the macrocyclization process was also demonstrated by the authors in the same paper. Another important reaction is reported by Yan and Rajan Babu in which the more reactive benzylic alcohol reacted with phthalimide to afford **269** (Scheme 66b).[815] In the preparation of phthalimide derivatives of resin-linked benzyl alcohol, Krchňák reported that adding DIAD to a solution of Ph_3P and phthalimide in anhydrous DMF and then adding the solution to the resin avoided the formation of side products significantly.[816] Other examples wherein a similar phthalimide route was put to use include the synthesis of (i) the antitumour agent batracylin,[817] (ii) the amine-functionalized crown chalcogenide 6-amino[14]aneS_4,[818] (iii) gem-diamine 1-*N*-iminosugars [α-L-fucosidase/glycosidase inhibitors],[819−821] (iv) α,α-difluoro-*β*-amino acids,[822] (v) amino-substituted triazoles,[823] (vi) gem-difluoroallenylamines,[824] (vii) 4-amino-*N*-methylproline derivatives (CLX peptide),[825] (viii) diaminocyclopentathiaphenes,[826] (ix) optically and diastereomerically pure *N*-protected (2*S*,3*R*)-2-amino-3-fluoroundecanoic and (3*R*)-3-amino-2,2-difluoroundecanoic acids,[827] (x) ditopic ligands containing both tetrazole and 1,2,4-triazole moieties,[828] (xi) *N*-methylphthalimide,[829] (xii) (*R*)-3-aminooctanoic acid (D-BAOA) from (*S*)-1-octyn-3-ol,[830] (xiii) aza-analogues of batracylins,[831] (xiv) 1α-amino- and 1,3-diamino-substituted 1α,25-dihydroxyvitamin D_3 analogues,[832,833] (xv) chiral macrocyclic bisamides derived from D-mannitol and L-threitol,[834] (xvi) chiral *trans*-2,3-bis(aminomethyl)norbornane,[835] (xvii) *N*-[1-(2-allyl-3-benzyloxy-4,6-dimethoxyphenyl)ethyl]acetamide,[836] (xviii) amino di(ethylene glycol)-terminated alkylthiol (AEG2) designed to form self-assembled monolayers (SAMs) on gold,[837] (xix) α-aminophosphonates [(Boc)NHP(O)$(OEt)_2$; HN_3 route was also used],[838] (xx) nor-seco-taxoids,[839] (xxi) 4-(aminoalkyl)estradiols,[840] (xxii) *tert*-butyl methyl-*N*-tributylstannyliminodicarbonates,[841] (xxiii) polyhydroxypiperidines,[842] (xxiv) 2-azaspiro[5.5]undecane,[843] (xxv) (−)-(*R*)- and (+)-(*S*)-mexiletine,[844] (xxvi) a bisubstrate inhibitor bound to the enzyme catechol-*O*-methyltransferase,[845] (xxvii) fused carbolines,[846] (xxviii) 5′-ethylenic modified L-nucleosides,[847] (xxix) the pineal hormone melatonin,[848] (xxx) 10-unedecene-1-amine,[849] (xxxi) chiral *N*-substituted phthalimides for liquid crystalline applications,[850] and (xxxii) 2′-*O*-aminoethyl adenosine.[851] The structural drawings pertaining to these references are given in the Supporting Information (Table S6).

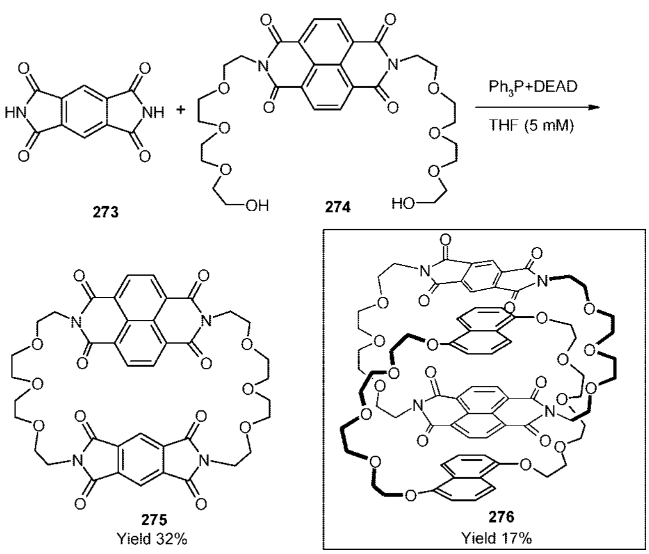
N-Alkylation has been applied for synthesizing a variety of donor tethered phthalimides and naphthalimides (e.g. **270**; Scheme 67) that underwent interesting photochemical reactions such as the one leading to **271**.[852] The more acidic tetrachlorophthalimide has been shown to be an excellent agent for displacement of primary OH groups in a wide variety of substrates.[853,854] Secondary alcohols also reacted readily, except in carbohydrates where the success rate was low. In a competition experiment between phthalimide and the tetrachloro counterpart, no trace of a product from the former could be found.

The reaction using phthalimide can be extended to those containing two phthalimide units that lead to polymeric materials with useful properties. Thus, Yoon and Shim have reported the synthesis of several NLO-functionalized polyimides by *N*-alkylation (Scheme 68). All the monomeric imide was consumed during the reaction.[855] These polymers showed high nonlinearity and good temporal stability. The $\chi^{(2)}_{33}$ value of **272** with a quartz crystal as the reference was found to be 82 pmV^{-1} (the SHG signal was stable up to 150 °C). Analogous polymers using a similar alcohol but with an azo functionality, also for NLO usage, were prepared by Lee and co-workers.[856] Many other applications on func-

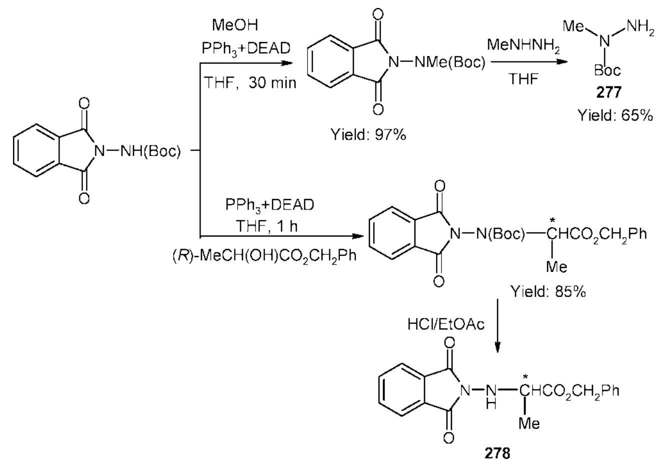
Scheme 68



Scheme 69



Scheme 70



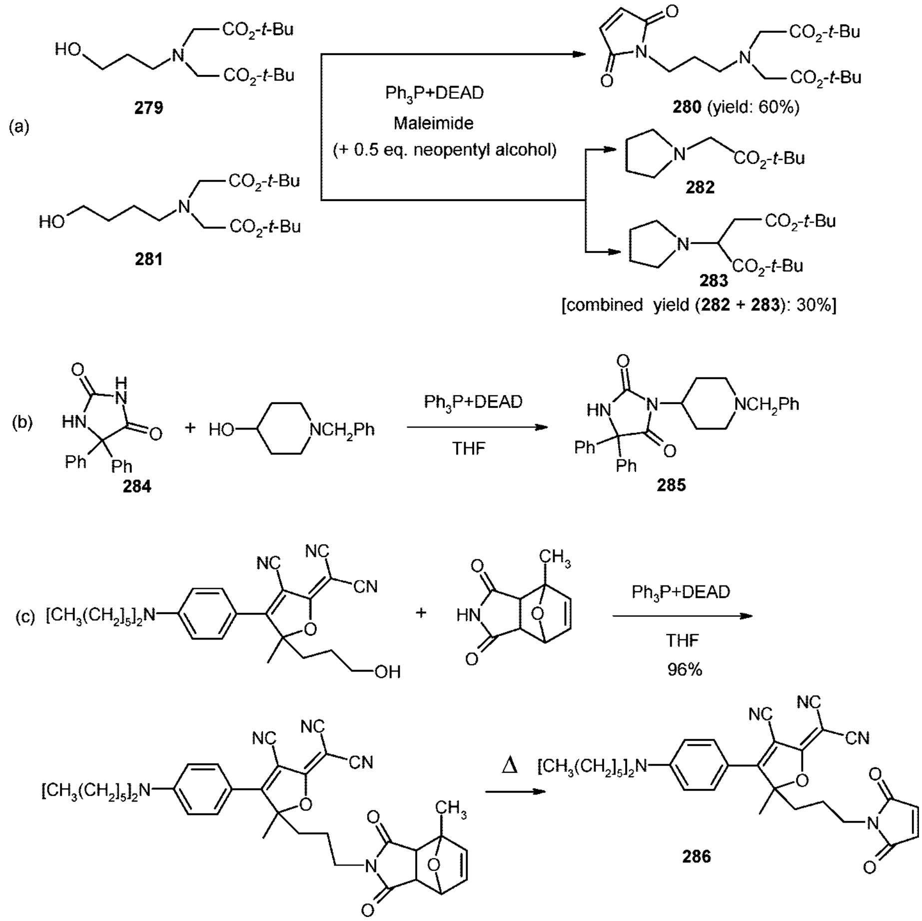
tionalized second-order NLO active polyimides have been reported.[857−863,700−703]

Use of a diimide in place of a monoimide can lead to macrocycles. An elegant display of such a result has been reported by Sanders and co-workers in the synthesis of a series of macrocycles (e.g. **275**) utilizing Mitsunobu alkylation of diimides (Scheme 69).[864,865] The same route led to the novel catenane **276** [**275** + naphthyl crown ether] by the Mitsunobu *N*-alkylation of **273** with **274** in the presence of a naphthyl crown ether. Donor−acceptor macrocycles incorporating tetrathiafulvalene and pyromellitic diimide were also synthesized using a similar strategy.[866]

A rapid and efficient two-step synthesis of monoalkylated *tert*-butylcarbazates via a Mitsunobu protocol using *N-tert*-butoxycarbonylaminophthalimide and other acylphthalimides as acid partners was developed by Jamart-Grégoire and co-workers (Scheme 70).[867−872] Synthesis of compounds such as **277** could be extended to obtain optically pure α-hydrazino esters. Removal of one of the protecting groups led to α-hydrazino esters (e.g. **278**). The same research group has also shown that aminophthalimide derivatives are better acidic partners than the aminoimidodicarbonate ($NBoc_2$) analogues and have reduced steric hindrance.[873] Solid phase synthesis of orthogonally protected α-hydrazine acid derivatives using activated phthalylhydrazines has been reported by Brosse and co-workers.[874]

In place of phthalimide, maleimide has also been utilized as the nucleophilic component.[875−878] Thus, by starting with **279**, the *N*-alkylated compound **280** was obtained (Scheme 71a).[875,876] However, when the amino alcohol **281** was used, unusual reactions took place, leading to the cyclic compounds **282** and **283** (Scheme 71a). Compound **282** was the sole product in the absence of maleimide and neopentyl alcohol.[877] In another report, maleimide moieties of poly(α-methylstyrene-*co*-maleimide) were connected to disperse red 1 (DR1) chromophore via the Mitsunobu reaction;[879] the same research group has also reported many other similar nonlinear optical polyimides using etherification.[880] The degree of substitution of the chromophore was dependent on the solvent as well as steric factors. *N*-Alkylation of phthalimide as well as a large number of analogous cyclic imides has been employed for the preparation of a variety of $P2X_7$ receptor antagonists.[881] The yield was excellent in the case of phthalimide but moderate in the case of other cyclic imides (e.g. thiazolidine-2,4-dione). Even glutaramide was used in the synthesis of (±)-lasubine I and (±)-lasubine II.[882] There is also a report on the use of cantharidinimide and $4\text{-RC}_6H_4CH_2OH$ (R = Me, Cl, NO_2) in the Mitsunobu *N*-alkylation.[883] A moderate excess of the reagents (1.5 mol equiv) afforded good yield of the product. Substituted hydantoins **284** have a (O)C-NH-C(O) skeleton similar to phthalimide, and this has been made use of in Mitsunobu *N*-alkylation (Scheme 71b).[884] The resulting product **285** was then converted in later steps to muscarinic M3 receptor antagonists, the diaryl imidazolidin-2-ones. *N*-Alkylation of triazolopyridazines possessing a −C(O)-NH-C(O)− skeleton was similarly effected to obtain the corresponding *N*-alkylated derivatives.[885] Solid supports linking nucleoside scaffolds have been obtained by alkylating hydroxyalkyl TentaGel-resin with an imino function of suitably modified nucleosides;[886] some of these were employed later for the preparation of uridine hybrids. Using 2-methylfuran-protected maleimide and an appropriate alcohol, Tweig and co-workers have synthesized a sizable number of dicyanodihydrofuran (DCDHF) fluorophores (e.g. **286**) in very good overall yields. These derivatives might be useful in single molecule fluorescence imaging.[887] Polyimides that can be coated on

Scheme 71

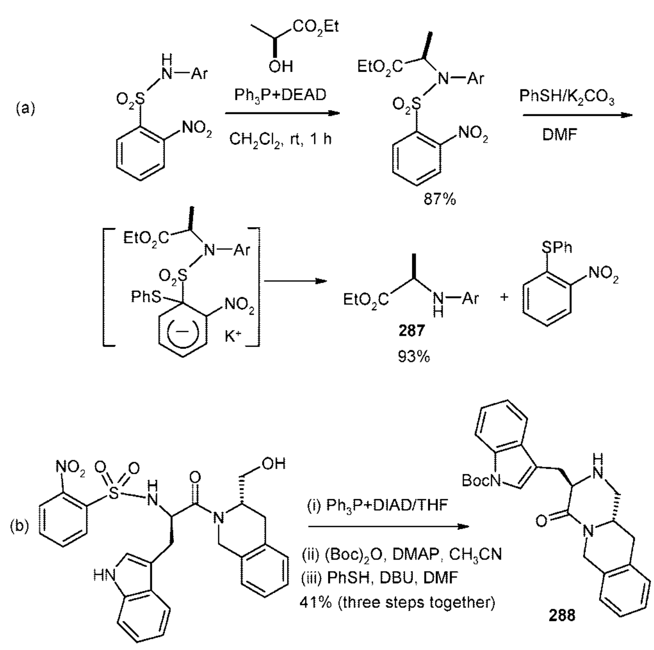


films and show optical anisotropy have been synthesized at room temperature by the reaction of diols with diimides using the Mitsunobu protocol.[888] This procedure was deemed useful for temperature sensitive applications.

5.2. *N*-Alkylation with Sulfonamides and Related Nucleophiles

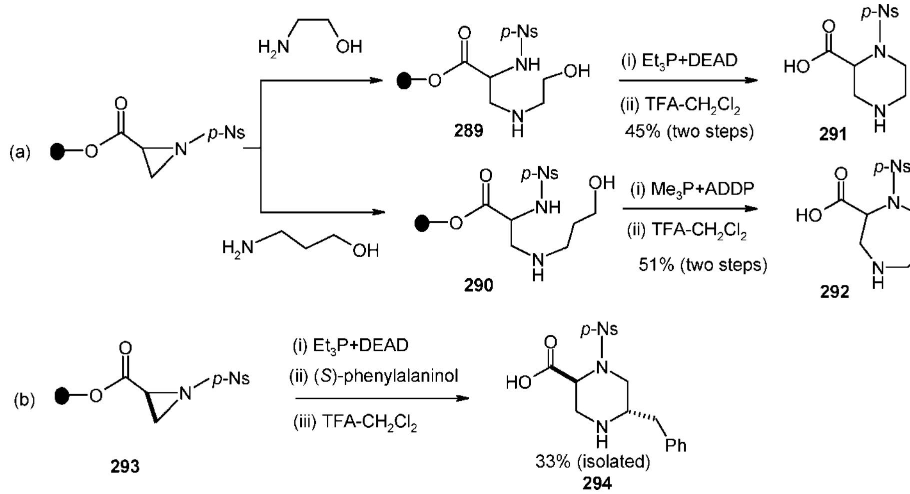
In Fukuyama's modification (Fukuyama−Mitsunobu reaction; *N*-alkylation of secondary sulfonamides under Mitsunobu conditions), either nitrobenzenesulfonamide (2- or 4-substituted) or 2,4-dinitrobenzenesulfonamide is employed as a pronucleophile (Scheme 72a).[889−891] A useful procedure for the preparation of one of the pronucleophiles, (Boc)NH(*o*-Ns) (*o*-Ns = *o*-nitrobenzenesulfonyl), is available.[892] After the *N*-alkylation, the sulfonamide portion can be readily removed by treatment with thiols. Secondary amines (e.g. **287**) are the final products. Fukuyama and co-workers have utilized their protocol in the total synthesis of lipogrammistin-A and (−)-ephedradine A.[893−895] The viability of this protocol has been improved upon by Guisado et al. through the use of the diphenylpyridinylphosphine and DTBAD.[896] Using this technique, they have prepared a complex lipopeptide (lung-targeted gene delivery agent). Pyrazine heterocycles (e.g. **288**, Scheme 72b) for peptidomimetic drug design were conveniently obtained by Zapf and co-workers by an intramolecular Fukuyama−Mitsunobu reaction.[897] Using this methodology, they were successful in obtaining several somatostatin receptor analogues. Chiral and achiral peptide nucleic acid (PNA) monomers have been prepared via *N*-(*o*-Ns) protected amino acid esters.[898] Here, deprotection of the *o*-Ns group in a later step was accomplished by

Scheme 72

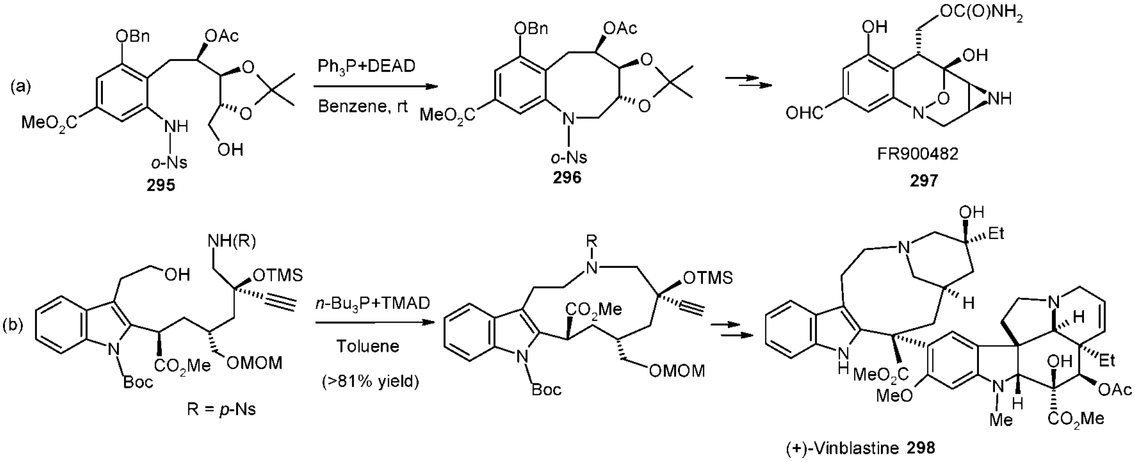


PhSH−K_2CO_3 in acetonitrile. Viirre and Hudson used the Fukuyama−Mitsunobu reaction on a resin bound amino acid to obtain similar PNA monomers.[899,900] In this case, the combination *n*-Bu_3P−TMAD in the presence of an excess of base had to be used; the normal reagent system Ph_3P−DEAD did not work. In the synthesis of tripeptides that are useful as potential peptide turn mimetics, Liskamp and co-workers have used *N*-(*o*-Ns) activation for

Scheme 73



Scheme 74

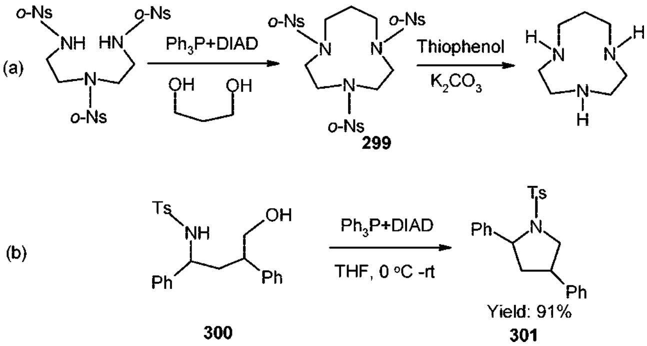


N-alkylation;[901,902] 5 mol equiv of the reagents per mole of the nucleophile were utilized. Functionalized piperazin-2-ones were also readily synthesized by intramolecular cyclization of precursor amino alcohols possessing an NH(*o*-Ns) group via the Mitsunobu protocol.[903] Olsen, Franzyk, and co-workers have checked various reagent combinations and found that the normal Ph_3P−DEAD or DIAD combination is sufficient to effect *N*-monoalkylation of peptides and sulfonamides.[904] In successive alkylation steps the yields dropped, and this was identified as a limitation of the Fukuyama−Mitsunobu reaction in the solid phase synthesis of polyamines by starting with secondary alcohols. Their group as well as Bycroft and co-workers have earlier used the same reaction for the solid-phase synthesis of polyamine toxins (e.g. PhTX4.3.3).[905,906] This Fukuyama modification has also been utilized recently for the solid-phase synthesis of mono-*N*-protected diamino acids **291** and **292** (Scheme 73a).[907] Here, the Me_3P−ADDP combination worked satisfactorily for 1,4-diazepanecarboxylic acid **292** but not for the piperazinecarboxylic acid **291**. For the latter, the Et_3P−DEAD combination gave reasonable yields. The precursors **289**−**290** in these reactions were obtained by the aminolysis of *p*-nitrobenzenesulfonyl (*p*-Ns) activated aziridines. The resin part was cleaved subsequent to the Fukuyama−Mitsunobu reaction using trifluoroacetic acid to obtain the desired products. This protocol was applied for the preparation of enantiopure piperazine carboxylic acid derivatives (e.g. **294**, Scheme 73b). Nuss and co-workers synthesized *N*-substituted α-amino acids and trisubstituted diketopiperazines (DKPs) in the solid phase and obtained excellent yields of the products with high purity.[908] Other interesting applications of solid-phase methodology include the synthesis of (i) agel 416, an acylpolyamine found in spiders, by Hone and Payne,[909] (ii) amine-bridged cyclic enkephalin analogues by Rew and Goodman,[910] (iii) tetrahydropyrazine-2-ones by Kung and Swayze,[911] and (iv) hydroxyindoline-derived tricyclic derivatives by Arya and co-workers.[912]

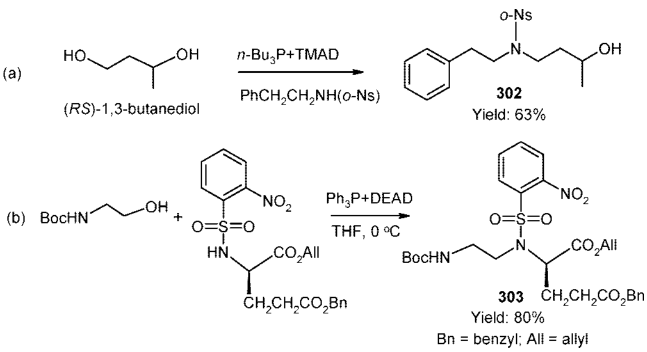
Generation of an eight-membered ring is also not too difficult, as shown by Fukuyama and co-workers in the enantioselective total synthesis of antitumor antibiotic FR900482 (**297**) (Scheme 74a).[913] The intermediate **296** was obtained in good yield (71%, including a previous step) via Mitsunobu *N*-alkylation. The synthesis of the racemic form was reported before.[914] They have also shown that this route is more general and can be adapted for the preparation of cyclic amines with eight to ten membered rings by starting with (*o*-Ns)NH(Boc).[915] The key macrocyclization step in the synthesis of the natural product vinblastine **298** was also accomplished via the Mitsunobu protocol by Fukuyama's group recently (Scheme 74b).[916]

A primary amino group can be made more nucleophilic by converting it to a pernosylated [*o*-Ns] derivative, as can be seen by the examples cited above. This feature has been utilized in the synthesis of azamacrocycles of type **299** (Scheme 75a).[917] It should be noted that preparation of these

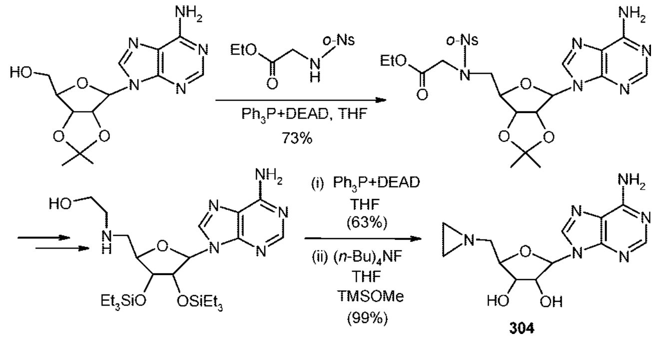
Scheme 75



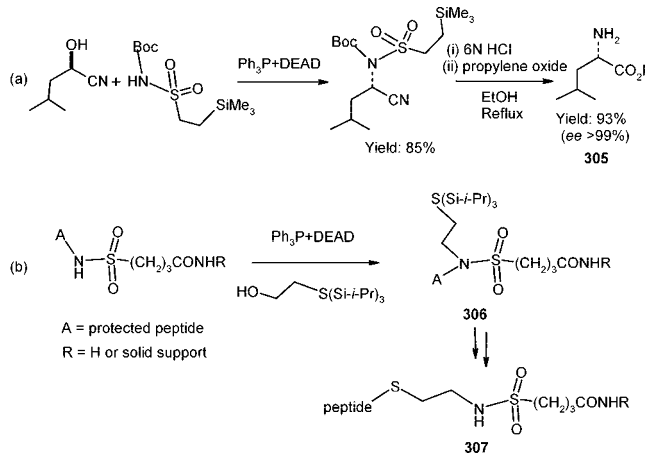
Scheme 76



Scheme 77



Scheme 78



1,4,7-triazacyclodecanes was not possible by starting with the corresponding tosylate in DMF in the presence of Cs_2CO_3. As discussed above (Scheme 74), intramolecular cyclization using amine and alcohol functionalities on the same molecule is also feasible. Thus, the amino alcohol **300** readily gave pyrrolidine **301** upon treatment with Ph_3P−DIAD (Scheme 75b).[918] The tosyl group was subsequently cleaved using Mg/MeOH to obtain the free amine for further reactions. The same route was utilized to construct four-membered rings[919] as well as macrocycles.[920] *N*-Alkylation of *o*-Ns-substituted amines was one of the important steps in solid phase combinatorial synthesis of macroheterocycles[921] developed by Ramaseshan et al. The same research group also used tosyl-substituted nucleophiles to prepare structural analogues of tirofiban.[922] Protected (*R*)-α-phenylproline derivatives were prepared by a similar methodology by Betsbrugge et al.[923]

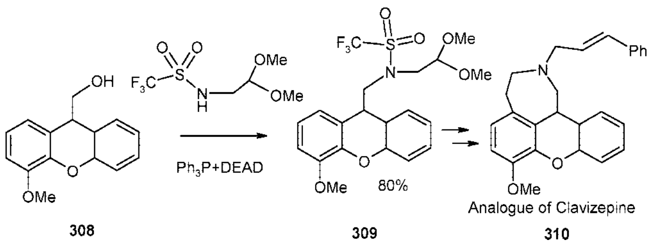
When (*R,S*)-1,3-butanediol was subjected to alkylation with 2-nitro-*N*(2-phenylethyl)benzenesulfonamide [$PhCH_2CH_2NH$(*o*-Ns)] using the *n*-Bu_3P−TMAD reagent pair, monoalkylation (63% yield) occurred predominantly at the primary alcohol site to lead to **302** (Scheme 76a).[924] This situation is different from that seen for esterification of 1,2-diols discussed above.[83,300] Only 4% of the dialkylation product was isolated. Further reaction with Me_3P−ADDP gave the bis-alkylated product readily in 66% yield. Using a similar activation at the nitrogen center, Kirillova and co-workers have shown that Mitsunobu condensation is a universal preparative method which allows the formation of different reduced peptides (e.g. **303**; Scheme 76b).[925] For the synthesis of many pseudo-peptides, reaction of *tert*-butoxycarbonyl-protected amino alcohols with Pmc-protected amino esters ($pK_a \sim 12$; Pmc = 2,2,5,7,8-pentamethylchroman-6-sulfonyl) has been utilized.[926] The best conversion was obtained with the *n*-Bu_3P−TMAD reagent system. Falkiewicz has reported the synthesis of a PNA type monomer backbone with a reduced peptide bond using Boc-aminoethanol (derived from an amino acid) and resin-bound *o*-nitrobenzenesulfonylglycine.[927] A similar reaction leading to *o*-Ns protected pseudopeptides was also reported by Boyarskaya et al.[928]

5′-Aziridinoadenylates of the type **304** and related nitrogen mustard variants allow conversion of biological methyltransferases into nucleoside transferases, thus providing powerful tools for investigating *S*-adenosyl-L-menthionine (SAM)-dependent methylation. A highly efficient synthesis of such molecules was achieved by using the Mitsunobu reaction in a multistep synthesis (Scheme 77).[929] Here, adenine base protection was not required.

Chiral cyanohydrins and an *N*-protected sulfonamide as substrates in *N*-alkylation afforded new amino acids (e.g. **305**, Scheme 78a).[930] Some of these amino acids have been obtained in high enantiomeric purity. In a few cases, however, there was no significant *ee*. *N*-Alkylation of peptides (e.g. **306**) containing a sulfonamide linker with a protected 2-mercaptoethanol has been conducted in solid phase (Scheme 78b) (fmoc = 9-fluorenylmethoxycarbonyl).[931] The product **306**, upon thiol deprotection (TBAF/AcOH) led to the corresponding thiol, which spontaneously rearranged to the thioester with a protected peptide; this, upon treatment with trifluoroacetic acid, furnished the free thioester **307**.

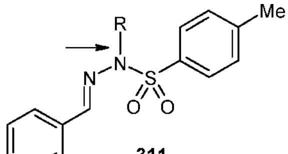
Many other amine nucleophiles and deprotection methods have been investigated for use, particularly in cases where sensitive functionalities are involved. One such precursor is $HN(SO_2CF_3)(CH_2CN)$. This was readily alkylated using Ph_3P−DEAD (81−94% yield) and an appropriate alcohol. Subsequent base-catalyzed elimination of trifluoromethanesulfinate yielded synthetically valuable iminoacetonitriles, RN=CH(CN).[932] Alternatively, Dominguez and co-workers

Scheme 79



utilized *N*-trifluoromethanesulfonamide as a pronucleophile to convert −OH to an −NHR group in the synthesis of clavizepine analogue **310**.[933] This substrate was regarded as more efficient than *N*-tosyl derivatives (discussed below), and it afforded a yield of 80% with only very minor amounts of side products (Scheme 79). The trifluoromethanesulfonamide group was replaced later by hydrogen via Red-Al. In another work, substituted trifluoromethanesulfonamides $CF_3SO_2N[(CH_2)_3R]_2$ ($R = C_nF_{2n+1}$; $n = 4, 6, 8, 10$) were obtained in high yields using $CF_3SO_2NH_2$ and perfluoroalkanols in the presence of Ph_3P−DEAD/diethyl ether.[934] Here, products were isolated by fluorous extraction and fluorous solid−organic liquid filtration. Wanner and co-workers utilized 1-phenyl-3-(2,2,2-trifluoroacetyl)urea [PhNHC(O)NHC(O)CF_3] in *N*-alkylation reactions to prepare many glycine equivalents.[935] Three other useful perfluoroalkyl group containing nucleophiles that have been shown to undergo facile *N*-alkylation are (i) substituted trifluoroacetamide,[936] (ii) perfluoroalkanesulfonamide, $C_8F_{17}SO_2NH(Et)$,[937] and (iii) $CF_3SO_2NH(Et)$.[938]

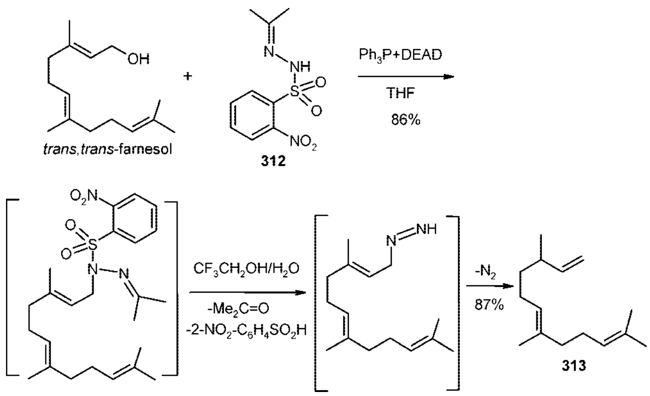
It is known that tosyl- and Boc-hydrazones are effective nucleophiles in the Mitsunobu reaction.[939] While tosyl hydrazones reacted cleanly with primary and secondary alcohols (ROH) when coadministered to a cooled Ph_3P−DTBAD or Ph_3P−DEAD complex to afford products of type **311**, Boc-hydrazones required electron-withdrawing substituents for the reaction to take place. It is also reported in the same paper that preformation of Ph_3P−DEAD complex prior to the addition of alcohol and hydrazones gave superior results. An interesting application of *N*-isopropylidene-*N*′-2-nitrobenzenesulfonyl hydrazine (IPNBSH, **312**; cf. Scheme 80) in the reduction of alcohols has been reported by Movassaghi and Ahmad recently.[940] The Mitsunobu derivative after removal of the sulfonate group underwent loss of nitrogen from monoalkyl diazene intermediate to afford the final product. This procedure has been adapted to obtain the triene **313** from farnesol. Earlier, a similar reaction using *o*-nitrobenzenesulfonylhydrazine (NBSH) was published by Meyers et al.[941] There, the reaction of NBSH with RCH_2OH yielded the alkane via the sequence $RCH_2N(NH_2)SO_2(2\text{-}O_2NC_6H_4) \rightarrow [RCH_2N{=}NH] \rightarrow RCH_3$.



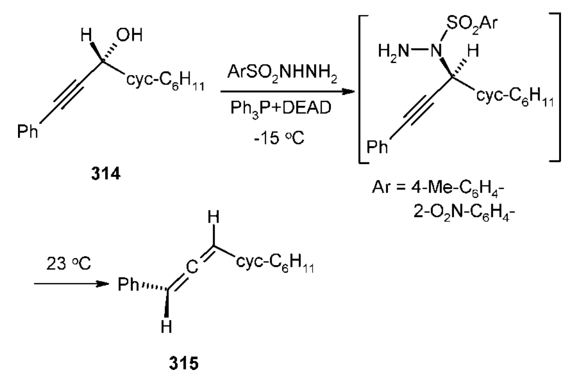
311

Synthesis of a diverse class of substituted allenes (e.g. **315**) was achieved by Myers and Zheng in a single step starting from propargylic alcohols (e.g. **314**) using an activated hydrazine nucleophile (Scheme 81).[942−945] Among several

Scheme 80



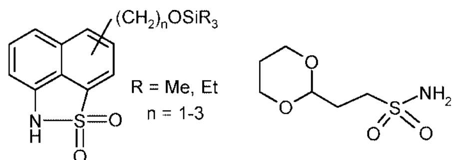
Scheme 81



such nucleophiles, *o*-nitrobenzenesulfonylhydrazine proved to be the best. Premixing Ph_3P (1.5 equiv) and DEAD (1.5 equiv) in THF at −15 °C and then adding the propargylic alcohol (1 equiv) and finally the substituted hydrazine (1 equiv) afforded the allenes in 72−77% yield in a single operation, after the extrusion of nitrogen and arylsufinic acid. This transformation proceeded with complete stereospecificity. It provides access to a wide range of optically active allenes, since a large number of optically active propargylic alcohols are available.

The silyloxy-substituted 1,8-naphthosultams **316** have been utilized to prepare many pharmacologically active anti-MRS carbapenem derivatives (e.g. L-786,392).[946−948] Bis(*β*-trimethylsilylethanesulfonyl)imide ($(Me_3SiCH_2CH_2SO_2)_2NH$ is another synthetically valuable precursor developed by Weinreb and co-workers. The protective group can be readily removed later by fluoride ion.[949] Many protected amine derivatives have been prepared by starting with this nucleophile. Unsymmetrical sulfamides were prepared by Ghassemi and Fuchs by alkylation of Boc-sulfamides [e.g. (Boc)NH(SO_2N(Me)Ph)] with alcohols using microwave heating (1−4 min); the Boc-group was removed later using silica-bonded toluenesulfonic acid.[950] The final sulfamides were released by treating the polymer sulfonate salt with NH_3/MeOH. Mitsunobu *N*-alkylation of a toluene sulfonamide [e.g. (Ts)NH(2-vinyl-C_6H_4)] was employed as one of the key steps by Theeraladanon et al. in the synthesis of (+)-(*S*)-angustureine, a novel quinoline alkaloid.[951] Tsunoda and co-workers have recently developed 2-(1,3-dioxan-2-yl)ethylsulfonyl (Dios) amides (e.g. **317**) for activating the amino group in reactions using their alternative Mitsunobu reagent, (cyanomethylene)tributylphosphorane (CMBP). This compound is stable under basic as well as reductive conditions and can be removed by heating in a hot aqueous

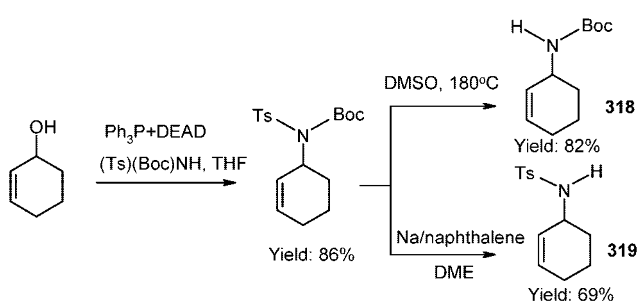
solution of trifluoroacetic acid.[952] They have also reported that even *p*-toluenesulfonamide could be readily alkylated by CMBP.[953] An interesting study on competitive *O*-(phenolic) vs *N*-(sulfonated/acylated) alkylation of tyrosine derivatives by Attolini et al. revealed that the selectivity was dependent on both steric factors and the pK_a values of the substrates.[954]

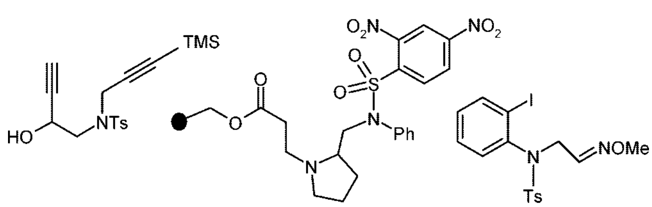


316 **317**

Synthetic procedures for *N*-activated precursors [*o*-NsNH-Boc, Ts-NH-Boc, etc.] that are useful in peptide chemistry, as well as several *N*-alkylations using these, have been reported by Kołodziejczyk and co-workers.[955] The compound Ts-NH-Boc as the nucleophile led to either *N*-tosylated or *N*-Boc-protected amines (e.g. **318**−**319**) via Mitsunobu *N*-alkylation followed by appropriate choice of the next deprotection step (Scheme 82).[956] The same precursor was also employed by Taguchi and co-workers to prepare several tosylated tertiary amines.[957] Other applications of sulfonamide activation include the synthesis of (i) highly functionalized isoxazoles via HN(Boc)(SO_2Ph),[958] (ii) marine product α-kainic acid via (substituted allyl)HN-(tosyl),[959] (iii) cyclic sulfamides via acyclic sulfonamides of the type RN(H)SO_2NH(Boc),[960] (iv) *N*,*N*-bis[[6-(hydroxymethyl)pyridin-2-yl]methyl]-2-nitrobenzenesulfonamide using (*o*-Ns)NH_2 and 2,6-pyridine-dimethanol,[961] (v) (solid phase) polyamines via nosyl terminal secondary amines,[962] (vi) fmoc-protected amides via (fmoc)(Ts)NH,[963] (vii) azabicyclic enones [and the alkaloid (−)-brunsvigine] using (Ts)NH(CH_2)$_n$CON(OMe)Me,[964] (viii) an *N*-connected NAD analogue via [PhCH_2NHSO_2]$_2$$CH_2$,[965] (ix) compound **320** via (Ts)HNCH_2C≡C(TMS),[966] (x) species **321** via 2,4-dinitro-*N*-phenylbenzenesulfonamides,[967] (xi) substituted *N*-hydroxysulfamides via (Boc)HNSO_2N(Me)(OTMBMS),[968] (xii) cyclic oxazo derivatives via HN(*p*-Ns)(CH(Bn)CH=CH_2),[969] (xiii) chiral 3,4,5-trihydroxy-2-piperidin-2-ones (solid phase) via (*o*-Ns)NH[CH(CO_2Me)CH_2CHMe_2],[970] (xiv) multisubstituted urea derivatives of hydrazines via tosylated hydrazine precursors,[971] (xv) aspidospermidine via 2-IC_6H_4NHMs,[972] (xvi) pitiamide A via (*o*-Ns)NH[C(O)CH_2CH_2CH=CH$CH_2CH_2CH_3$],[973] (xvii) queuine from ribose and (*o*-Ns)NH[$CH_2CH_2CH_2$OTBDMS],[974] (xviii) tosyl-substituted iodoanilines **322**, which were required later for the synthesis of heterocyclic oximes,[975] (xix) fluoride containing RCM precursors via (Ts)NHCH_2C(=CH_2)F,[976] (xx) fosmidomycin (antimalarial drug) analogues via (*o*-Ns)NHOBn,[977] (xxi) (−)-metazocine via MeC(O)CH(CH_2Ar)NH(*o*-Ns),[978] (xxii) orthogonally-protected α,β-diaminopropionic acids via (Ts)N-H(Boc),[979] (xxiii) *N*-linked carbohydrate derivatives via glucose-6-sulfonamides,[980] (xxiv) functionalized cyclopentenyl amines via BocNH(*o*-Ns),[981] (xxv) ketopiperazines using a sulfonamide connected to a 2,4-dimethoxybenzyl arylhydrazine (DMBAH) linker (solid phase),[982] (xxvi) substituted oxopiperazines via sulfonamide activated amines,[983] (xxvii) 4-methoxybenzenesulfonyl-*N*-benzylleucinamide (solid phase),[984] (xxviii) 2-chloroethylnitrososulfamides,[985] (xxix) *N*-alkylsulfonamides (solid phase),[986] (xxx) *N*-alkylamino acids,[987] (xxxi) azasugars,[988] (xxxii) aminodeoxyconduritols,[989] (xxxiii) amino acid−carbohyhydrate hybrids,[990] (xxxiv) Boc-protected blastidic acid,[991] (xxxv) *N*-tosylated allylamines,[992,993] (xxxvi) *N*-acyl-*N*-arylalanine ethyl esters,[994] (xxxvii) benzhydryl *N*-methyl-*N*-tosyl-*S*-aminosulfeniminocephalosporinate,[995] (xxxviii) diprotected alkylhydrazines,[996] (xxxix) N^2,N^5-substituted five-membered cyclic sulfamides,[997] (xl) cyclic sulfamoyl carbamates/ureas,[998] (xli) reversed chain modified oligopeptides,[999] and (xlii) *N*-sulfamoyloxazolidinone and chiral substituted 1,2,5-thiadiazolidine 1,1-dioxides.[1000,1001] The structural drawings pertaining to these references are given in the Supporting Information (Table S7).

Scheme 82





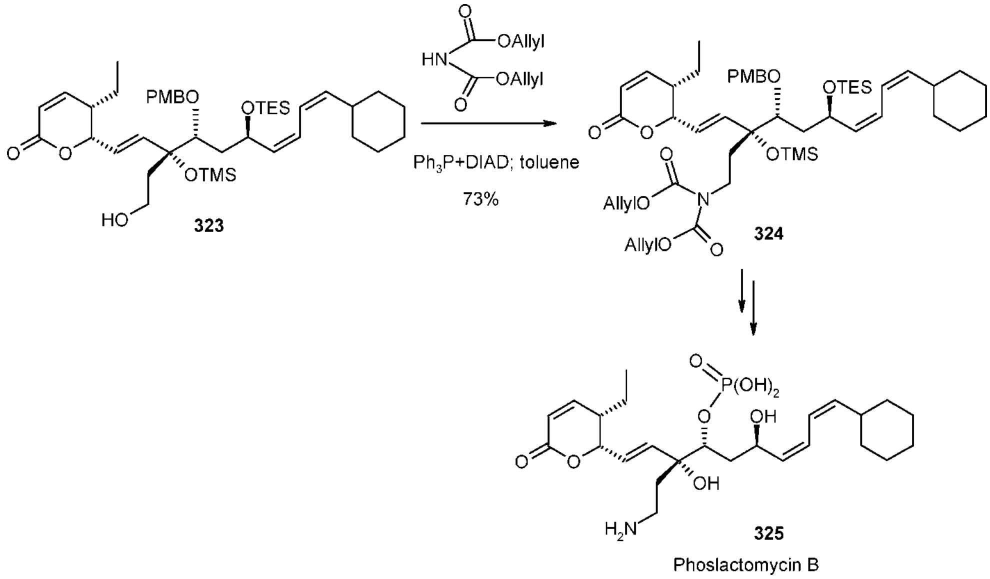
320 **321** **322**

Sun and Pelletier have recently reported that the reaction of alcohols with PS−PPh_3−DTBAD/$(Boc)_2$NH followed by addition of trifluoroacetic acid in a single vessel is a convenient procedure to convert alcohols to primary amines.[1002] For the synthesis of the antitumor, antibacterial, and antifungal agent phoslactomycin B (**325**) via **324**, an *N*-alkylation of the allyl compound HN(CO_2-allyl)$_2$, in which the proton connected to nitrogen is sufficiently acidic, was utilized (Scheme 83).[1003] The deallylation at the nitrogen end to the amine was accomplished by Pd(PPh_3)$_2Cl_2$/Bu_3SnH in a later step to afford the required compound **325**. Thus, use of HN(CO_2-allyl)$_2$ offers another alternative for the conversion of a primary alcohol to the corresponding primary amine. This nucleophile has also been utilized for the synthesis of tricyclic carbapenems (trinems) before.[1004]

The phosphoramidate **326** underwent ready alkylation with *n*-butanol under Mitsunobu conditions (Scheme 84). This reaction shows that a phosphoryl group together with another activating group can make nitrogen sufficiently nucleophilic to undergo *N*-alkylation even with the traditional Ph_3P−DIAD system.[1005]

As was mentioned earlier, the presence of two electron-withdrawing groups on nitrogen should lower the pK_a of the N−H bond, and hence, bis-protected hydroxylamines are good Mitsunobu nucleophiles. Many of them were readily prepared by a Schotten−Bauman route in which an ice-cold aqueous THF solution of $HONH_2$·HCl containing sodium carbonate was reacted with 2 equiv of the respective chloroformate.[1006] A variety of protecting groups (Alloc,

Scheme 83



Scheme 84

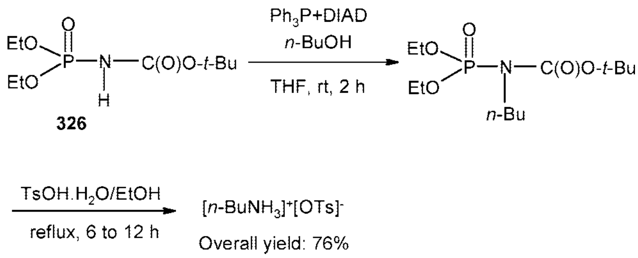
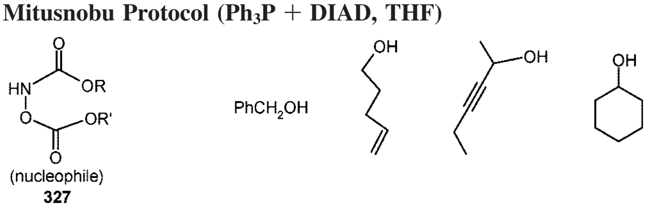


Chart 4. Yields of *N*-Alkyl Hydroxylamines Using a Mitusnobu Protocol (Ph_3P + DIAD, THF)

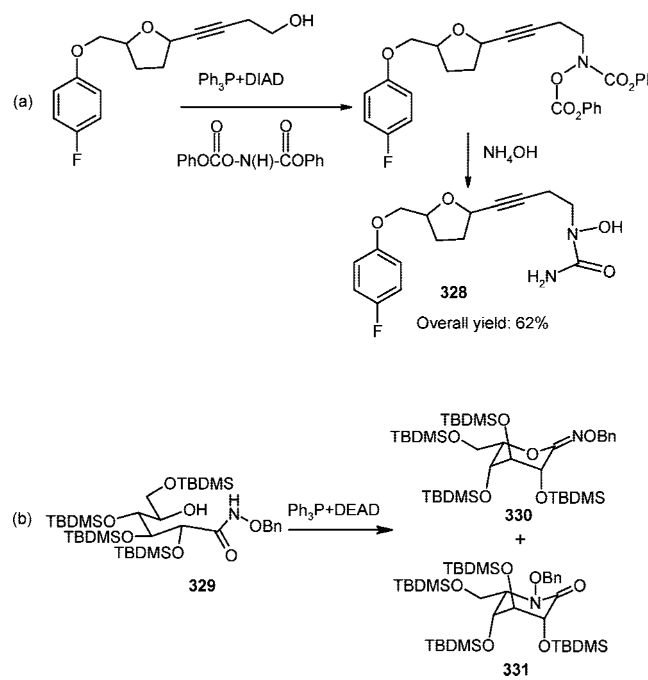


(nucleophile) 327	$PhCH_2OH$			
R = R' = *t*-Bu	78	82	–	–
R = R' = $PhCH_2$	87	73	69	22
R = R' = $CH_2CH=CH_2$	96	91	80	38
R = R' = CH_2CCl_3	83	75	69	38
R = R' = $(CH_2)_2SiMe_3$	90	76	68	17
R = $CH_2CH=CH_2$, R' = $PhCH_2$	79	69	62	33

Troc, Boc) for the *N*,*O*-protection of hydroxylamine **327** could be utilized for the synthesis of *N*-alkylhydroxylamines via a Mitsunobu protocol, as shown in Chart 4. It was noted that *older samples of the azodicarboxylate often delivered inferior yields, but recently procured samples usually restored good yields*.

Reaction of the homopropargyl alcohol with *N*,*O*-bis(phenoxycarbonyl)hydroxylamine HN[C(O)(OPh)][OC(O)(OPh)] followed by aminolysis afforded 5-lipoxygenase inhibitor CMI-977 (**328**; see Scheme 85a).[1007] The nitrogen nucleophile was prepared via hydroxylamine hydrochloride and phenylchloroformate; the nitrogen center is sufficiently reactive because of the attachment of two electronegative groups. A similar Mitsunobu protocol has also been utilized in the synthesis of an oxepane derivative.[1008] In the cyclization of TBDMS-protected δ-hydroxybenzyloxamate **329** that

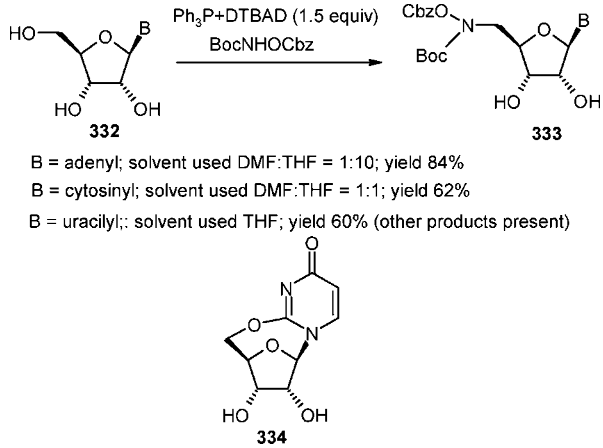
Scheme 85



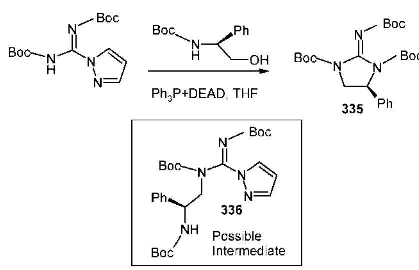
also has a -O-NHC(O)- type activation, a higher ratio of *O*-cyclization (**330**) was observed in C_6F_6 and toluene while *N*-cyclization (**331**) preferentially occurred in CH_2Cl_2, DMSO, MeCN, and EtCN (Scheme 85b).[1009] Similar *N*-cyclization has been reported by the same research group in the synthesis of 1-deoxy-azasugars.[1010]

Li and Miller utilized *N*-(*tert*-butoxycarbonyl)-*O*-(benzyloxycarbonyl)hydroxylamine (BocNHOCbz) to prepare a variety of 5′-deoxy-5′-*N*-hydroxylaminonucleosides (Scheme 86).[1011] The yield of the products was critically dependent on the reaction conditions. Thus, in the reaction using uracil compound **332** (B = uracil residue), the cyclized product **334** was obtained in a significant amount (33%) and became predominant when the solvent system was DMF/THF (1:10). Similar cyclized derivatives were the only products obtained when the base residue was guanine. Use of (Boc)HN[$OCH_2C\equiv CH$] has been made in the synthesis of cyclic peroxides by Tae and co-workers after *N*-alkylating

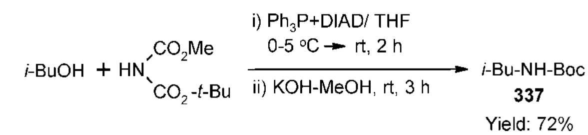
Scheme 86



Scheme 87



Scheme 88

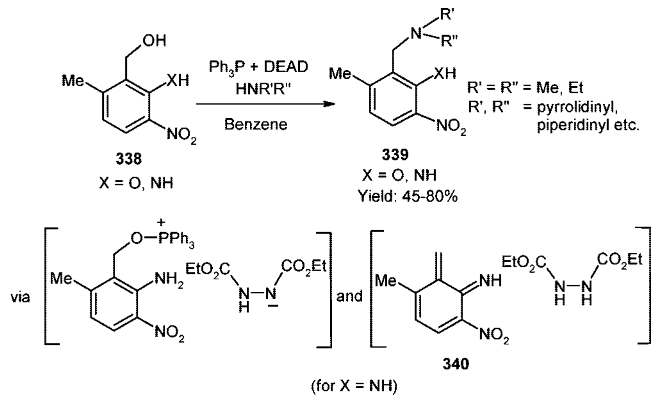


this compound with allylic alcohols.[1012] Govuverneur and Lalloz used PhOC(O)NHO(Boc) and α-hydroxy phosphonates to obtain *N*-hydroxy-α-aminophosphonate derivatives.[1013] In general, no side products were detected and the products were obtained in good yields.

For the synthesis of disubstituted guanidines, only a limited number of routes exist.[1014−1016] An elegant approach to these involving the extrusion of pyrazole is depicted in Scheme 87. Here, species **336** is the proposed intermediate prior to the formation of the product **335**.[1014] Solid-phase synthesis of an 880-member library of trisubstituted arylguanidines, also involving pyrazole displacement and Mitsunobu *N*-alkylation, has been reported by Pátek et al.[1017] To effect optimal conversion, they used a 25-fold excess of the alcohol and the reagents. For the preparation of guanidyl-substituted (at the side chain) prolines, *N*-alkylation utilizing tri-Boc guanidine has been successful.[1018] Sim and co-workers utilized *N*,*N′*-BocNHC(SMe)=NBoc as the masked guanidine nucleophile in the synthesis of guanidinoglycosides.[1019] Other viable precursors in this connection are (Cbz)NHC(NH_2)=NCbz, (Boc)NHC(NH_2)=NBoc, and [(Boc)HN]$_2$C=NH; these have been used in the synthesis of α-helix mimetics by Oguri et al.,[1020] mimics of cyclic CXCR4 pentapeptide antagonists by Cluzeau et al.,[1021] and guanidine containing ketopiperazines by Chen et al.[1022]

It is even possible to use a substrate such as HN(CO_2Me)(Boc), HN(Cbz)$_2$, or ethyl oxamate [EtO_2CC(O)-NHBoc] to prepare *N*-Boc amines (e.g. **337**; Scheme 88) in good yields after suitable deprotection.[1023−1025] The latter nucleophile EtO_2CC(O)NHBoc has been obtained by starting

Scheme 89

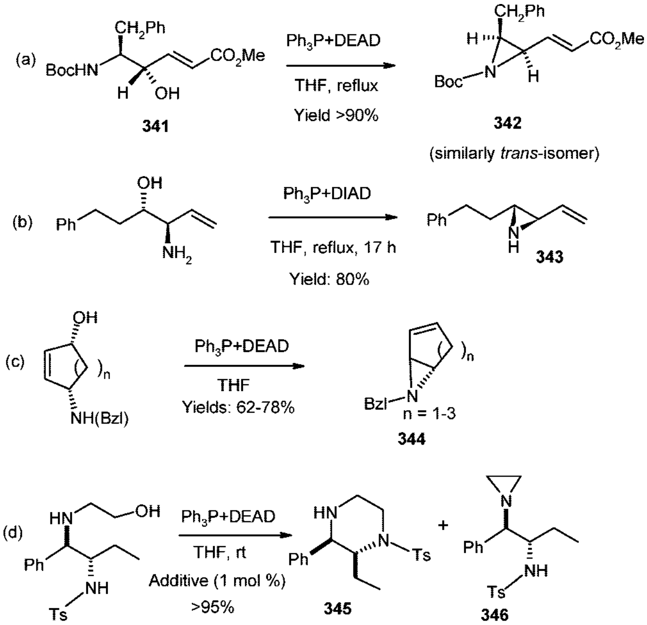


with ethyl oxamate.[1025] The trityl group also activates nitrogen in aziridine formation from 1-amino-2-alcohols, as reported by Somfai and co-workers.[1026,1027] Kim and Kahn have performed the Mitsunobu *N*-alkylation of Boc-protected amino-oxazoles and -thiazoles with lysinol and argininol to obtain reduced peptidyl azoles.[1028] 2-Acetamido-6-chloro- or -6-bromo-9*H*-purines were also readily alkylated;[1029] the reaction worked better with the bromopurine using (*i*-PrO)$_3$P−DIAD.[1030] Resin-bound carbamates underwent *N*-alkylation to afford secondary aryl or heteroaryl amines.[1031]

Benzylamines are versatile intermediates for the synthesis of a variety of pharmaceutically active nitrogen heterocycles. The Mitsunobu route involving the reaction of primary and secondary amines with activated benzyl alcohols of type **338** afforded the substituted benzylamines **339** (Scheme 89).[1032] It is important to note that here the amine nucleophile was not activated, but still the reaction took place readily. Only amines with $pK_a < 9$ or sterically hindered ones gave low yields. It was crucial to have the *ortho*-functionality (OH or NH_2) for this reaction to be effective. Involvement of an azaquinomethane intermediate of type **340**, formed after the elimination of Ph_3PO and the hydrazine, was proposed for the observed reactivity.

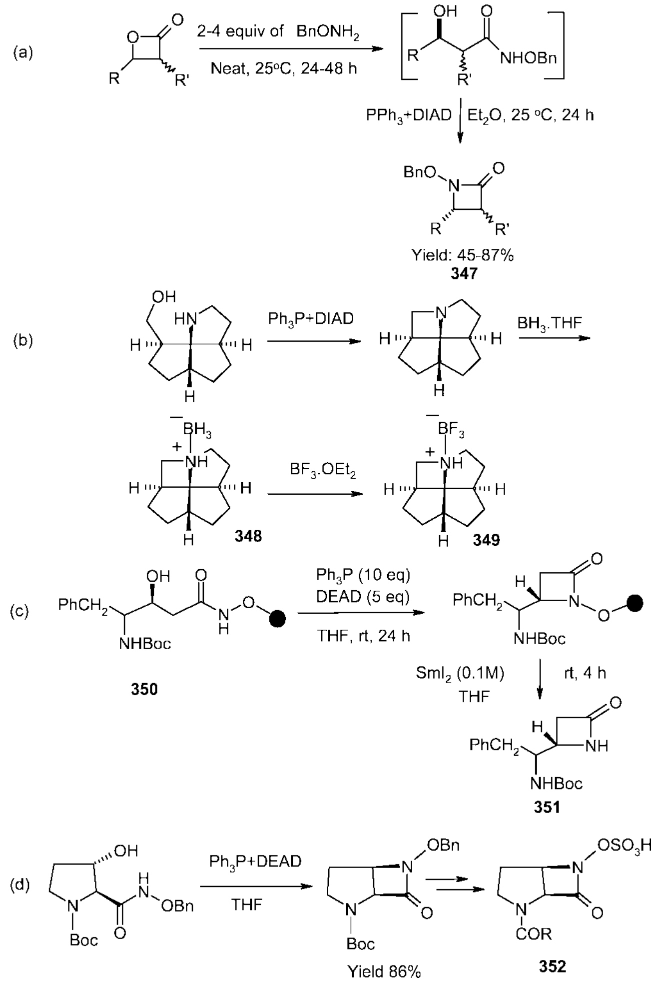
Mitsunobu cyclodehydrative *N*-alkylation allows access to a good number of nitrogen heterocycles. The *cis*- and *trans*-isomers of the aziridine **342** were synthesized in high yields from the diastereomeric alcohols **341** using a Mitsunobu protocol (Scheme 90a).[1033] This procedure gave higher yields than the one using DAST. Chiral aziridines (e.g. **343**) were also synthesized by starting with chiral 1,2-amino alcohols without any activation at the nitrogen center (Scheme 90b).[1034] The straightforward route to NH-vinylaziridines by ring-closure of vicinal amino alcohols possessing vinyl substituents via a Mitsunobu protocol gave good yields of the products. This method was shown to be more useful compared to the sulfate ester route to aziridines for small scale synthesis.[1026] 1,4-Amino alcohols that contain a double bond between C(2) and C(3) also underwent Mitsunobu aziridination readily to lead to vinylaziridines **344** (Scheme 90c).[1035] In general, good yields were obtained. Obviously, reorganization of the substituents must have taken place at an intermediate stage in order to form the three-membered ring in this reaction. A unique additive dependent regiochemical switching of cyclization mode of vicinal diamines with pendant hydroxyl group leading to **345** or **346** has been recently reported by Anderson and Chapman (Scheme 90d).[1036] The authors have offered a possible rationalization based on the involvement of $Et_3N \cdot HCl$ for these interesting results. Other examples involving aziridine formation pertain

Scheme 90



Additive	Ratio		
None	>95	:	5
$Et_3N.HCl$	>5	:	95

Scheme 91

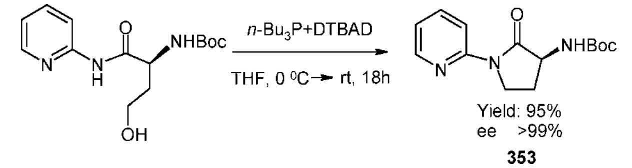


to the synthesis of (i) 2-(2-hydroxy-substituted) piperidine alkaloids,[1037] (ii) peptidomimetics via a *N*-2,4,6-trimethylphenylsulfonyl (Mts)-protected amino alcohol,[1038] (iii) pyrrolyl aziridines via the corresponding inactivated 1,2-aminoalcohols,[1039] (iv) aziridine sulfides based on reduced (*R*)-cysteine,[1040] (v) nosyl-substituted aziridines derived from L-serine,[1041] (vi) exocyclic γ-aminoolefins,[1042] and (vii) tosyl aziridine-2-carboxylates.[1043]

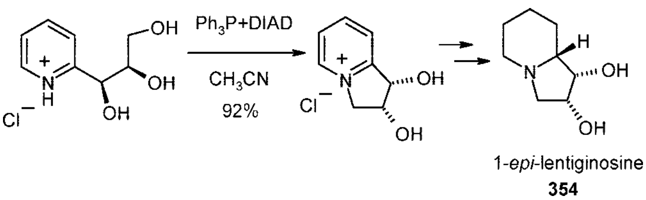
Direct formation of a lactam ring from 1,3-amino(amido) alcohols is fairly straightforward, and several examples of this type are known.[1044] An elegant single-pot, mild conversion of β-lactones to β-lactams (e.g. **347**) via hydroxyhydroxamic acid derivatives and involving an intramolecular Mitsunobu reaction has been reported by Yang and Romo (Scheme 91a).[1045] Prior conversion of β-lactones to the corresponding *N*-benzyloxyhydroxamic acid derivatives was achieved under neat conditions. The synthesis of azafenestrane with a strained four-membered ring could also be efficiently accomplished by means of Mitsunobu cyclization.[1046] The corresponding borane adduct *c,c,c,c*-[4.5.5.5]-1-azafenestrane·BH_3 (**348**) was readily separated from the byproducts in 87% overall yield (Scheme 91b). Confirmation of the structure (X-ray crystallography) was done by means of the analogous BF_3 adduct **349**. The β-lactam ring that contains a four-membered ring is the key component of commonly used antibiotics such as penicillin, carbapenem, thienamycin, etc. The lactams **351** with such a four-membered ring were conveniently synthesized by using solid support and freshly distilled DEAD in THF medium (Scheme 91c).[1047] Five mole equivalents of DEAD and 10 mol equiv of Ph_3P per mole of the substrate **350**, however, had to be used. The support was delinked later using SmI_2. Using an acyl hydroxylamine functionality and an internal alcoholic OH group, bicyclic β-lactamase inhibitors (e.g. **352**, Scheme 91d) have been obtained by an intramolecular Mitsunobu cyclization.[1048] *N*-Tosyl-2-*C*-carbamoyl glycosides possessing the α-L-arabino- and β-D-xylo-configurations led to a β-lactam ring that was fused to the pyranoid ring.[1049] There was no interference from either epoxide or γ-lactam formation in this case. Interestingly, in the enantioselective synthesis of the carbacephem antibiotic loracarbef, $(EtO)_3P$−DIAD in toluene at elevated temperature (90 °C) was found to be the best for the β-lactam formation.[780] This result clearly shows that, at least in some cases, the traditional phosphine [Ph_3P] can be replaced by a more readily hydrolytically degradable phosphite. The mechanistic pathway also could be different (cf. section 2). Formation of four membered azetidinone lactams was also utilized in the synthesis of lankacidins,[1050] 3-(hydroxymethyl)carbacephalosporin,[1051] azapeptidomimetics,[1052,1053] and an intermediate for thienamycin.[1054] Highly functionalized azetidines[1055] and 1,2-diazetidines[1056] were also easily generated via *N*-tosylated 1,3-amino alcohols and 1-(1-hydroxypropan-2-yl)hydrazine-1,2-dicarboxylate, respectively.

Mitsunobu *N*-alkylation with cyclization can lead to pyrrolidinones with heterocyclic functionality that is not compatible with other known methodologies. Thus, many optically active 3-aminopyrrolidinones with a β-lactam skeleton (e.g. **353**; Scheme 92) have been synthesized.[1057] A variety of substituents on the amide nitrogen were tolerated. Here the nucleophilic NH center was activated by the presence of an adjacent carbonyl group and an aromatic residue. Synthesis of five-membered ring heterocycles, isotussilagine and tussilagine, was accomplished by Ma and Zhang using a similar protocol.[1058] *N*-unprotected azacyclopentylidene complexes of chromium and tungsten that contain a five-membered nitrogen heterocycle have been

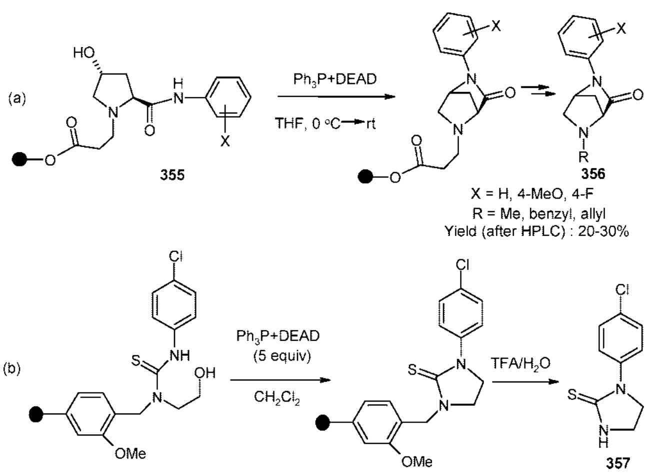
Scheme 92



Scheme 93



Scheme 94

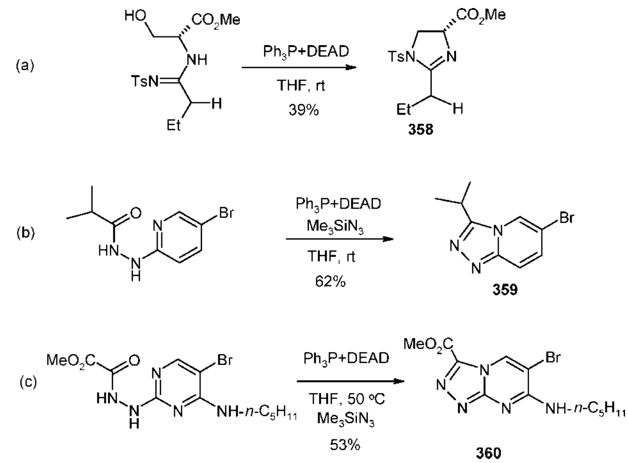


prepared by Dötz and co-workers.[1059-1061] Poullennec and Romo utilized a system with a (Cbz)NH(O_2CR) group in an *N*-alkylation with cyclization for the enantioselective total synthesis of (+)-dibromophakellstatin.[1062]

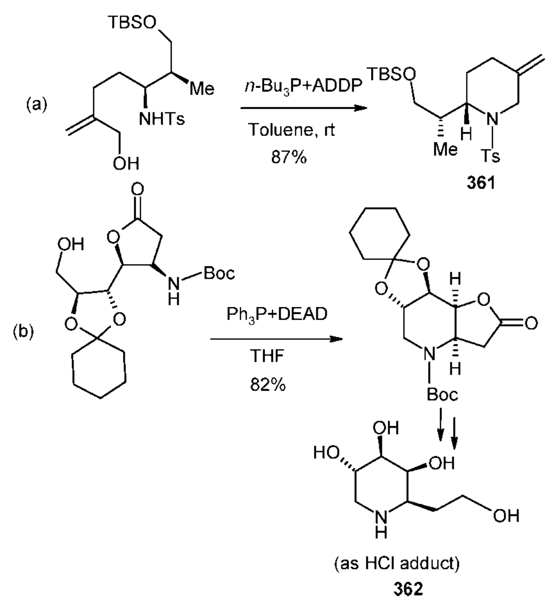
An elegant use of *N*-alkylation with cyclization has been reported recently by Azzouz et al.[1063] In this case, a pyridinium salt played the role of the nucleophile and a five-membered ring was formed preferentially. This route was used in the total synthesis of 1-*epi*-lentiginosine alkaloid **354** (Scheme 93). There is also another report of *N*-alkylation with cyclization leading to a fused five-membered *N*-heterocycle, but the reaction was performed with a neutral precursor using pyridine as the solvent.[1064]

Bicyclic γ-lactams **356**, competitive inhibitors of β-lactamases, were efficiently synthesized using intramolecular coupling reactions of amide functionalities **355** with alcohols in the solid phase (Scheme 94a).[1065] An earlier study by Page and co-workers involved a similar lactam formation in solution phase.[1066] Such annulations leading to five-membered rings are generally straightforward, and a solid phase synthesis of imidazolones **357** has been reported recently (Scheme 94b).[1067] Although *S*-cyclization was also possible, the main products were those with *N*-cyclization. Highly substituted γ-lactams with five-membered rings that are analogues of a thiazolidine follicle stimulating hormone receptor have been synthesized by Pelletier et al.[1068] The reaction occurred stereoselectively. Substituted, enantiomerically pure dihydroimidazole-4-carboxylic acid derivatives (e.g. **358**) were prepared by *N*-alkylation at an imine center, as shown in Scheme 95a.[1069] In a recent paper by Roberge,

Scheme 95



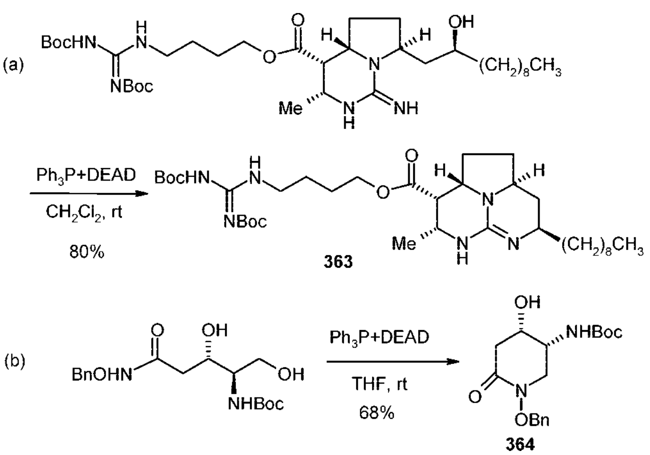
Scheme 96



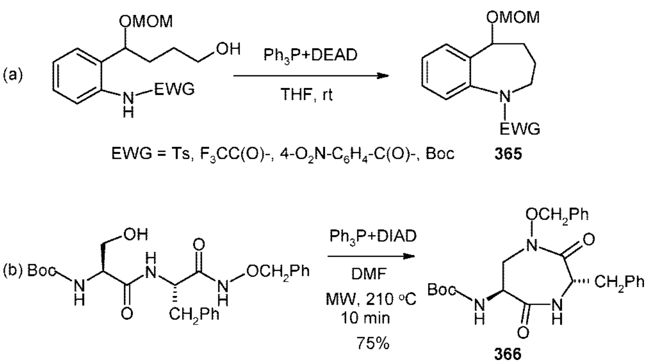
Ewinge, and co-workers, a unique Mitsunobu dehydration assisted by Me_3SiN_3 leading to triazolo pyridines (**359**) and pyrimidines (**360**) has been reported (Scheme 95b and c).[1070] Here, two protons need to be shifted for the cyclization process to occur.

N-Alkylation of *p*-toluenesulfonamide has been used to synthesize the intermediate **361** in the preparation of deoxynupharidine (Scheme 96a).[1071] Here, the reagent combination *n*-Bu_3P−ADDP provided a good yield of the product. For the preparation of 1-deoxy-D-galactohomonojirimycin **362**, Achmatowicz and Hegedus generated a six-membered nitrogen heterocycle via *N*-alkylation (Scheme 96b);[329] in the same paper, they have also described a lactonization with retention of configuration at the chiral alcohol center. Batzelladines are polycyclic guanidine alkaloids isolated from Bahamian and Jamaican sponges. In their studies on the synthesis of batzelladine D, Nagasawa and co-workers have reported an interesting cyclization reaction involving *N*-alkylation on an imine nitrogen leading to **363**.[1072] Batzelladine D was obtained in a later step by treating **363** with TFA/CH_2Cl_2. Synthesis of (+)-batzelladine A has also been reported by the same research group.[1073] A similar cyclization leading to a six-membered ring was employed in the

Scheme 97

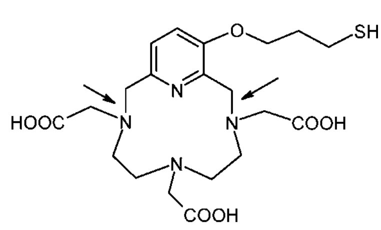


Scheme 98



synthesis of (i) the cytotoxin lepadiformine,[1074] (ii) *cis*-4,5-disubstituted piperidin-2-ones (e.g. **364**) using a reactive HN(OBn)C(O)− group (Scheme 97b),[1075] (iii) thyrotropin-releasing hormone (thyroliberin, TRH) analogues,[1076] (iv) *N*-alkoxy analogues of 3,4,5-trihydroxypiperidine,[1077] (v) pipecolinic acid derivatives,[1078,1079] (vi) 2,6-dimethyl piperazines,[1080] (vii) piperaz-2-ones (δ-lactams),[1081] (viii) 6-substituted analogues of 1-deoxymannojirimycin that contain a piperidine ring,[1082] (ix) *N*-arylpiperazinones,[1083,1084] and (x) piperazic acid derivatives.[1085]

Lazaro and co-workers utilized both tosyl and trimethylsilylethylsulfonyl (SES) groups for *N*-activation in the synthesis of perhydro-(1,4)-diazepin-2-ones in which a seven-membered ring was newly generated.[1086,1087] Functionalized benzazepine derivatives **365** could be obtained by intramolecular Mitsunobu reaction, when the corresponding nitrogen was fairly activated by means of groups such as 4-Me-C_6H_4-SO_2- (Ts), $CF_3C(O)$-, 4-O_2N-$C_6H_4C(O)$-, or *tert*-BuOC(O)-(Boc). Use of the tosyl group gave the best yields (Scheme 98a).[1088] The Mitsunobu protocol was used by Goldstein and Wipf in the synthesis of the tricyclic hydroindole core system of a *Stemona* alkaloid that involved the formation of a seven-membered *N*-heterocycle.[1089] Taddei and co-workers adapted high-temperature MW conditions for the preparation of conformationally constrained peptidomimetics (e.g. **366**) based on the 1,4-diazepan-2,5-dione skeleton (Scheme 98b).[1090] This route was more efficient than the one using DMF/rt/12 h without the MW conditions. Thiol-appended pyridine-based polyaminocarboxylic acids (e.g. **367**) have also been prepared using a similar methodology.[1091]



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5.3. *N*-Alkylation of Heterocyclic Compounds (Excluding Nucleobases)

The NH group of several unsaturated heterocycles readily undergoes Mitsunobu *N*-alkylation. A brief discussion of this aspect is presented in this section.

A regioselective N^1-alkylation of 3,4-dihydropyrimidin-2(1*H*)-ones **368** to lead to **369** was accomplished using the highly reactive coupling reagent combination *n*-Bu_3P−TMAD and primary alcohols (Scheme 99a).[1092] Although the *n*-Bu_3P−ADDP combination also worked well, 4 mol equiv of the reagents had to be used, which posed problems during purification. With the *n*-Bu_3P−TMAD combination (2 mol equiv) in dry dioxane, complete conversion was achieved in about 1 h. Brandi and co-workers have demonstrated the synthesis of pyrolidine derivatives, affording exclusively N^1-alkylated derivatives using unprotected pyrimidine bases **370** (Scheme 99b) by judicious choice of the solvent.[1093] The choice of such a solvent (which reduced the *O*-alkylated products) was based upon a previous paper by Chu and co-workers.[1094] *N*-Alkylation of cinnolines was conveniently performed in the solid phase by Sereni et al.[1095] Although alkylation occurred at both the ring nitrogen atoms, only one product prevailed over a period of time.

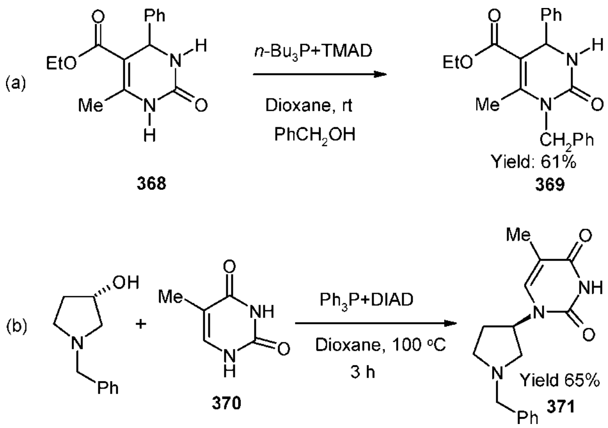
For the preparation of chiral *N*-alkyl-substituted imidazoles and the corresponding ionic liquids, the Mitsunobu reaction offers a convenient route. Although imidazole has rather a high pK_a (14.5) and hence is less reactive as a nucleophile, under slightly forcing conditions using an excess of the reagents *n*-Bu_3P−TMAD, the yields of the products **372** could be substantially improved, and this is what Ko and co-workers have reported recently (Scheme 100).[1096] However, in the synthesis of pyrrole alkaloid polycitone A, Steglich and co-workers could effect ring *N*-alkylation by using the normal Ph_3P−DEAD system.[1097]

Trisubstituted 1,2,4-triazoles **373**−**374** were readily synthesized by *N*-alkylation of disubstituted triazoles with amino alcohols; a library of products could thus be obtained.[1098] Interestingly, both the regioisomers of the trisubstituted derivatives were formed (Scheme 101). In the alkylation of naphtha-1,2,3-triazines, substitution at either N^1 or at N^2 occurred, with the N^2 isomer as the major product.[1099]

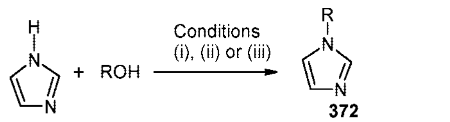
Guo et al. reported the synthesis of several GnRH antagonists wherein Mitsunobu *N*-alkylation was utilized in the penultimate step (Scheme 102).[1100] The best compound (**375**) from the initial SAR study had a K_i value of 37 nM. The authors also utilized solid-supported triphenylphosphine to synthesize these compounds, which was useful when the polarities of the products and $Ph_3P(O)$ were similar in terms of isolation.

A comparative study of *N*-alkylation of 1*H*-indole and 9*H*-carbazole derivatives with alcohols leading to **376**−**377** was performed using classical Mitsunobu reaction conditions, i.e.

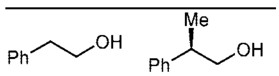
Scheme 99



Scheme 100

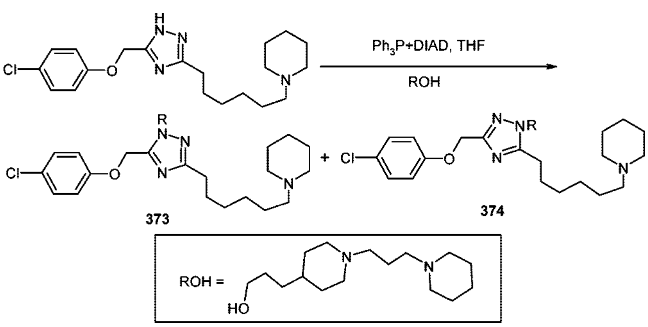


ROH



	Yield of **372** (%)	
(i) Ph_3P+DIAD (10 equiv)	62	37
(ii) Ph_3P+ADDP (1 equiv)	71	57
(iii) *n*-Bu_3P+TMAD (10 equiv)	94	76

Scheme 101



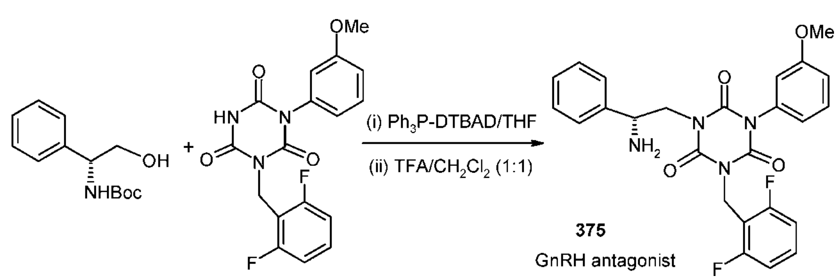
Ph_3P−DEAD or *n*-Bu_3P−TMAD, or using phosphorane derivatives such as Me_3P=CH(CN) [CMMP, cf. Scheme 103].[1101] The authors concluded that CMMP was the reagent of choice for the *N*-alkylation of 1*H*-indole and 9*H*-carbazole derivatives with alcohol derivatives. Two equivalents of the reagents were needed to get good yields.

In indolyl compounds, the acidity of the NH can be increased by introducing 2-chloro-substitution (carbon next to nitrogen) to make the *N*-alkylation proceed smoothly. This approach has been utilized by Sahagún and co-workers in the synthesis of unsymmetrical indolopyrrolocarbazoles. The reaction was conducted using the reagent combination Ph_3P−DEAD.[1102] 2-Chlorobenzimidazole also did not need any activation and readily reacted with alcohols such as 2-(2-hydroxyethyl)pyridine under normal Mitsunobu conditions at 0 °C to afford the *N*-alkylated products.[1103] Zembower and co-workers noted that Ph_3P−DIAD was effective in the *N*-glycosylation of indoles also.[1104] This protocol was a key step in the total synthesis of indolocarbazole topoisomerase I poisons reported by these researchers. However, application of this method to larger quantities was beset with difficulties in separation.

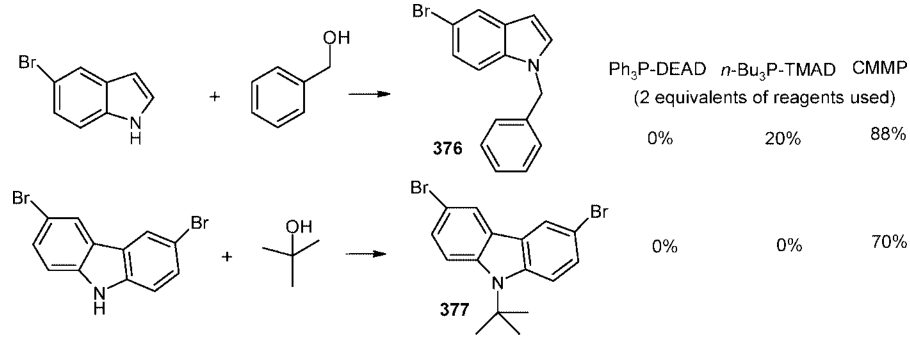
Interesting cyclization reactions leading to different types of 6-membered rings occurred when the heterocycle **378** was subjected to Mitsunobu *N*-alkylation (Scheme 104a).[1105] Formation of **380** probably involved a proton shift prior to cyclization. The NH of a pyrrole is also sufficiently active to take part in the Mitsunobu reaction as shown in Scheme 104b, which depicts the formation of the seven-membered heterocycle **381**.[1106]

Other useful applications of *N*-alkylation on nitrogen heterocycles include synthesis of the following: (i) bridged aza-rebeccamycin analogues with a 7-azaindole moiety,[1107] (ii) polymer-bound 1,2,4-oxadiazol-5-one[1108] (iii) *N*-substituted 1,2,4-triazolones,[1109] (iv) precursors for poly(*N*-substituted pyrrole)s,[1110] (v) N^3-alkylation products of 1,3,4-oxadiazol-2(3H)-ones,[1111] (vi) bicyclic pyridones,[1112] (vii) pseudonucleosides containing oxazolidin-2-ones,[1113] (viii) 3-aryl-2-pyridones,[1114] (ix) the N^1-functionalized xanthine scaffold for phosphodiesterase 5 PDE5 inhibitors,[1115] (x) alkylated mellitic triamide (residue obtained by decomposition of ammonium mellate),[1116] (xi) N^3-alkylated 1,3,5-triazine-2,4-diones,[1117] (xii) a library of N^9-alkylated mono- and trisubstituted purines,[1118,1119] (xiii) (solid phase) D- and L-cycloserine derivatives,[1120] (xiv) tussilagine and isotussilagine (pyrrolidine alkaloids),[1121] (xv) N^1-substituted indazoles,[1122] (xvi) 1-(primary alkyl)benzotriazoles,[1123] (xvii) camptothecin analogue GI147211C[1],[1124] (xviii) *N*-alkylated isatoic anhydride (pK_a 8.25),[1125] (xix) *N*-methylated diketopiperazines,[1126] (xx) N^3-alkylated flavins,[1127] (xxi) *N*-alkylated indoles via 2-cyanoindole,[1128] (xxii) 1-alkyl-4-chloropyrazolo[3,4-*d*]pyrimidines,[1129] (xxiii) 2-substituted tetrazoles,[1130] (xxiv) reversed azole nucleosides,[1131] (xxv) *N*-substituted phthalazinones (along with ring rearranged products),[1132] (xxvi) 1-alkyl-4-aminopyrazoles,[1133] (xxvii) dissymmetric indolocarbazole glycosides,[1134] (xxviii) 2,9-disubstituted[1135] or 2,6,9-trisubstituted purines,[1136] (xxix) (+)-(*S*)-3-(4-nitropyrazol-1-yl)-propane-1,2-diol,[1137] and (xxx) N^3-alkyl-5-fluorouracils.[1138] The structural drawings pertaining to these references are given in the Supporting Information (Table S8).

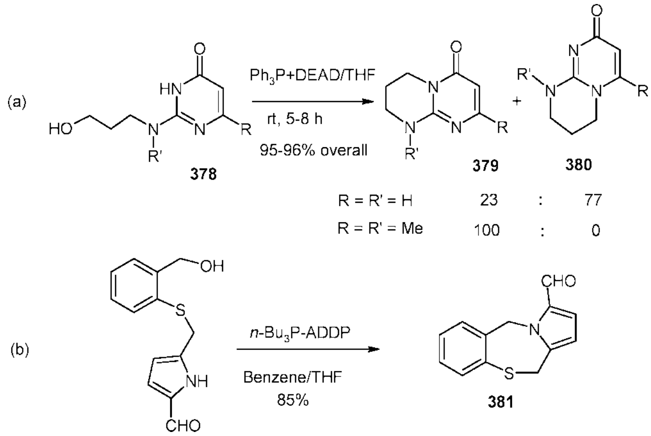
Scheme 102



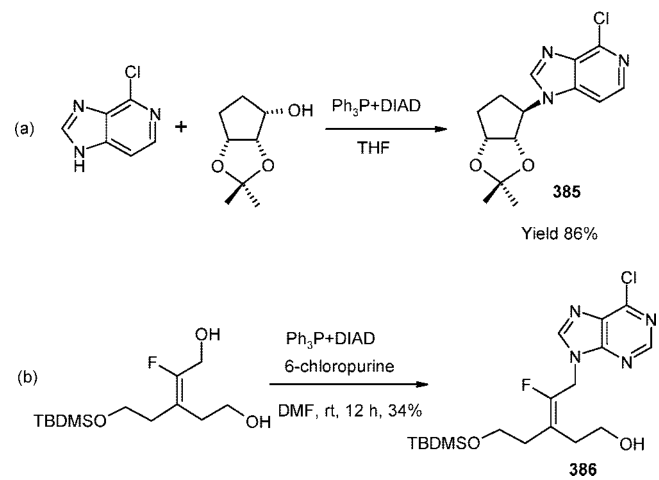
Scheme 103



Scheme 104

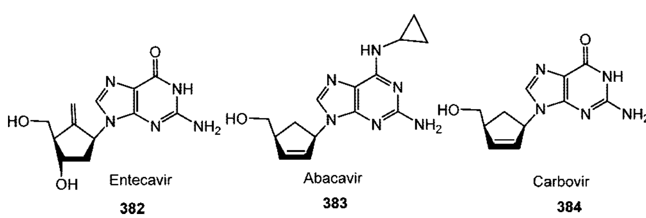


Scheme 105



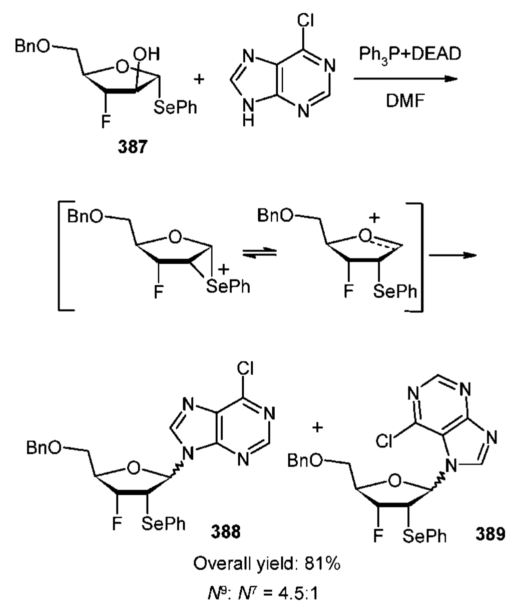
5.4. *N*-Alkylation of Nucleobases Including 6-Chloropurine

There are a large number of pharmaceutically important molecules that contain a nucleobase residue. For example, entecavir (**382**, Baraclude) is an oral antiviral drug used in the treatment of hepatitis B infection approved by the FDA. Abacavir (**383**) as its sulfate (Ziagen) is a carbocyclic nucleoside and is effective for the treatment of HIV-1. Carbovir (**384**) is another compound with analogous activity. There is enough scope for improving the efficacy of these compounds by changing the substituents. Thus, coupling of nucleobases with suitable alcohols including carbohydrates, in principle, should lead to a large number of medicinally useful derivatives. The NH end of these bases is sufficiently nucleophilic under Mitsunobu conditions. However, one of the major problems in using direct Mitsunobu coupling is the solubility of the nucleobases/carbohydrates. The second problem is the selectivity, which may sometimes be enhanced by suitable protection. These aspects, as investigated by several researchers in this area, are discussed below. Reactions using 6-chloropurine are also included here, since this chlorine can later be readily substituted by other groups.



The coupling of 6-chloropurine with several cyclopentyl-based secondary alcohols provided an efficient entry into N^9-substituted 3-deazapurine carbocyclic nucleosides (e.g. **385**) of antiviral potential (Scheme 105a).[1139] In some cases, N^7 products were also obtained. To convert the product into an adenine derivative, amination of the C−Cl bond was required. In lieu of this, straightforward use of adenine may be thought of, but in general, adenine is a poor nucleophile with low solubility in the most common solvent, THF. This problem was circumvented by replacing the NH_2 with a $N(Boc)_2$ group in adenine that increased both solubility and reactivity, as shown by Schneller and co-workers recently.[1140] In a competitive reaction of the −OH groups with 6-chlo-

Scheme 106



Scheme 107

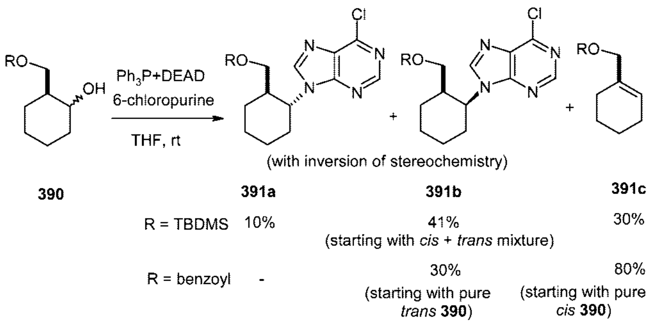
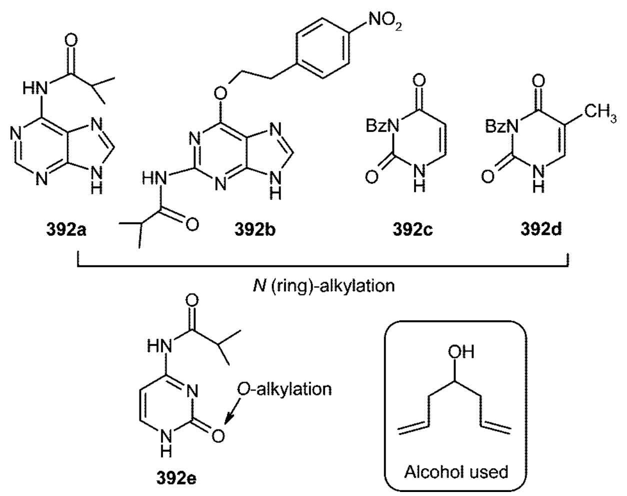
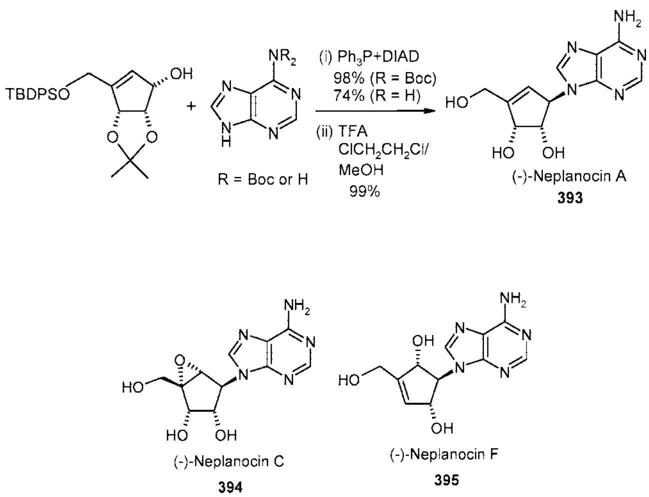


Chart 5



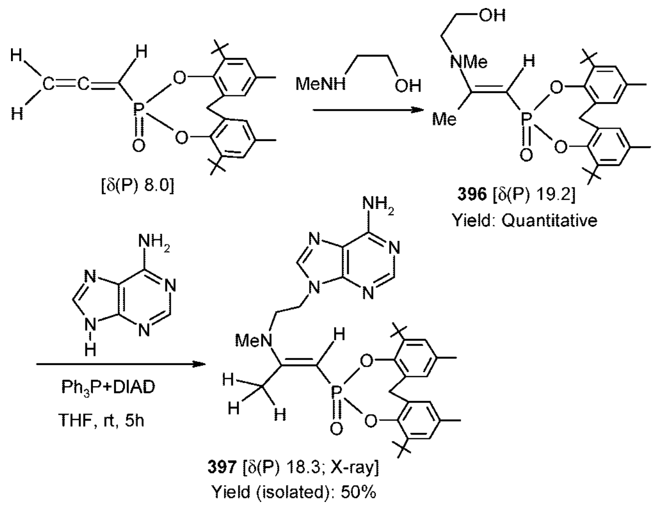
Scheme 108



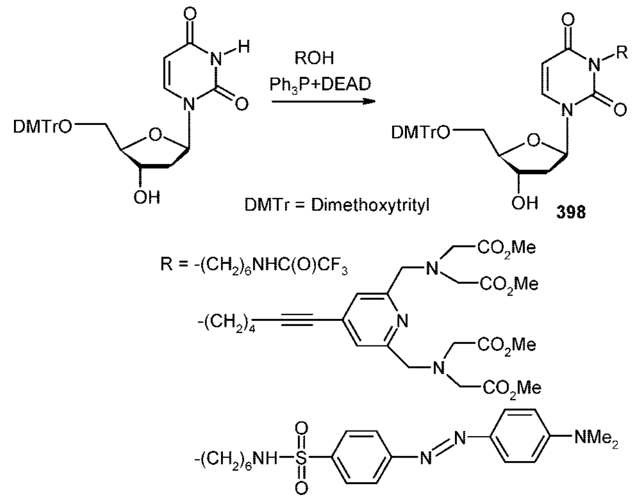
ropurine *via* a Mitsunobu procedure, substitution of the primary hydroxyl group occurred preferentially at the allylic (e.g. **386**) as compared to the homoallylic position, most likely due to enhanced acidity and/or the assistance of the neighboring π-system (Scheme 105b).[1141] However, the success was rather limited when an attempt was made to optimize N^9/N^7 regioselectivity using *N*-protected adenine derivatives. In another study, alkylation of a chiral secondary alcohol with 6-chloropurine led to inversion, as expected.[1142]

In the glycosylation of 6-chloropurine with the selenocarbohydrate **387**, Poopeiko et al. have reported an interesting 1,2-selenophenyl migration as shown in Scheme 106.[1143] Although the *N*-alkylation took place at two sites of the 6-chloropurine to lead to a mixture of products, the overall

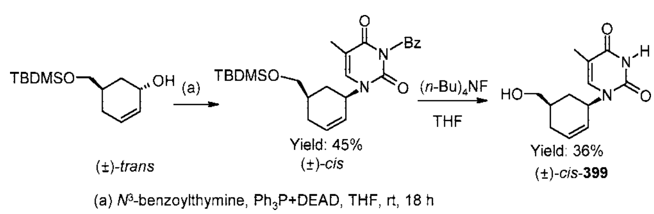
Scheme 109



Scheme 110



Scheme 111



yield (**388** + **389**) was good. Hence, this method may be applicable for the synthesis of many other nucleosides. A related reaction involving a thiophenyl group was also reported by the same group.[1144]

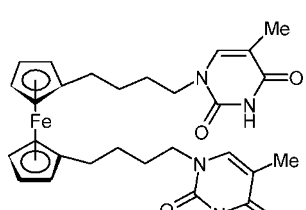
In the synthesis of cyclohexyl nucleosides **391a–b**, it was found beneficial to use a sterically bulky *tert*-butyldimethylsilyl rather than benzoyl protecting group to avoid the formation of elimination product in Mitsunobu *N*-alkylation with 6-chloropurine (Scheme 107).[1145] When the benzoyl protecting group was used, the *trans*-product **391a** that arose from the *cis*-**390** could not be obtained. Only the elimination product **391c** was isolated. The *cis*-product **391b** was obtained in fair yields when either of the protecting groups was employed. There are also several other cases in which 6-chloropurine or 2,6-dichloropurine has been utilized to introduce nucleoside bases indirectly.[1146−1149]

In an important study that should be useful while using Mitsunobu *N*-alkylation in nucleoside chemistry, guanine, adenine, thymine, and uracil derivatives were prepared directly by coupling the protected base with 1,6-heptadien-4-ol.[1150] However, coupling of protected cytosine and alcohol gave an *O*-alkylated product. More importantly, the authors noted that the guanine, adenine, thymine, and uracil derivatives could be used without protection in this reaction. The protected bases (**392a−e**) used in this study are shown in Chart 5.

(−)-Neplanocin A (**393**), a carbocyclic nucleoside, isolated from the soil fungus *Ampulliariella regularis*, is a potent antiviral and antitumor agent (but is cytotoxic). Michel and Strazewski have successfully synthesized **393** in an enantiopure form in the highest published overall yield using N^6-bis-Boc-protected adenine (Scheme 108).[1151] An overall yield of 59% was obtained by starting with D-ribose. Adenine itself could be used for the *N*-alkylation, but the yield was relatively low. (−)-Neplanocin C (**394**) and (−)-neplanocin F (**395**) have also been isolated from the same fungus. Mathé and co-workers reported that coupling of the precursor alcohol with 6-chloropurine (instead of adenine itself) gave low isolated yields of the intermediate alkylated product required for the synthesis of (−)-neplanocin F.[1152] Synthesis of (−)-neplanocin A and many analogues was reported earlier by Chu and co-workers, using suitably protected/masked purine/pyrimidine bases.[1153] Several other publications on the synthesis of neplanocin A and C analogues wherein a Mitsunobu protocol is used are also available.[1154−1156] Synthesis of cyclohexene analogues of **394** (in place of a cyclopentene ring), using unprotected adenine as the nucleophile, has been reported recently by Herdewijn and co-workers.[1157] In another study, by simple *N*-methylethanolamine addition to the allenes, the product **396** with an intact −OH group was obtained. This residual −OH group underwent facile Mitsunobu coupling with adenine to give the *N*-alkylated product **397** (Scheme 109), thus offering adenyl functionality at the *ω*-position of the phosphonate.[1158] It is possible that extension of this work will lead to many pharmaceutically interesting phosphonates.

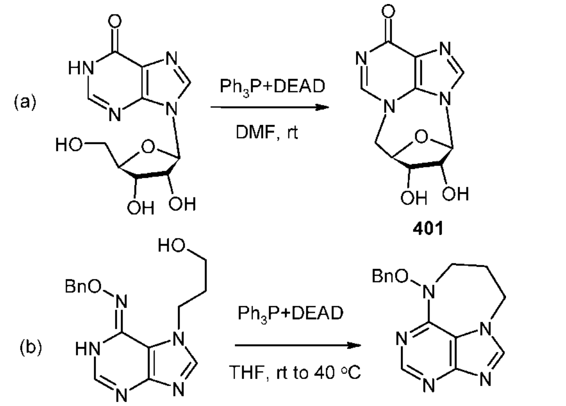
In the reaction of 2′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-uridine with alcohols to lead to N^3-substituted derivatives **398**, 3′-*O*-protection of the nucleoside was not required and the Mitsunobu products were obtained in high yields (Scheme 110).[1159] It is noteworthy that the functionalities on the alcohol also did not adversely affect the reaction.

A series of purine and pyrimidine *cis*-substituted cyclohexenyl and cyclohexanyl nucleosides (e.g. **399**), some of which showed moderate antiviral activity against HSV1 and *coxsackie* viruses, were synthesized through a key Mitsunobu step (Scheme 111).[1160] A similar method was employed to prepare the analogous cytosine and adenine derivatives.[1161] Another interesting recent paper by Ganesh and co-workers relates to ferrocene linked thymine−uracil conjugates (e.g. **400**).[1162] Bucci et al. have also reported a ferrocenemethyl−thymidine nucleoside by the Mitsunobu route.[1163]

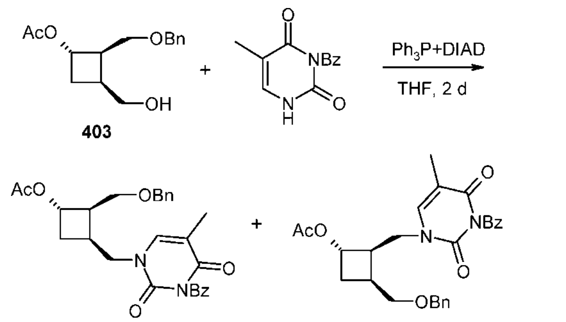


400

Scheme 112



Scheme 113

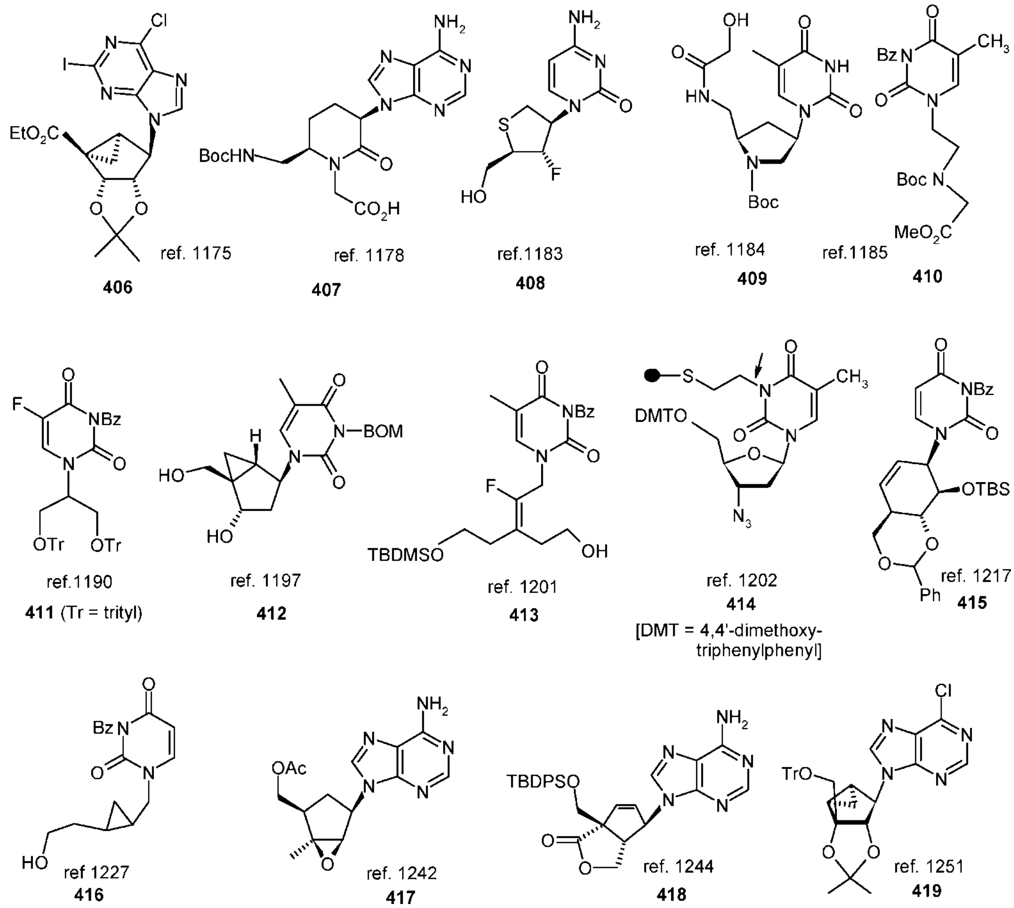


Cyclonucleosides have also been prepared by intramolecular Mitsunobu *N*-alkylation. In the reactions shown in Scheme 112, a seven-membered ring is generated via *N*-alkylation.[1164] The yield of the product **401** is quite good (80%). Somewhat analogous cyclization has also been reported recently by Chun et al.[1165] Another cyclization reaction leading to the fused heterocycle **402** was reported by Pappo and Kashman.[1166]

Normally the benzyl protecting group does not reorganize in the Mitsunobu reaction. However, in the alkylation of the alcohol **403** with N^3-benzoyl thymine, Marsac et al. observed such a feature and obtained **404** and **405** in the ratio 3:1 (Scheme 113).[1167] When adenine or thiophenol was used as a nucleophile, only the normal products were observed.

There are numerous other reports on the normal ring *N*-alkylation of nucleobases.[144,155,187,707,713,1168−1303] In some cases, *O*-alkylation could also occur.[1304] The resulting products are generally carbocyclic nucleosides. The structures of some of these (**406−419**) are given in Chart 6; additional data is provided in the Supporting Information (Table S9). In these studies, the nucleobase used is one or more of 6-chloropurine, 2-amino-6-chloropurine, adenine, 6-chloro-2-iodopurine or 6-chloro-2-methylthiopurine, thymine, N^3-benzoyl thymine, N^3-benzoyl uracil, *O*-protected-2-*N*-isobutyrylguanine, anisoyl cytosine/adenine, 4-*tert*-butylbenzoyl cytosine, isobutyryl/diphenyl-carbamoyl guanine, 2,6-diaminopurine, 2-amino-6-benzoyloxy purine, N^4-benzoylcytosine, N^6-phenoxyacetyladenine, N^2-acetyl-6-*O*-diphenylcarbamoylguanine, N^3-benzoyl-5-chlorouracil, 6-azauracil, 5-chlorouracil, and $(Boc)_2$adenine [*Note*: Removal of Boc can be effected with 50% HCO_2H]. If one needs to use unprotected adenine, dioxane or dioxane−DMF mixtures could be a convenient reaction medium.[1170−1172,1176,1178,1180,1217,1219,1236,1240,1245,1257] For N^3-benzoyl uracil and N^3-benzoylthymine,[1201,1218,1220,1221,1249]

Chart 6



THF works well in many cases but N^3-benzoylthymine does lead to *O*-alkylation also.[799] 2-Amino-6-chloropurine may give problems because of insolubility,[1252] although success has been achieved in some cases.[1247] For these reactions dioxane is a better solvent.[1304] Some more useful points are listed below.

(1) Ludek and Meier noted that, in the synthesis of pyrimidine nucleosides, to achieve maximum N^1-alkylated product, MeCN or DMF was a better choice as solvent. They used cyclopentanol as the reference alcohol for these studies.[1239] Thymine-O^2 alkylated derivatives were also obtained as minor products. They reported that, in the coupling of thymine with cyclopentanol, N^3-BOM protection was the best for *N*-alkylation, while the use of the 2,6-dimethyl-benzoyl group led exclusively to O^2-alkylation.[1198] In general, the benzyloxymethyl group (BOM) on N^3 of pyrimidines led to an improved product N^1/O^2 ratio compared to the standard benzoyl protected derivative using MeCN as the solvent.[1197] With N^3-benzoylthymine, while 1-pentanol or benzyl alcohol provided the *N*-alkylation exclusively, 2,2,2-trichloroethanol gave a 3:2 mixture of N^1:O^2 alkylated products.[1199]

(2) Mitsunobu ribosylation/glucosylation of inosine and uridine using *n*-Bu_3P−ADDP afforded the N^1- and 6-*O*-glycosylinosine and N^3-glycosyluridine derivatives, respectively.[1214]

(3) Use of adenine as nucleophile sometimes led to both N^9 and N^3 coupled products.[1219]

(4) N^4-Benzoyl cytosine has a poor solubility in THF/dioxane,[1191] and the reaction may not work well. Cytosine derivatives could be prepared via uracil to cytosine base conversion.[1194]

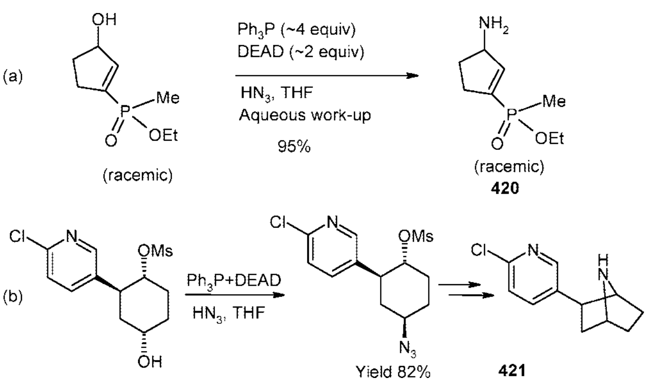
(5) For guanine-based nonsugar nucleosides, use of *O*-carbamate-*N*-acetate protected guanine as the nucleophile in THF at 70 °C with Ph_3P−DIAD added twice, 1 equiv each time, provided the best yields.[1206] This result has been utilized to obtain 6-chloropurine derivatives in good yields. In addition, the results obtained vindicated an S_N2 process in the Mitsunobu *N*-alkylation.

(6) Di Fabio and co-workers reported that a 2-(phenylthio)ethyl residue could be easily and regiospecifically inserted at the N^3-position of the pyrimidine by 2-(phenylthio)ethanol to selectively achieve *O*-alkylation of ribose moieties connected to the nucleobase at a later stage.[1305] The protective group could be removed by oxidation followed by a β-elimination process.

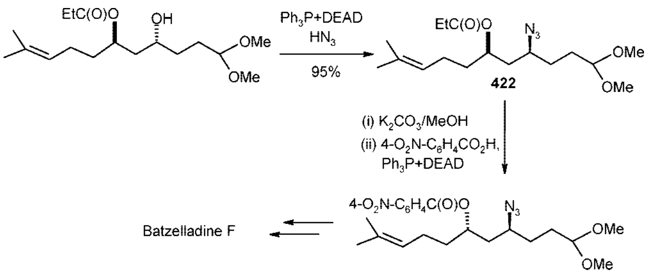
5.5. Mitsunobu Reaction with Azides

Hydrazoic acid or a suitable azide source such as trimethylsilyl azide (Me_3SiN_3), diphenyl phosphoryl azide [$(PhO)_2P(O)N_3$, DPPA], zinc azide, sodium azide, or nicotinoyl azide do take part in Mitsunobu coupling with alcohols. Since the resulting azides can be readily transformed to other functional groups, this protocol has been widely utilized in various syntheses, as can be realized from the following discussion. Inversion is the expected outcome where a chiral center is involved. Catalytic quantities of phenol may activate an alcohol toward azidation by HN_3.[1306]

Scheme 114



Scheme 115

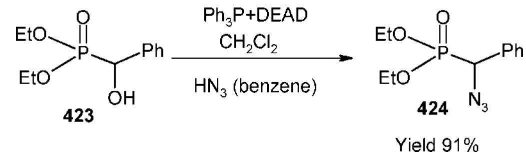


A noteworthy point is that if the phosphine is used in a larger stoichiometry (than the azodicarboxylate), the azide product may react with the phosphine to lead to products with a $R_3P{=}N-$ group. The $N{=}PPh_3$ group can be transformed to an $-NH_2$ group rather readily. Such a procedure is quite common, and two recent examples include (i) the synthesis of (3-aminocyclopentene)>alkylphosphinate **420** by Hanrahan and co-workers (Scheme 114a)[1307] and (ii) a similar azidation on cyclopentenyl alcohol synthesis of the transfer-RNA nucleoside queuosine by Carell and co-workers.[1308] In the latter case, the authors also reported that rearrangement of the allylic azide could be suppressed by performing the reaction at 0 °C, thus enhancing selectivity. Between the two general Mitsunobu protocols to convert $-OH$ to $-NH_2$, one using the phthalimide/hydrazine and the other using HN_3/Staudinger/hydrolysis, the latter was found to be simpler and time-saving.[1309] Amination of an alcohol can be conducted by means of an azide functionality introduced via the Mitsunobu protocol through either hydrazoic acid or a metal azide as the nucleophile.[1310−1320] The bridge-head nitrogen in (+)-epibatidine **421** is introduced in this way (Scheme 114b).[1310]

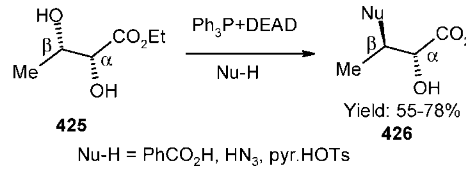
Inversion of stereochemistry at two different secondary alcohol sites sequentially by azide substitution (cf. **422**) followed by deprotection of the second site and esterification as utilized by Cohen and Overman (Scheme 115) illustrates the value of the Mitsunobu protocol nicely.[1321] This sequence has been useful in ascertaining the correct structure of batzelladine F later. In their work using α,*β*-diaminobutyramide derivatives, Carter et al. also utilized HN_3 as the nucleophile for the azidation of the precursor alcohol.[1322] They noted that $Zn(N_3)_2$ or DPPA failed in their system. In the azidation of fmoc-protected amino alcohols [e.g. fmoc-Gly-ol] also, HN_3 worked while DPPA, Me_3SiN_3, and $Zn(N_3)_2(pyr)_2$ did not.[1323]

The α-hydroxyphosphonates **423** underwent ready azidation *via* Mitsunobu reaction using HN_3 (Scheme 116).[1324] These azides (e.g. **424**) could later be converted to the corresponding α-aminophosphonates that show a wide range of biological activity. Similarly, *β*-hydroxyphosphonates have been converted to *β*-azidophosphonates and then to *β*-aminophosphonates.[1325] Many enantiopure *β*-aminophosphonates could thus be synthesized. In the synthesis of sialyltransferase transition-state analogue inhibitors also, Mitsunobu azidation of α-hydroxyphosphonates via HN_3 with inversion has been found to be quite effective.[1326,1327] A recent review by Gajda and Gajda highlights the work on azidophosphonates that includes Mitsunobu azidation.[1328]

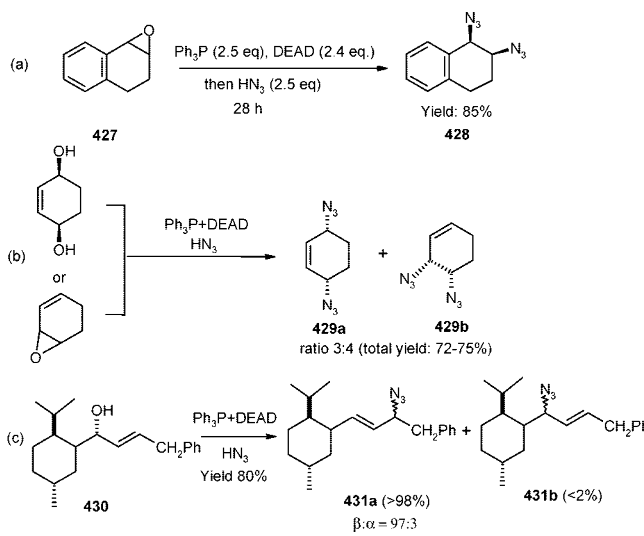
Scheme 116



Scheme 117



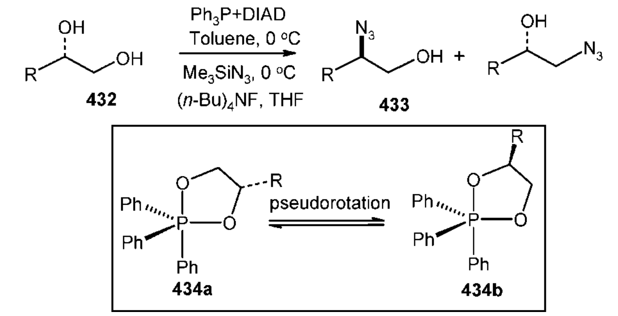
Scheme 118



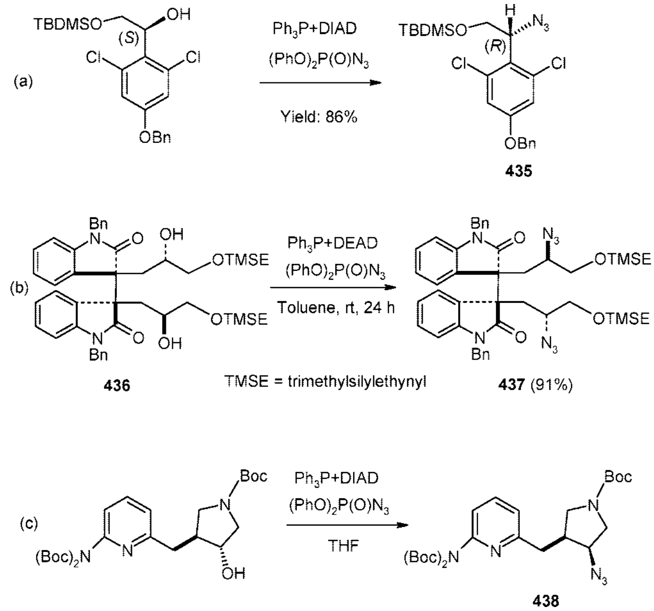
Azidation, benzoylation, and tosylation of *syn*-2,3-dihydroxy esters **425** under Mitsunobu conditions exhibit complete regioselection for the *β*-hydroxyl group, leading to **426** (Scheme 117).[1329] The configurational inversion accompanying the Mitsunobu protocol offers a means for *syn/anti* diastereochemical diversity.

Both diols and epoxides can undergo double azidation. Thus, epoxides **427** react with HN_3 under Mitsunobu conditions to yield 1,2-diazides **428** stereospecifically (Scheme 118a).[1330] These azide groups were later converted to other functionalities. In earlier studies, Skmewski and Gupta as well as Sasaki et al. obtained diazides from diols.[1331,1332] Interestingly, the double Mitsunobu azidation of *cis*-cyclohex-2-ene-1,4-diol, 3,4-epoxycyclohexene, or *trans*-2-azidocyclohex-3-en-1-ol gave a mixture of *cis*-3,6-diazidocyclohexene (**429a**) and *cis*-3,4-diazidocyclohexene (**429b**) (Scheme 118b).[1333] Likewise, *cis*-cyclohept-2-ene-1,4-diol, 3,4-epoxycycloheptene, and *trans*-2-azidocyclohept-3-en-1-ol gave a mixture of *cis*-3,7-diazidocycloheptene and *cis*-

Scheme 119



Scheme 120



3,4-diazidocycloheptene. The results were rationalized by invoking a [3,3] sigmatropic rearrangement. Spino and coworkers reported that the allylic alcohols **430** undergo Mitsunobu azidation to give the rearranged allylic azides **431a** exclusively (Scheme 118c) with no detectable amount of the S_N2 product **431b**. The stereoselectivity was also very good.[1334] Azidation via HN_3 is also utilized to prepare (i) 5-azido-3,4-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-sorbopyranose,[1335] (ii) epothilone analogues 15(*R*)- or 15(*S*)-aza-12,13-desoxyepothilone B,[1336] (iii) antibacterial 3-fluoro-D-alanine,[1337] (iv) protected 2,3-diamino esters,[1338] (v) kabiramide C analogues,[1339] and (vi) enantiomerically pure amines from (2*S*,R_S)-1-(*p*-tolysulfinyl)-2-butanol,[1340] and (vii) 3 *β*-aminosteroids.[1341]

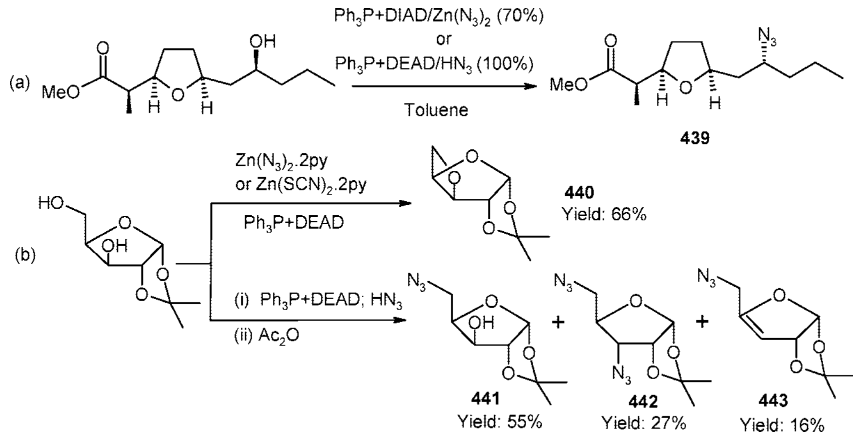
It was shown that the regio- and stereospecific azidation reactions of 1,2- and 1,3-diols (e.g. **432**) with azidotrimethylsilane (Me_3SiN_3) *via* a Mitsunobu protocol predominantly led to substitution of the *secondary* rather than the *primary* hydroxyl group (e.g. **433**; Scheme 119).[1342] Among the solvents used [THF, dichloromethane, and toluene], toluene gave the best regioselectivity for 1,2-diols. The *ee* of 1,2- and 1,3-diols was essentially unaltered during the course of the reaction. A phosphorane (**434**) mediated pathway, originally suggested by Mathieu-Pelta and Evans,[1343] was proposed for the observed stereo- and regiochemistry. Application of the same reaction conditions to a 1,4-diol led to the exclusive formation of the cyclic ether rather than the azido product.

The commercially available diphenylphosphoryl azide (DPPA) has been utilized earlier for amination via azide formation. Thus, enantioselective synthesis of (*R,R*)-solenopsin B was accomplished.[1344] This is perhaps a safer approach than directly using the hydrazoic acid. In a more recent application of this reagent in Mitsunobu azidation, Bringmann et al. have prepared the optically pure azido diether **435** (Scheme 120a) in 86% yield.[1345] In the synthesis of the alkaloid *ent*-WIN 64821, stereospecific incorporation of two C−N bonds for converting two secondary alcohol functionalities to the corresponding azides with inversion of configuration has been accomplished (Scheme 120b).[1346] The "inverted" diazide **437** thus obtained from **436** was converted to the desired *ent*-WIN 64821 in several other steps. In a protected 2-aminopyridine system, Silverman and co-workers were able to do the required azidation by remote group protection.[1347] Thus, when the 2-amino group was sufficiently blocked by two Boc groups or a (Boc+benzyl) group, they were able to obtain the normal Mitsunobu reaction of the alcoholic group with inversion (cf. **438**, Scheme 120c). When the NH(Boc) was present instead of $N(Boc)_2$, cyclization involving the pyridine nitrogen of the 2-aminopyridine group took place. This reaction is similar to the one reported earlier by Yasuda et al.[1348] Although the latter was not the intended reaction, it added to the variety of reactions which the Mitsunobu reagent combination Ph_3P−DEAD could do. This reagent combination along with DPPA has been utilized in the synthesis of (i) HIV-1 protease inhibitors based on acyclic carbohydrates,[1349] (ii) desferrisalmycin B,[1350] (iii) apratoxin A,[1351] (iv) the side chain of the aminoglycoside amikacin,[1352] (v) the insecticide (−)-spinosyn A,[1353] (vi) unnatural *β*-L-enantiomers of 2-chloroadenine pentofuranonucleoside derivatives,[1354] (vii) 3-azido/4-azido-substituted L-proline,[1355] (viii) dolastatin 10,[1356] (ix) C_2-symmetric chiral 1,4-diamines,[1357] (x) 3-azido-2,3,6-trideoxy-L-hexoses,[1358] (xi) malamycin A analogues,[1359] (xii) (*R*)-(−)-rolipram (antidepressant),[1360] (xiii) azido-2′,3′-dideoxy-*β*-L-adenosines,[1361] (xiv) vancomycin skeleton,[1362] (xv) methoxy-substituted 1-aminotetrahydronaphthalene,[1363] (xvi) azido-substituted POE-POP_{1500} resin,[1364] (xvii) chiral azido pyrrolidines,[1365] (xviii) l-azido-2-(*R*)-hydroxy-3-phenylbutane,[1366] (xix) (+)-1-deoxylycorine,[1367] (xx) 5-amino-2-fluorocyclohex-3-enecarboxylic acid (GABA aminotransferase inactivator),[1368] and (xxi) (−)-slaframine alkaloid,[1369] (xxii) 1-*r*-(*C*-4-ethylcyclohexa-2,5-dienyl)amine hydrochloride,[1370] (xxiii) 1,3-diamino carboxylic acids,[1371] (xxiv) amiclenomycin,[1372] (xxv) *γ*-amino-*β*-hydroxy acid of hapalosin,[1373](xxvi) 2-acetamido-4-amino-2,4,6-trideoxy-D-galactopyranose,[1374] (xxvii) 3-aminocholan-24-oic acid esters,[1375] (xxviii) the dimethyl ester of 1-deoxy-L-idonojirimycin-1-methylenphosphonate, [1376] (xxix) the hexahydroazepine moiety of (−)-balanol,[1377] (xxx) methyl 3b-azido-5b-cholan-24-oate,[1378] and (xxxi) polyprotected 2-deoxystreptamine (2-DOS) derivatives.[1379]

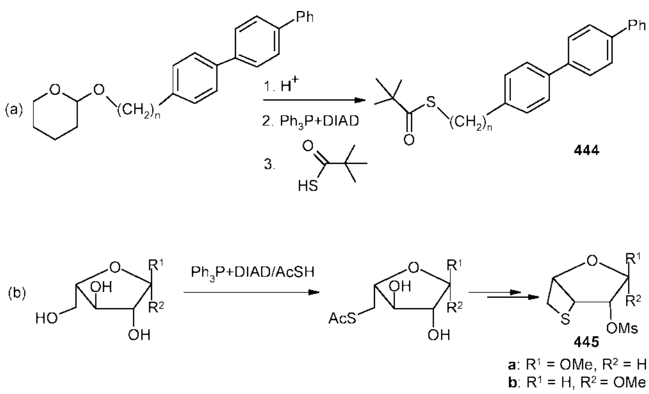
Nicotinoyl azide has also been used instead of DPPA for the conversion of alcohols to azides.[1380]

It has been shown earlier that zinc azide along with Ph_3P−DIAD in toluene is effective in the azidation of secondary alcohols.[1381] Such a route was utilized in the synthesis of a larger fragment of pamamycin-607 (**439**); however, use of the HN_3 route gave better yields (Scheme 121a).[1382] In another paper by Moravcova et al., it is reported that the reaction of 1,2-*O*-isopropylidene-α-D-xylofuranose via Ph_3P−DIAD/$Zn(N_3)_2$ (or zinc thiocyanate or zinc *N*,*N*-dimethyldithiacarbamate) led only to cyclic 3,5-anhydro product (**440**) without azidation although use of HN_3 did

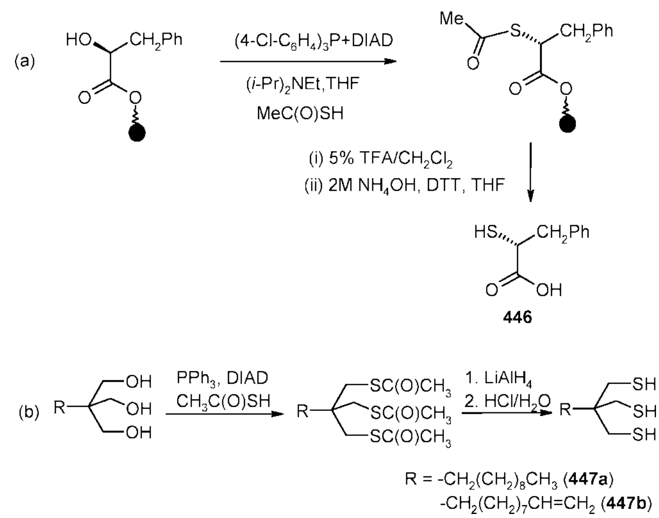
Scheme 121



Scheme 122



Scheme 123



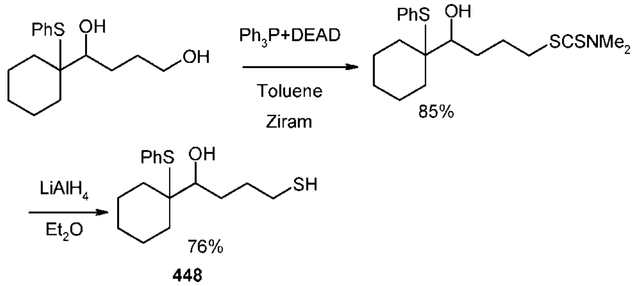
yield a mixture of azido products **441**−**442** along with a small quantity of dehydration product **443** (Scheme 121b).[1383] Use of 1,2-*O*-isopropylidene-α-D-ribofuranose as a substrate, however, afforded the C^5-substituted products in decent yields (60−65%). The yields varied depending on the reaction time and the molar ratio of reagents. $Zn(N_3)_2(pyr)_2$ has been effectively used by Wu et al. to obtain aminoalkylazetidines (after subsequent treatment of the azide with $NaBH_4$ in the presence of $NiCl_2 \cdot 6H_2O$)[1384] and by Wulff and co-workers for the synthesis of allocolchicine.[1385] In the latter case, an excellent yield of 92% with inversion at the chiral alcohol center was achieved. Use of NaN_3 for azidation in the synthesis of 2′-modified nucleosides is also reported.[1386]

6. Sulfur Nucleophiles: C−S Bond Forming Reactions

It has long been known that appropriately activated sulfur nucleophiles will participate in the Mitsunobu reaction with alcohols to lead to thioesters or thioethers with inversion of configuration.[1387] In the preparation of terphenylalkanethiols with different chain lengths, this method was applied to introduce the sulfur functionality leading to **444** (Scheme 122a).[1388] Here a thioacid, which is a better nucleophile than a thiol, was used. Unprotected L-arabinofuranosides, D-ribofuranosides, and D-xylofuranosides could be converted into their corresponding *S*-acetyl-5-thio derivatives, which were subsequently transformed to **445** (Scheme 122b).[1389] However, unprotected D-glucitol led to 5-*O*-acetyl-1,4-anhydro-6-thio-D-glucitol in one step by this thio-Mitsunobu reaction.[1390] This study was in continuation of the previous work by the same research group, in which they had prepared the thioacetate of methyl α-D-glucopyranoside; only moderate yields were obtained here, probably because of the oxidation of the sulfur nucleophile by the azodicarboxylate.[1391]

Mitsunobu thioesterification using thioacetic acid has been utilized for the synthesis of amide alkaloids. The cleavage of the acetyl group was accomplished by KOH/MeOH to obtain the thiols.[1392] A similar methodology was employed earlier for the preparation of oxytocin antagonists, but the acetyl group was cleaved by using NaOH.[1393] Polchow-Stein and Voss have similarly prepared methyl-1-*S*-acetyl-1-thio-L-sorbofuranosides with mesylate leaving groups.[1394] In the synthesis of thioester and thiol inhibitors (e.g. **446**) of IMP-1 metallo-*β*-lactamase, a solid-phase reaction was employed (Scheme 123a).[1395] Here, a solid support based on Rapp TentaGel S-NH_2 resin with a mild acid-cleavable HMPB linker was used. The authors noted that this reaction was accelerated if (4-Cl-C_6H_4)$_3$P in conjunction with an additional base such as *i*-Pr_2NEt was used in place of the traditional Ph_3P. For conversion of ester to thiol, ammonium hydroxide in the presence of dithiothreitol (DTT, to suppress disulfide formation) was employed. Thiobenzoic acid can also be used as the acidic component in these reactions. Removal of the PhC(O)- group can be done by treatment with NaOMe/MeOH.[1396] Such thiobenzoate esters of steroids (e.g. cortisol, prednisolone) have been synthesized as precursors for potential glucocorticoid receptor imaging agents by Wuest et al. recently.[1397] Two equivalents of Ph_3P−DIAD and

Scheme 124



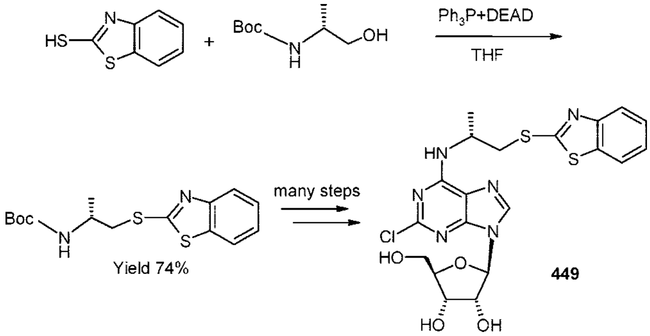
thiobenzoic acid were used to obtain decent yields (75−82%) of the thioesters. In the thioesterification [with MeC(O)SH or PhC(O)SH] of 2-amino-l,3-propanediols, the stereochemistry of the products was dependent upon the substituents on the nitrogen.[1398] The tristhiols 1,1,1-tris(mercaptomethyl)-undecane (**447a**) and 1,1,1-tris(mercaptomethyl)dec-9-ene (**447b**) were synthesized by starting with the corresponding tris(hydroxymethyl) compounds (Scheme 123b).[1399] These compounds are potential substrates for the monolayer protection of 2D surfaces and nanoparticles. Related chemistry using thioacids has been made use of in the synthesis of (i) 2,5-anhydro-3-azido-2-thio-D-lyxofuranosides and 3,5-anhydro-2-azido-3-thio-D-lyxofuranosides,[1400] (ii) highly oxygenated triterpene quassinoids,[1401] (iii) anhydro-thiohexofuranosides,[1402] (iv) dihydrothiophene derivatives,[1403] (v) (2*S*,3*E*)-5-(isopropylsulfanyl)-3-pentenes,[1404] (vi) thio-disaccharides,[1405] (vii) mercaptopyrrolidines,[1406] (viii) 2-oxa-7-thiabicyclo[4.2.0]octane derivatives with the D-*galacto* and D-*gulo* configurations,[1407] (ix) functionalized long-chain ether-linked thiols for use in developing monolayers of gold,[1408] (x) (*R*)-4,4,4-trifuoro-2-mercaptobutyric acid starting from (*S*)-malic acid,[1409] (xi) diastereoisomeric 3-methoxy-2-oxa-6-thiabicyclo[3.2.0]heptan-4-ols,[1410] (xii) α-acetylsulfanylphosphonates,[1411] (xiii) *S*-adenosyl-L-homocysteine analogues,[1412] (xiv) 3-mercaptoproline derivatives,[1413] (xv) L-methionine/L-homocysteine from the protected homoserine,[1414] (xvi) allenic monocarboxylates,[1415] (xvii) C^5 thioalkynyl nucleosides,[1416] (xviii) azole nucleoside 5′-monophosphate mimics (PIMs),[1417] and (xix) anhydro-thiohexofuranosides.[1418]

Another route to thiol from a primary alcohol involved the use of zinc dimethyldithiacarbamate (Ziram) in the Mitsunobu protocol.[1419,1420] A primary −OH group selectively formed the dithiacarbamate, which was converted to the thiol by treatment with $LiAlH_4$ (cf. **448**, Scheme 124). Thus, this route offers a way to distinguish between a primary and a secondary alcohol in the transformation of −OH to −SH functionality. Use of Ziram in the preparation of mercaptides has also been reported by Jacobi and co-workers and earlier by Rollin.[1421,1422]

Thiols as nucleophiles have been exploited for the synthesis of neuroprotective A1 agonists (e.g. **449**, Scheme 125),[1423] 2-(4-bromocholest-4-en-3α-ylthio)benzothiazole,[1424] benzothiazolyl sulfides,[1425] saccharidic benzothiazol-2-yl sulfones,[1426] and thiol-modified nucleoside phosphoramidites.[1427] In the last example, the authors used tritylmercaptan as the sulfur nucleophile. There is also a report on the synthesis of *S*-ribosyl-L-homocysteine, but the azodicarboxylate used is not clear.[1428]

As one of the key steps for the synthesis of the macrolide (+)-zampanolide, the primary alcohol **450** was treated with 1-phenyl-1H-tetrazolo-5-thiol (PTS-H) and Ph_3P−DEAD in

Scheme 125

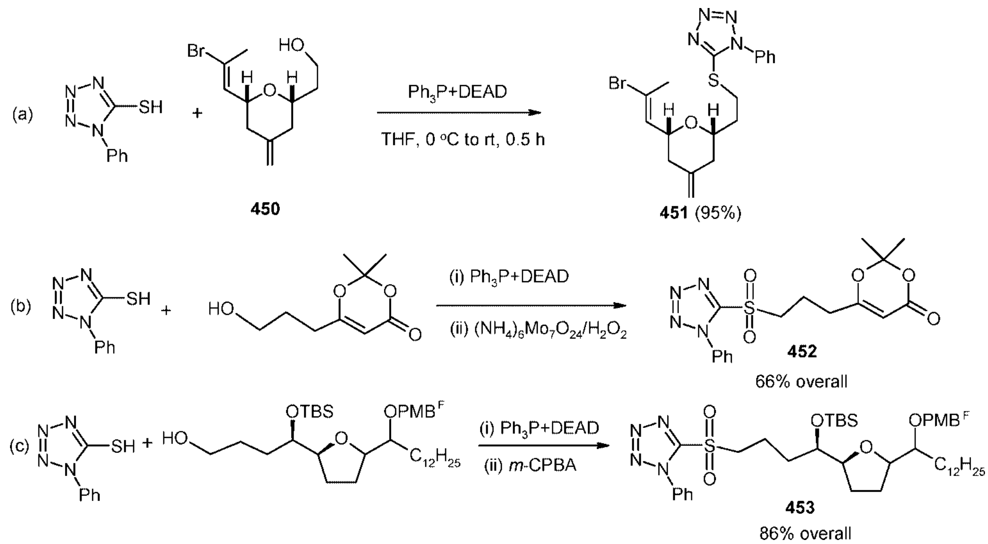


THF at 0 °C to obtain the tetrazolo sulfide **451** (Scheme 126a).[289,1429] This reaction nicely illustrates the use of aryl/heteroaryl thiols as nucleophiles. Three recent examples of this type of reaction pertain to the synthesis of (i) cyclindramide subunit **452** by Laschat and co-workers (Scheme 126b),[1430] (ii) (+)-brefeldin A by Trost and Crawley,[1431] and (iii) a library of murisolin stereoisomers (as many as 28 isomers) with fluorous phase separation technology (Scheme 126c) by Curran and co-workers.[1432] In the last case, the resulting compound **453** was an intermediate in the synthesis of murisolin isomers. In this work, Mitsunobu esterification also was utilized extensively for inversion of configuration at a secondary alcohol.

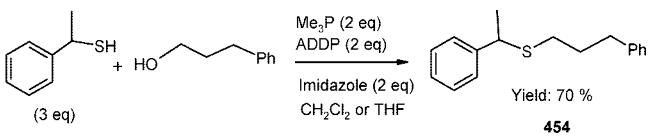
As mentioned above, aliphatic thiols generally lack sufficient acidity to participate in Mitsunobu condensation efficiently. Unsymmetrical alkyl thioethers **454** were, however, prepared from aliphatic thiols and unhindered alcohols under modified conditions with Me_3P−ADDP in the presence of 2 equiv of imidazole (Scheme 127).[1433] Thiophenols also reacted with primary alcohols in the presence of *n*-Bu_3P−ADDP; this reaction was used to synthesize chiral sulfoximines.[1434] In the absence of any alcohol, *ω*-dithiols reacted with Ph_3P−DIAD and were converted into monomeric and polymeric disulfides.[1435] Ethane-1,2-dithiol gave a polymeric material whereas propane-1,3-dithiol afforded 1,2-dithiolan.

Thioglycosides have been synthesized from 1-thiosugars and a series of alcohols using a Me_3P−ADDP combination (cf. **455**, Scheme 128a).[1436] The conditions were compatible with a large number of functionalities and protecting groups. Similarly, suitably protected L-aspartic acid pentafluorophenyl ester **456** underwent smooth thioetherification with 5-aminopentanol in the presence of Me_3P−ADDP.[1437] The final product, glycosyl amino acid ester **457** (Scheme 128b), could be separated easily because one of the byproducts, $Me_3P(O)$, was removed by aqueous workup. Such a study has been extended for the one-pot preparation of *S*-glycosyl amino-acid building blocks suitable for automated combinatorial syntheses of highly glycosylated *β*-peptides that can serve as potential mimics for complex oligosaccharides (e.g. **458**) or for studying carbohydrate−protein interactions.[1438] Ichikawa and co-workers have used the combination *n*-Bu_3P−ADDP in the synthesis of a *β*-*N*-acetylglucosaminyl-1-thio-*N*-fmoc-serine derivative that was obtained in 53% yield.[1439] In an analogous thioetherification, resin bound thiosugars were employed by Malkinson and Falconer to prepare *C*-terminal thio-linked glycopeptides.[1440] THF as a solvent promoted good solvation of the polymer backbone. With suitable intramolecular −OH and −SH groups at the 1,5-positions, thiacyclization leading to a six-membered ring takes place, as shown by Hashimoto et al. in the synthesis

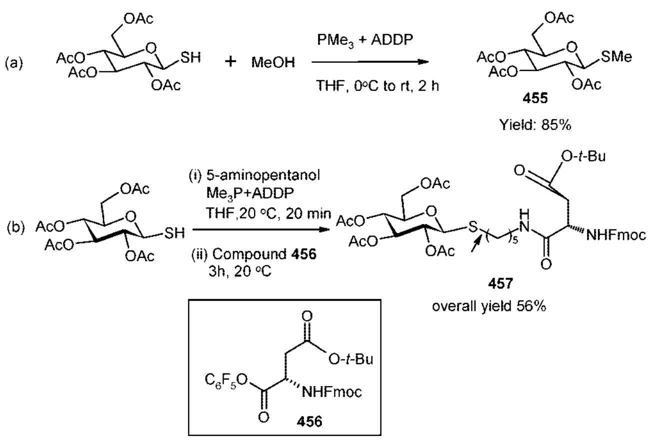
Scheme 126



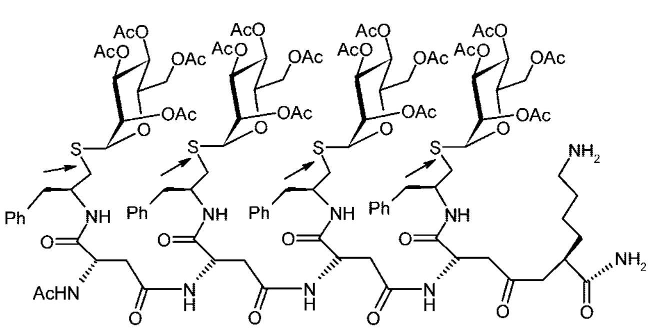
Scheme 127



Scheme 128

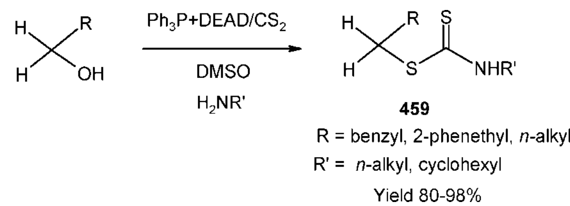


of both α and *β* forms of 5-thio-D-glucopyranosides.[1441] Protected lanthionines have been prepared by Tabor and co-workers via a Mitsunobu thioetherification of *N*-trityl-(*R*)-serine allyl ester with fmoc-Cys-O-*tert*-Bu using Me_3P–ADDP in the presence of zinc tartrate as an additional component.[1442] A single isomer of the required product was obtained.



458

Scheme 129

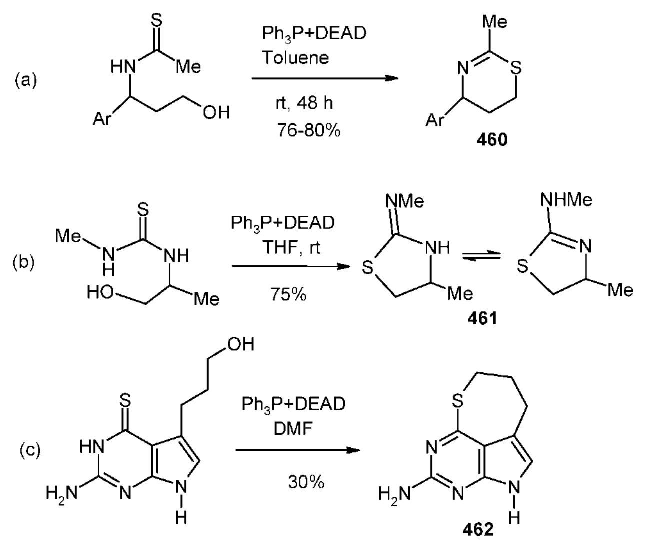


Chaturvedi and Ray have reported an efficient one-pot Mitsunobu protocol for the high-yield synthesis of a large number of dithiacarbamates RC–S–C(S)NHR′ (**459**) starting with alcohols, amines, and carbon disulfide (Scheme 129).[1443] DMSO was the solvent of choice. It was proposed that the initially formed dithiacarbamic acid reacted with MBH betaine followed by reaction with the alcohol to generate the alkoxyphosphonium-dithiacarbamate salt in the intermediate steps. A similar approach has been adapted by the same group for the preparation of carbamates, xanthates (*O*,*S*-dialkyl dithiacarbamates), trithiocarbonates, and substituted ureas.[1444−1449]

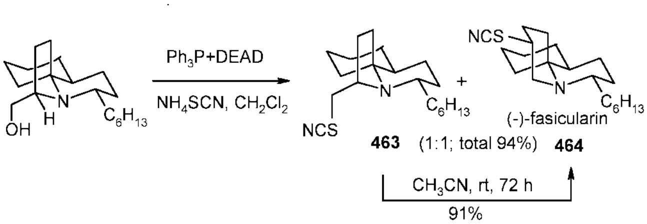
Analogous to the occurrence of *O*-alkylation when a nucleophile with a NH–C(=O) group is available, *S*-alkylation is possible if NH–C(=S) is present. This was demonstrated by Dallemagne and co-workers in the synthesis of 1,3-thiazine derivatives **460** by starting with thioamides (Scheme 130a).[1450] The authors stated that the main problem was the difficulty in separation. By contrast, it is worth noting that only *N*-cyclization of *N*-(2-hydroxyethyl)thioureas took place in the solid-phase synthesis of 2-imidazolidinethiones.[867] Reaction of *N*-(2-hydroxyethyl)-*N*′-phenylthioureas under Mitsunobu conditions gave both *N*- and *S*-cyclized products.[1451] Selective sulfur alkylations leading to cyclic thioethers **461** and tricyclic pyrrolo[2,3-*d*]pyrimidine **462** have also been reported (Scheme 130b and c).[1452,1453] A similar *S*-alkylation has been utilized by Wrona and Zakrzewski for the synthesis of ferocenyl conjugates of cholesterol and stigmasterol.[1454] Other applications involving thioether formation involve the synthesis of (i) phosphonylated thiazolines,[1455] (ii) thioalkylated pyrimidine nucleosides,[1456] (iii) methyl 5′-thio-α-isomaltoside,[1457] (iv) curacin A,[1458] and (v) 8,2′-*S*-cyclopurinenucleoside.[1459]

Firouzabadi and co-workers have reported a selective method using Ph_3P–DEAD and NH_4SCN for conversion of

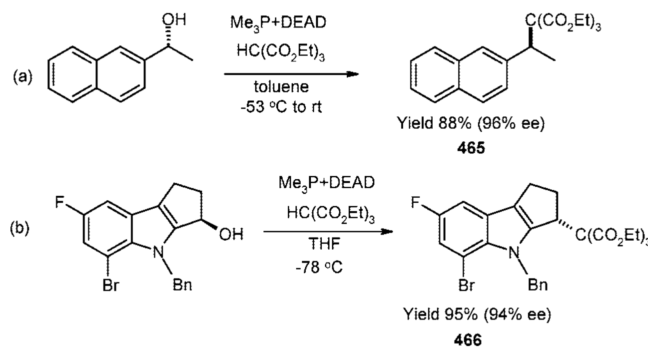
Scheme 130



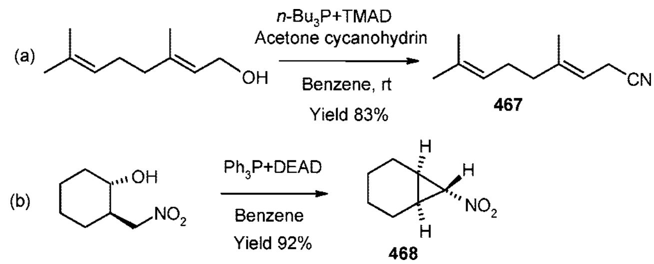
Scheme 131



Scheme 132



Scheme 133



alcohols/tetrahydropyranyl ethers, thiols, carboxylic acids, silyl ethers, and silyl carboxylates to thiocyanates.[1460,1461] In this route, NH_4SCN can be construed as a masked source of the nucleophile HSCN. Use of Ph_3P−DEAD/NH_4SCN has also been made in the synthesis of the marine alkaloid (−)-fasicularin (compound **464**, Scheme 131).[1462] An interesting rearrangement has taken place while forming **464** from **463**.

7. Carbon Nucleophiles: C−C Bond Forming Reactions

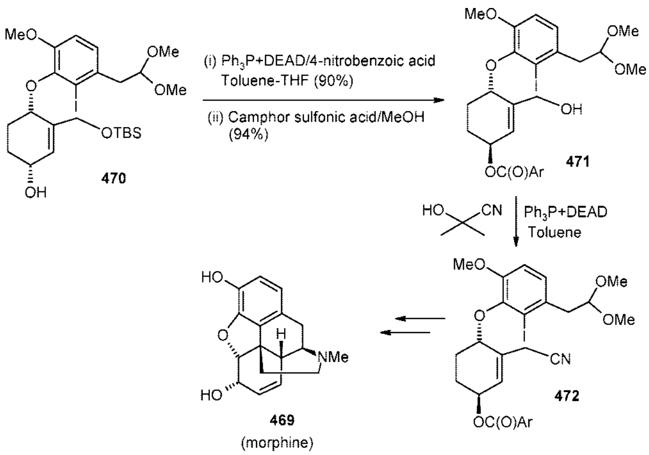
In early work, Mitsunobu and co-workers showed that the −OH group in (*R*)-2-octanol could be displaced with ethyl cyanoacetate using Ph_3P−DEAD, though the product was isolated in low yield with poor enantiomeric purity.[15] Macor and co-workers found that (*o*-nitroaryl)acetonitriles were also good nucleophiles in the Mitsunobu reaction.[88] For carbon nucleophiles such as triethyl methanetricarboxylate (TEMT, commercially available) with a reasonably low pK_a value of 7.5, the best results were obtained with the sterically less crowded phosphine Me_3P (2 equiv), giving 85% of the product **465** in a THF−toluene mixture (1:1) at low temperature (Scheme 132a).[1463] No reaction was observed when the sterically crowded phosphine $(cyclohexyl)_3P$ was used in place of Me_3P. Neutral and electron-poor substrates underwent mostly inversion while electron-rich and biaryl systems led to significant racemization. Toluene as the reaction medium helped in some cases to preserve optical purity. In a later paper on the synthesis of cycloalkyl-[*b*]indoles also, Hillier et al. made a similar observation that the sterically less hindered Me_3P worked better, with the product **466** (Scheme 132b) being obtained in high yield and high enantiomeric excess.[1464] They reported that the use of bis(2,2,2-trichloroethyl) azodicarboxylate in place of DEAD provided higher enantiomeric purity. Cravotto et al. had earlier utilized TEMT for alkylating primary, benzylic, and allylic alcohols to obtain reasonable yields of the products.[1465] The same carbon nucleophile was employed by Palmisano and co-workers in the synthesis of the pyrrolizidine alkaloid, (−)-pyrrolam A.[1466]

Similar to the conversion of −OH to $-N_3$ using metal azides, it is possible to convert −OH to −CN using lithium cyanide or acetone cyanohydrin by a Mitsunobu protocol in the case of primary and unhindered secondary alcohols.[1467−1469] Either *n*-Bu_3P−TMAD or (cyanomethylene)trimethylphosphorane (CMMP) mediated transformation of primary and secondary alcohols into the corresponding nitriles in the presence of acetone cyanohydrin (source of hydrogen cyanide) has been accomplished (e.g. **467**, Scheme 133a).[1470] Use of 1.5−3 equiv of reagents gave better yields. In many cases, such as conversion of 3β-cholestanol to 3α-cyanocholestane or for the synthesis of carbasugar derivatives, the CMMP reagent worked better.[1470,1471] The methylene group in the $-CH_2NO_2$ moiety is also sufficiently activated to undergo an internal Mitsunobu cyclization, as shown by the synthesis of α-nitrocyclopropanes **468** (Scheme 133b).[1472]

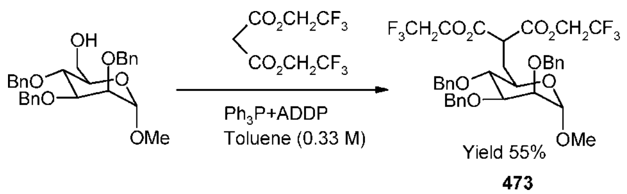
Morphine (**469**) is an efficient analgesic and has been in use for the treatment of pain associated with cancer. In a recent report on the synthesis of its racemic form, Fukuyama and co-workers have made use of the Mitsunobu reaction in two important steps. One of these is the inversion of configuration at the secondary alcohol **470** (Scheme 134).[1473] More interesting is the reaction using acetone cyanohydrin $Me_2C(OH)CN$ and a primary alcohol, in which the net result is the conversion of an −OH group in **471** to a −CN group in **472**. Use of acetone cyanohydrin has also been reported in the synthesis of (+)-jasplakinolide, a 19-membered cyclic depsipeptide.[1474]

Chain elongation of the primary alcohol end of saccharides is of chemical as well as biological interest. Such an elongation of the primary alcohol of saccharides (α-D-ribose, α-D-glucose, α-D-mannose) has been done using bis(2,2,2-trifluoroethyl)malonate as nucleophile to give **473** (Scheme 135).[1475] Use of ADDP instead of DEAD, and a fairly concentrated solution in toluene (0.33 M) rather than in THF,

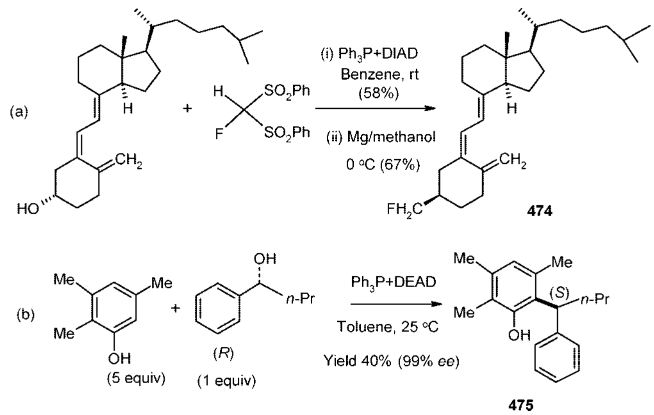
Scheme 134



Scheme 135



Scheme 136



gave better yields. Similar mono- and dialkylations using the same nucleophile have been reported earlier by Takacs et al.[1476] Alkylation of polymer-supported alcohol (polymer)-4-HN(O)C$-C_6H_4-CH_2OH$ with active methylene compounds $(EtO_2C)CRR'H$ [R = H, Me; R′ = CO_2Et, C(O)Me, etc.] in the presence of n-Bu_3P−TMAD afforded the desired monoalkylated products (polymer)-4-HN(O)C$-C_6H_4-CH_2C(CO_2Et)RR'$.[1477] Even compounds of type RCH(CN)-SO_2Ph and Meldrum's acid were utilized in similar *C*-alkylation reactions.[1478,1479] A unique stereoselective monofluoromethylation of primary and secondary alcohols using a sulfonated fluorocarbon nucleophile in Mitsunobu *C*-alkylation has recently been reported by Surya Prakash et al.[1480] Here the normal reagent combination of Ph_3P−DEAD worked well and pharmaceutically interesting compounds such as monofluoromethylated Vitamin D_3 (**474**, Scheme 136a) could be synthesized. The bis(2,2,2-trifluoroethyl)-malonate $CH_2(CO_2CH_2CF_3)_2$ also took part in *C*-alkylation when it reacted with the hydroxyl at the C^6 position, but it underwent *O*-alkylation when the reaction occurred at the C^1 position of protected mannose. The latter reaction took place via the tautomeric form $(F_3CCH_2CO_2)CH{=}C(OH)(OCH_2CF_3)_2$.[1481] The Mitsunobu reaction of *ortho*-substituted phenol derivatives with an optically active benzyl alcohol also leads to C−C bond formation. For example, 2,3,5-trimethylphenol reacted with (*R*)-1-phenylbutan-1-ol under Mitsunobu conditions to afford the *ortho*-alkylated compound **475** in high enantiomeric purity in yields of 7−40% depending on the solvent. Considering the yield and the enantiomeric purity, toluene was a good solvent (Scheme 136b).[1482]

Transannular spirocyclization under Mitsunobu conditions using n-Bu_3P−ADDP, leading to a cyclopropane ring via the formation of a new C−C bond, has been utilized in the synthesis of antitumor antibiotic natural product (+)-duocarmycin A (**477**; Scheme 137a).[1483,1484] It may be noted that the saturated six-membered ring in **476** is replaced by five- and three-membered rings in **477**. Salaün and co-workers have reported the intramolecular reaction of the allylic alcohol (6*S*)-**478** in the presence of 2 equiv of Me_3P−DEAD in THF at room temperature, which led to a 73:7 mixture of (*E*)- and (*Z*)-**479** (77% yield; *de* 82%), along with **480** (15%) (Scheme 137b).[1485,1486] The yield and diastereoselectivity were lower when n-Bu_3P was used in place of Me_3P. The traditional phosphine Ph_3P was ineffective.

Another interesting reaction, cyclopropanation (instead of cyclic ether formation), leading to the spiro-cyclopropyl derivative **481** (Scheme 138), has been reported by Coppola.[1487] This result was rationalized by tautomerization of the precursor to its 4-keto form, which has a highly acidic proton at the C^3 carbon. Thus, although the cyclopropane ring is more strained compared to five-membered furan rings, the reaction led only to the former in this case.

8. Miscellaneous Reactions

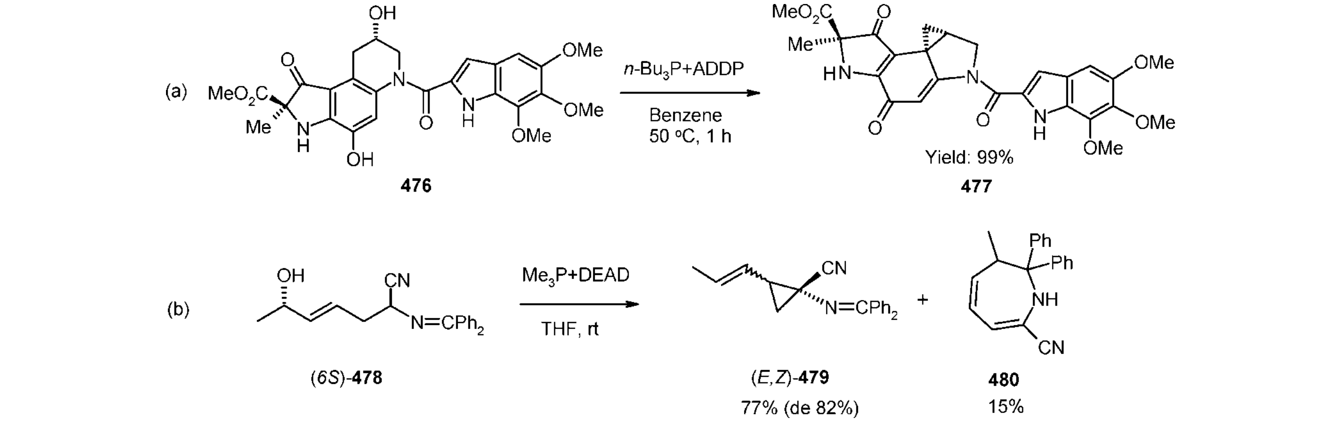
8.1. Halogenation

Halogenation of alcohols can be effected if a metal salt (e.g. lithium halide) is used in addition to Ph_3P−DEAD (Scheme 139a; from ref 1467).[1467,1488] Although there are several methods for halogenation of alcoholic −OH groups, the Mitsunobu approach may be useful when other sensitive functionalities are present in the substrate. It is also possible to use methyl iodide in conjunction with Ph_3P−DEAD for iodination in some cases (Scheme 139b; from ref 1489).[1489,1490] Inversion at the chiral center is an important outcome.[1483] This iodination route was used earlier by Dormoy.[1491] It is likely that the cyclization shown in Scheme 139c, which was facilitated by the additional component $ZnCl_2$, also occurred via a chlorinated intermediate as shown.[1492] Reaction in the absence of $ZnCl_2$ gave very poor (or none) yield of the cyclization product. The product **484** was an important precursor for the synthesis of the antibacterial agent levofloxacin. For bromination of the primary alcohol groups, the combination Ph_3P−DEAD/CBr_4 has also been used.[1493] Simon et al. prepared 6*β*-bromo-codeine and morphine derivatives using the precursor codeine and morphine hydrochloride salts as the source for halogen.[1494]

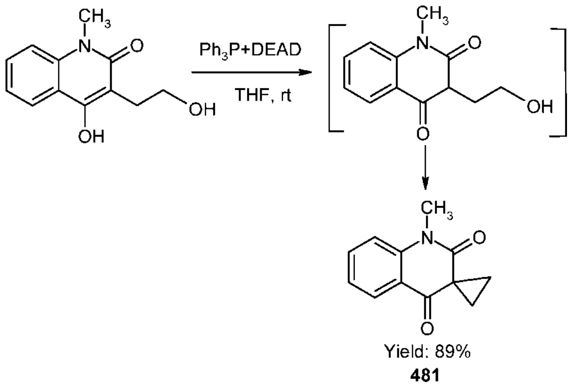
8.2. Reaction in the Presence of CO_2

Primary alkylamines gave high yields of isocyanates **485** when treated with carbon dioxide and Morrison−Brunn−Huisgen intermediate **15** in dichloromethane (Scheme 140).[1495,1496] With aromatic amines, depending upon the amine, they gave other products such as carbamoyl hydrazine **487** or/and triazolinone **488** in addition to the isocyanate **486**.

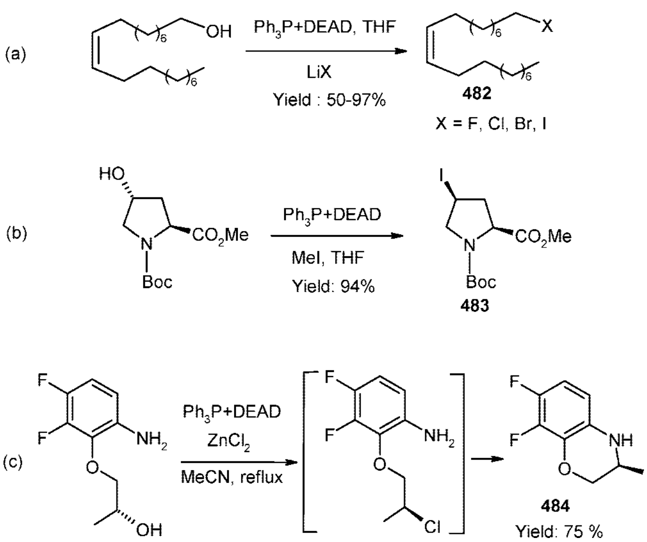
Scheme 137



Scheme 138



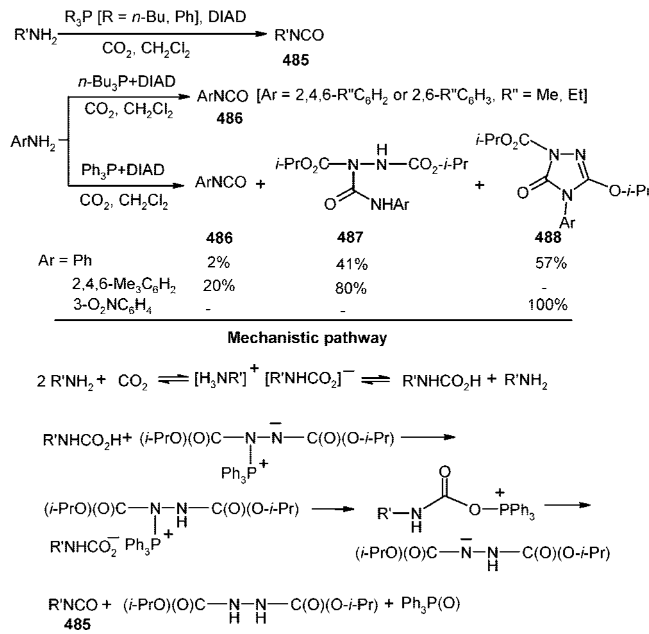
Scheme 139



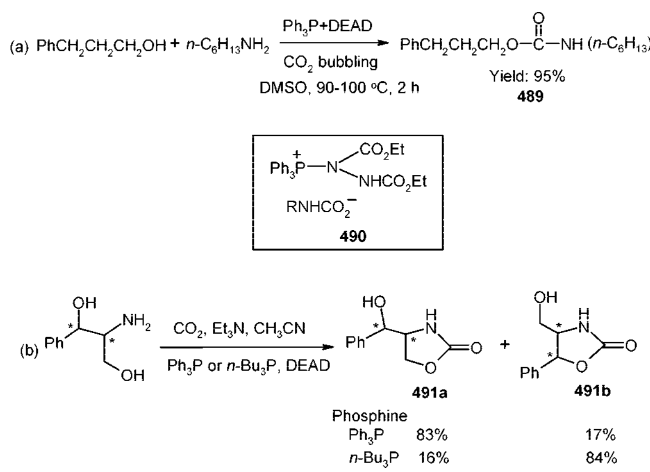
In such cases, use of *n*-Bu_3P improved the yield of the isocyanates dramatically. Aniline, however, gave mainly carbamoyl hydrazine with either Ph_3P or *n*-Bu_3P The pathway for the formation of isocyanates is also shown in Scheme 140.

A novel one-step process for the synthesis of *N*-alkyl carbamate esters **489** by mild carboxylation of alkylamines with CO_2 followed by *O*-alkylation with an alcohol has been developed using a Mitsunobu protocol (Scheme 141a).[1497] An intermediate of type **490** was proposed for the reaction. 1,2-Aminoalcohols reacted with CO_2/Et_3N under Mitsunobu conditions to lead to 2-oxazolidones **491a–b** (Scheme 141b).[103] Such a reaction can be considered for the fixation

Scheme 140

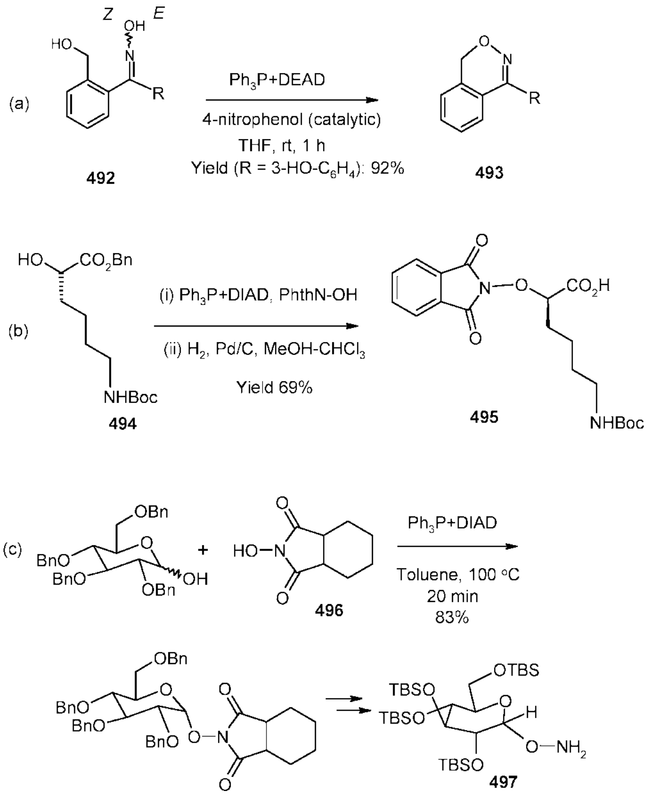


Scheme 141



of CO_2. Since there was a significant change in the product ratios depending upon the phosphine used, it was assumed that there was a change in the mechanistic pathway at the intermediate stages. Dinsmore and Mercer have recently shown that the stereochemical course is dependent on whether the carbamic acid intermediate is *N*-substituted with hydrogen (retention) or carbon (inversion).[1498] The best

Scheme 142

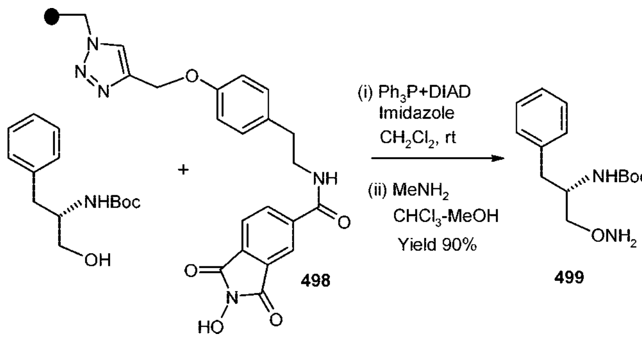


conditions for the formation of carbamate with normal amino alcohols were found to be (i) to pretreat the amino alcohol with DBU (0.1 equiv)-CO_2 for 45 min and (ii) to use n-Bu_3P and DTBAD (2.1 equiv each).

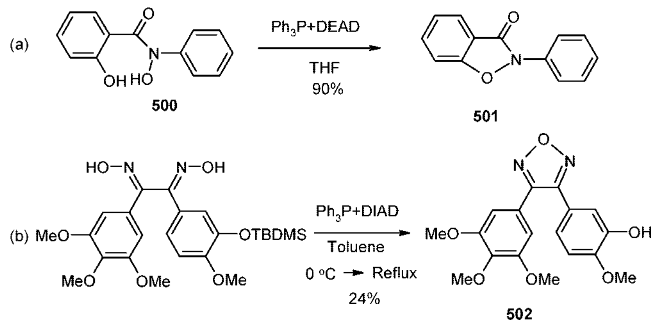
8.3. Use of Oximes as Nucleophiles

Oximes contain the ═N—OH group that can act as the nucleophile in the Mitsunobu reaction. Thus, an intramolecular Mitsunobu procedure was utilized for the synthesis of herbicidal benzoxazines **493** from 2(hydroxyiminomethyl)benzyl alcohols **492** (Scheme 142a).[1499] It was surmised that the *Z*-isomer was the one that reacted. One can use the more readily available *N*-hydroxylphthalimide as a nucleophile to couple intermolecularly with different alcohols.[1500] This reagent was quite useful in the synthesis of many aminooxy acids. The other substrate in these cases was a protected hydroxy acid. Thus, D-PhthN-*O*-Lys(Boc)-OH (**495**), a lysine analogue, was prepared from commercially available L-NH(Boc)-Lys(Cbz)-OH (**494**) (Scheme 142b).[1501] The hydroxyphthalimide route has been employed to prepare (i) chiral diamides that are useful in conformational studies related to N—O turns in peptides,[1502] (ii) *N*-ethoxy-morpholino-oxime ethers with antifungal properties,[1503] (iii) pyrazolyl propynyl-hydroxylamines that can serve as precursors for isoxazoles,[1504] (iv) protected spermidine and spermine oxa-analogues,[1505] (v) 2′-*O*-[2-[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)oxy]ethyl] nucleosides,[1506] (vi) *N*-/*O*-glycosylated α-aminooxy acids,[1507] (vii) chiral β^3-aminoxy acids or amides,[1508] (viii) methylene(methylimino) (MMI) linked oligodeoxyribonucleotide dimers,[1509] (ix) allyl hydroxylamine derivatives,[1510] and (x) α-aminoxy amino acids.[1511] A review on dehydrative glycosylation with 1-hydroxy donors including *N*-hydroxyphthalimide is also available.[1512] In place of *N*-hydroxyphthalimide, it was possible to use compound **496**, containing a saturated six-membered ring, to obtain **497**. The latter product was a precursor for trichostatin D (Scheme 142c).[1513] The hydroxylamine Bz[H_2C═CH—C(O)]NOH[1514] and *N*-hydroxy-4-methylthiazole-2(3*H*)-thione[1515] are also nucleophiles that undergo similar *O*-alkylation.

Scheme 143



Scheme 144



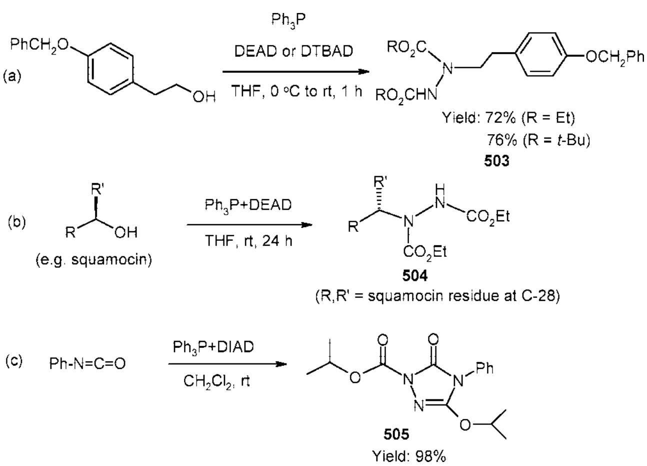
As an alternative to the above, the *N*-hydroxyphthalimide moiety was anchored to a polymer solid support and then the normal reaction was performed (Scheme 143).[1516] This study also highlighted the importance of the linker and a specific base effect for the Mitsunobu reaction. The best result was obtained when a spacer was provided between the polymer backbone and the phthalimide residue as in **498**. The Mitsunobu reaction was carried out at room temperature during 24 h in CH_2Cl_2 using 5 equiv of Ph_3P—DIAD/imidazole to obtain various *O*-alkyl hydroxylamines (after subsequent methylaminolysis, e.g. **499**) with yields in the range 51—94%. In an earlier study, Floyd et al. modified Wang resin using *N*-hydroxyphthalimide to prepare polymer bound *O*-hydroxylamine-hydroxamic acids.[1517] By using this route, tripeptides and sulfonamido hydroxamic acids that could be useful as inhibitors of metalloproteinases were synthesized. 1-Hydroxyimidazole was also easily loaded onto -CH_2OH terminal Wang resin using a n-Bu_3P—ADDP reagent system.[1518]

Salicylhydroxamic acids **500** underwent cyclization to form 1,2-benzisoxazolin-3-ones **501** rather readily under Mitsunobu conditions (Scheme 144a).[1519] Substituted 1,2-benzoxazoles have also been prepared similarly.[1520] A new protocol using the Mitsunobu reaction was used for the synthesis of furazan **502** *via* vicinal dioximes that have pK_a values in the range 8—11 (Scheme 144b).[1521] During the course of the reaction, the protecting group was also removed. Thus, these dioximes behave in a manner similar to diols.

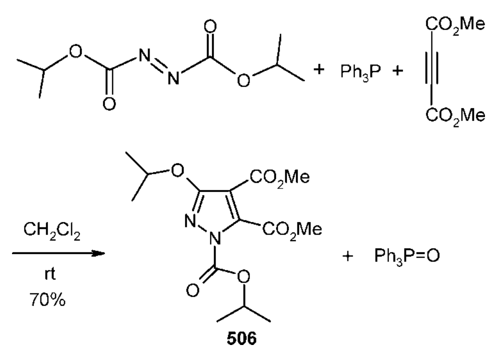
8.4. Reaction in the Absence of a Nucleophile

In case a nucleophile is not available, the alcohol itself can react with the azocarboxylate intermediates to lead to

Scheme 145



Scheme 146



protected hydrazines of type **503** (Scheme 145a).[1522] Also, if the betaine is not able to abstract the proton of the nucleophilic precursor (pK_a >13), it is possible that the hydrazine portion of the reagent may itself react with the alcohol (cf. **504**, Scheme 145b).[1523] New triazoles (e.g. **505**) may be formed if isocyanates are present (Scheme 145c).[1524]

The reaction shown in Scheme 146 leading to pyrazole **506** is an important one because if one uses substrates containing activated alkynes in the Mitsunobu reaction, it is possible that products (such as pyrazoles) other than the expected ones may form by just utilizing the acetylenic functionality.[1525] As can be seen from the reaction, the phosphine can pick up the oxygen from the azodicarboxylate (instead of an alcohol) to form the phosphine oxide.

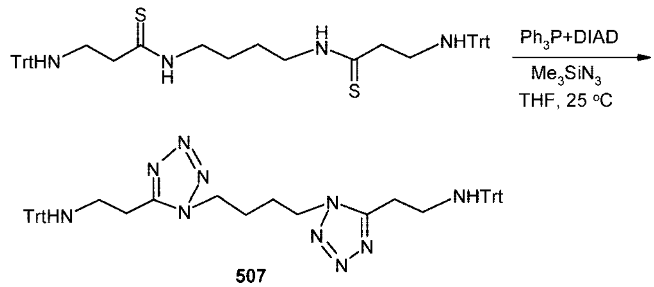
8.5. Formation of Tetrazoles via Thioamides and Azide

Bis-tetrazole derivatives **507** have been conveniently prepared from *N,N'*-ditritylated *ω*-amino thioamides and trimethylsilyl azide (Scheme 147). Although the corresponding amides reacted, the reaction was sluggish and only thioamides gave better results.[1526] A similar methodology was utilized for the preparation of many other polyamines bearing 1*H*-tetrazol-5-yl units.[1527]

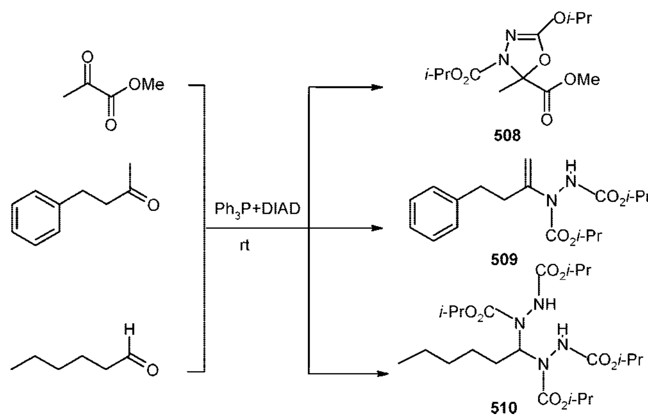
8.6. Reactivity toward Carbonyl Compounds

The Morrison−Brunn−Huisgen intermediate **15** showed excellent reactivity toward carbonyl compounds to generate a variety of products (e.g. **508**−**510**) depending on the substituents present on the carbonyl carbon (Scheme 148).[1528] Although this is not a Mitsunobu reaction, one needs to be aware of this possibility when such functional groups are

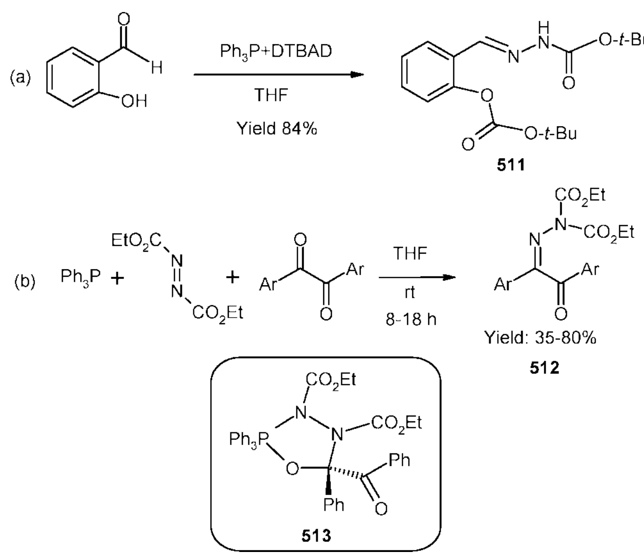
Scheme 147



Scheme 148



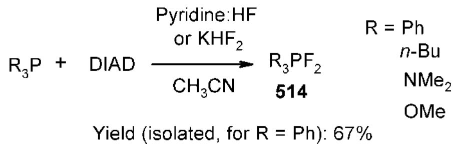
Scheme 149



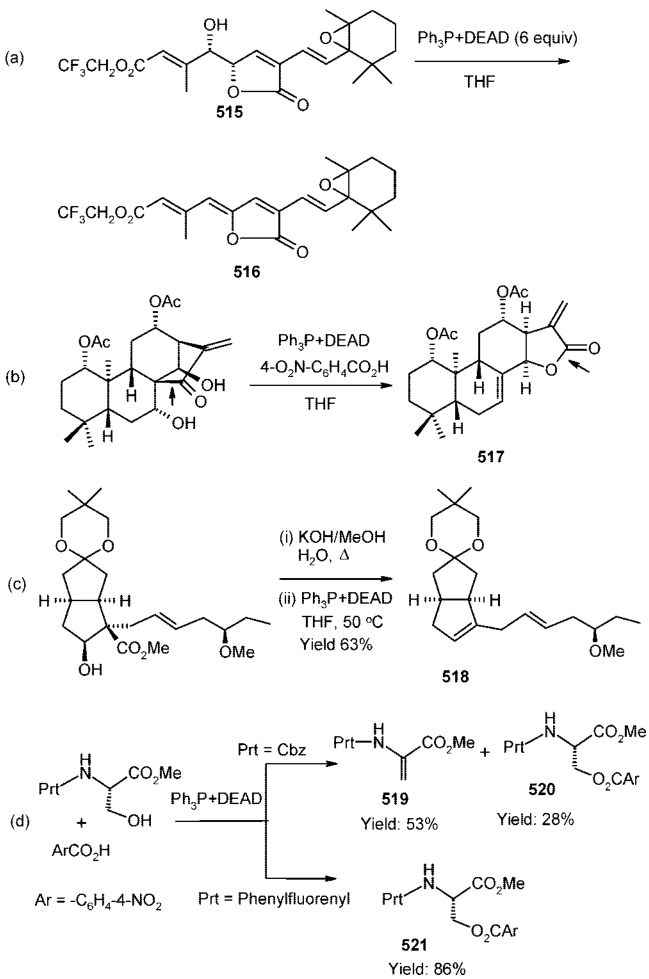
present in the substrate. Products analogous to **509** were observed previously by Liu et al. when ketones were treated with tributylphosphine and dimethyl azodicarboxylate in dichloromethane at room temperature.[1529]

In the reactions of 2-hydroxybenzaldehydes with the Ph_3P−DTBAD combination, derivatives such as hydrazones **511** are formed as major products rather than the expected alkyl aryl ethers (Scheme 149a).[1530] The reaction of diaryl-1,2-diones with Ph_3P−DEAD afforded *N,N*-dicarboethoxy-monohydrazones **512** by a novel *nitrogen to nitrogen migration* of a carboethoxy group (Scheme 149b).[1531] It was proposed that this reaction took place via the MBH betaine **15** and the pentacoordinate intermediate **513**. This reaction may be contrasted with that of Otte et al. and Liu et al. wherein other types of products were obtained with aldehydes, ketones, or keto-esters (cf. Scheme 148 above).[1528,1529]

Scheme 150



Scheme 151



8.7. Synthesis of Fluorophosphoranes

In the presence of pyridine·HF, the difluorophosphoranes, R_3PF_2 (**514**) [R = Ph, *n*-Bu, Me_2N, MeO] have been isolated. These compounds are quite stable and can be isolated in good yields by using sonication (Scheme 150).[1532]

8.8. Alcohol Dehydration

In the synthesis of butenolactone **516**, Schmidt-Leithoff and Brückner used the Mitsunobu dehydration of alcohol **515** (Scheme 151a).[1533] The driving force here was perhaps the extended conjugation in the product. An analogous water elimination reaction leading to butenolides has also been reported by O'Doherty and co-workers.[1534] Such dehydration (followed by ring closure) has been elegantly utilized by Greshock and Williams in the total synthesis of complex alkaloids such as stephacidin A.[1535] An unusual dehydration/rearrangement is observed in the Mitsunobu reaction involving kaurene derivatives which was reported by Takeya and co-workers (Scheme 151b).[1536] It may be noted that dehydration occurred in one of the six-membered rings, but the five-membered ring present in the final compound was different from what was there in the precursor. The best result (yield 58%) was obtained with 2.2 equiv of DEAD, a 0.0058 M concentration of the substrate, and 2.4 equiv of 4-nitrobenzoic acid as a proton source under reflux for 1 h. The bonds that were cleaved/formed are shown by an arrow in the drawing. Compound **517** was characterized by X-ray crystallography. A dehydrative decarboxylation route was used in the preparation of isomers of the anti-androgen cyoctol **518** by Mulzer et al. (Scheme 151c).[1537] Ollp and Brückner have utilized antiselective dehydration of γ-(α-hydroxyalkyl)-butenolides under Mitsunobu conditions to obtain γ-alkylidenebutenolides.[1538] A large scale synthesis of optically pure *trans*-(+)-sobrerol by dehydration was reported by Wang et al.[1539] *N*-Protected serine methyl esters underwent ready β-elimination rather than azidation with HN_3 under Mitsunobu conditions.[1540] Nitro derivatives of nitrilotriacetic acid and ethylenediaminetetraacetic acid were prepared by dehydration of serine derivatives, and subsequent conjugate addition of nitromethane was presented by Meunier et al.[1541] As shown in Scheme 151d, protective groups have a role to suppress the side reactions (like elimination, cf. compound **519**) while synthesizing serine derivatives (e.g. **521**).[1542] Kobayashi and co-workers have utilized alcohol dehydration as well as Mitsunobu inversion in the total synthesis of khafrefungin.[137]

8.9. Some Unusual Reactions

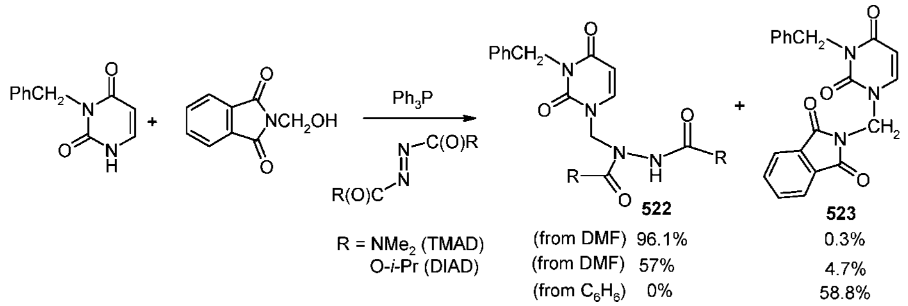
N[3]-Benzyluracil when treated with *N*-hydroxymethylphthalimide in the presence of the Mitsunobu reagent gave an unusual product **522**, bearing a hydrazylmethyl group and or the condensate **523** (Scheme 152),[1543] particularly when TMAD (*N*,*N*,*N'*,*N'*-tetramethylazodicarboxamide) was used in place of DIAD. If the expected Mitsunobu reaction is not feasible due to steric or other reasons, the DEAD may get attached to the acid RC(O)OH to lead to a derivative of the type RC(O)-O-N(CO_2Et)-NH(CO_2Et).[1544]

The reaction shown in Scheme 153 is a bit peculiar in the sense that a *dehydrogenation* rather than a *dehydration* has occurred to lead to the product **524** (25% yield).[1545] The same product was obtained via oxidation of the precursor with lead tetraacetate. The formation of **524** is almost certainly a result of MBH betaine-catalyzed cyclization followed by aerial oxidation during workup. Another interesting reaction is the *in situ* quantitative formation of triphenylphosphinimines from polymer bound 2-aminobenzimidazoles and Ph_3P−DEAD reported by Houghten and co-workers, wherein a simple dehydrogenation had taken place.[1546]

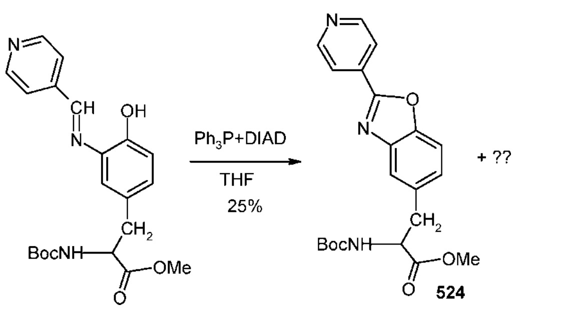
3-Aminofuran-2-carboxylate esters (e.g. **525**, Scheme 154a) were readily synthesized via the reaction of an α-cyanoketone with ethyl glyoxylate followed by treatment of the vinyl ether so obtained with NaH.[1547] In the first step, a tautomeric $-CH_2-C{=}O$ to $-CH{=}C(OH)$ shift of the proton may be envisaged prior to the product formation. This method, however, is limited to the synthesis of 5-alkyl-, 5-aryl-, and 4,5-fused bicyclic furans. In another reaction involving the synthesis of a part of the skeleton (**526**, Scheme 154b) of the proteasome inhibitor TMC-95A, a decarboxylative 1,3-elimination step utilizing Mitsunobu conditions was involved and lactonization did not take place.[1548,1549] This reaction is similar to that shown in Scheme 151c for the formation of **518**.

Evans and co-workers have reported an unusual skeletal rearrangement (Wagner−Meerwein) of the bicyclo[3.1.1]-heptanol skeleton under standard Mitsunobu conditions

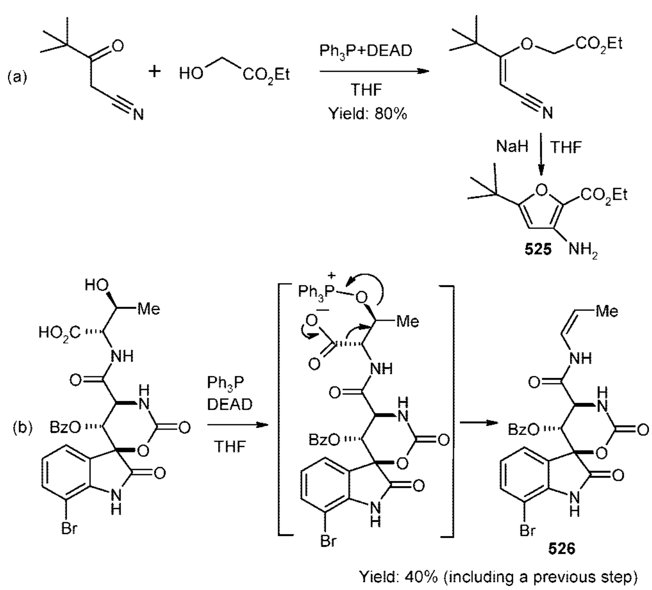
Scheme 152



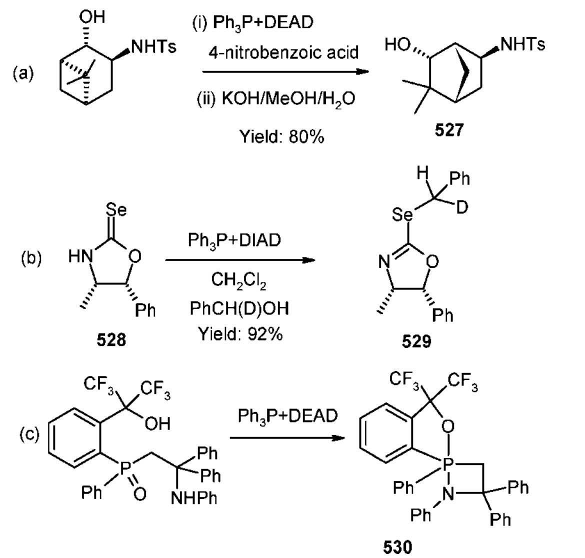
Scheme 153



Scheme 154



Scheme 155



(Scheme 155a).[1550] A possible pathway for the formation of the product **527** has been proposed by the authors. Reaction of D,L-alcohol with the selone (e.g. **528**) chiral derivatizing agent (CDA) via the Mitsunobu reaction has given rise to Se-alkylated adducts (e.g. **529**, Scheme 155b) in yields ranging from 82 to 92%.[1551] Another novel reaction involved intramolecular N−P and O−P bond formation to give the *N*-apical 1,2-λ^5-azaphosphetidine **530** with pentacoordinate phosphorus (Scheme 155c) reported by Kawashima et al.[1552] A very unusual reaction reported by Hanessian and co-workers involved fragmentation of the sugar-like ring in bafilomycin A 1 and isobafilomycin A 1, leading to an olefinic ester.[1553] There is also a report on the *N*-alkylation of sulfamides with alkyl bromides using MBH betaine **15** as a mild base.[1554] Seth and co-workers have developed a solid-phase synthesis of *N*-aryl-*N*′-carboalkoxy guanidines based on Mitsunobu alkylation of resin-bound Fmoc-guanidines with a variety of alcohols.[1555]

8.10. Additional Literature

In addition to what has been discussed in the above sections, a search through *SciFinder* revealed a few more cases wherein the Mitsunobu reaction has been applied. These include the preparation of (i) 2-substituted 2,3-dihydro-4-quinolones by sulfonamide activated *N*-alkylation,[1556] (ii) entecavir,[1557] (iii) cyclic peptolides,[1558] (iv) benzothiadiazine dioxide,[1559] (v) thymine containing pseudopeptides via *N*-alkylation by *o*-Ns activation,[1560](vi) anhydro-nucleosides from cyclization of 6-amino-7H-purine-8(9H)-thione,[1561] (vii) 5-{4-[2-(methyl-*p*-substituted phenylamino)ethoxy]benzyl}-thiazolidine-2,4-diones by *O*-alkylation (ether formation),[1562] (viii) furan containing macrolactones,[1563] (ix) C(1)−C(7) and C(17)−C(28) subunits of didemnaketal A and B, respectively,[1564,1565] (x) prenylflavanones,[1566] (xi) boonein from bisbenzyloxymethyl-substituted bicyclo[2.2.1]ketone,[1567] (xii) pseudo-aminosugars, (+)-valienamine and (+)-validamine,[1568] (xiii) the monomethyl ether of 1,1′-binaphthol as a precursor for poly(meth)acrylates with a pendant 1,1′-binaphthyl group,[1569] (xiv) esters of *syn*-diisopropyl-1-bromo-2-hydroxy-2-(*p*-methoxyphenyl)ethylphosphonate,[1570] (xv) racemic cyclopent-3-en-1-yl nucleoside analogues,[1571] (xvi) pregnane ketols,[1572] (xvii) aminopropyl phosphonate nucleosides with purine and pyrimidine bases,[1573] (xviii) high glass transition polyimides via etherification for NLO applications,[1574] (xix) liquid crystalline aromatic azo compounds (esterification),[1575] (xx) peptide nucleic acid monomers based on *N*-[2-(*tert*-butoxycarbonylaminomethyl)-*trans*-4-hydroxy]-tetrahydropyrrole acetic acid Me ester,[1576] (xxi) chiral liquid crystalline polyacrylates based on L-isoleucine (esterification),[1577] (xxii) 20-hydroxyhepoxilins (inversion/rearrange-

ment),[1578] (xxiii) α-mercaptomethyl amino acids from α-hydroxymethyl amino acids,[1579] (xxiv) β-lactamase hydrolysis resistant penicillin analogues,[1580] (xxv) (3*R*)-2′3′-dihydro-β,β-caroten-3-ol,[1581] (xxvi) deuterium- and tritium-labeled multidrug resistance modulator LY 335979 (etherifcation),[1582] (xxvii) acyl glucuronides of *R*-(−)- and (*S*)-(+)-ibuprofen,[1583] (xxviii) 2,3-dideoxy-2,3-epimino and 3,4-dideoxy-3,4-epimino derivatives of 1,6-anhydro-β-D-hexopyranoses,[1584] (xxix) azaoxamacrobicyclic ligands,[1585] (xxx) tetrahydropyrido[2,1-*b*]quinazolin-11-ones,[1586] (xxxi) reversed imidazole nucleosides,[1587] protected (3-*N*-hydroxyamino-1-alkenyl)phosphonates via BocNHOBoc,[1588] (xxxii) poly(etherimide)s with attached NLO moieties,[1589] *N*-(β-phenethyl)-*N*-triflylvaline (*N*-alkylation),[1590] and (xxxiv) (−)-cladospolide B.[1591]

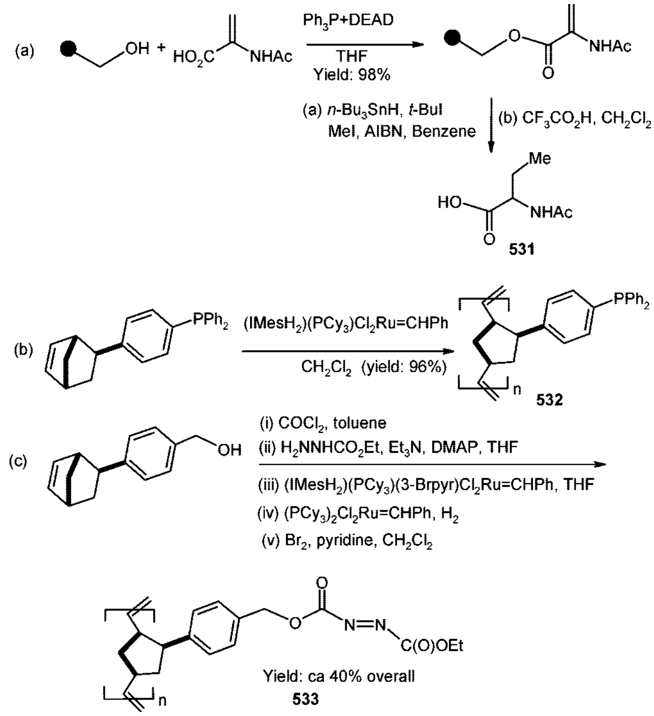
9. Modification of Mitsunobu Protocol

9.1. Polymer Supports in the Mitsunobu Reaction

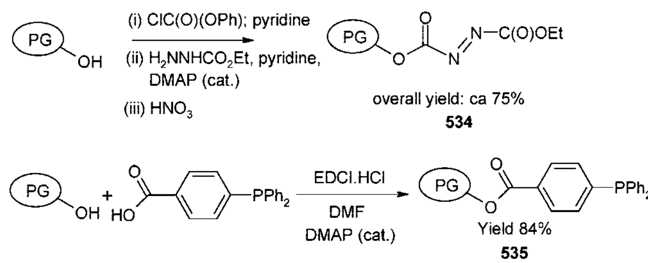
The generation of phosphine oxide and hydrazinecarboxylate as byproducts in the Mitsunobu reaction often haunts the synthetic chemist in the isolation of the desired product. Many efforts have been directed toward modifying triphenylphosphine or azodicarboxylate reagents to facilitate isolation and purification of the products. In this context, three types of separation approaches are established with their own limitations: acidic or basic aqueous workup, postreaction sequestration (solution or solid-phase reaction), and polymer-assisted phase-switching or solid phase immobilization.[32,506,1592−1594] Two excellent reviews, one by Dembinski and the other by Dandapani and Curran, have appeared fairly recently.[33,35] Another review by Nam, Sardari, and Parang gives an overall picture of solid-supported reagents.[32] This section primarily deals with polymer-supported reagents/reactions; several reports are already covered under different sections above. The use of polystyryldiphenylphosphine resin (used in excess) can circumvent the problem of removal of Ph_3PO because the resulting oxide is also anchored to the polymer and thus can be readily filtered off. Reduction of the oxide back to reusable resin can be effected by treating it with trichlorosilane.[1592] Polymer-supported triphenylphosphine prepared from brompolystyrene (bead size up to 600 nm) has also been utilized for esterification reactions.[1595,1596]

Esterification may be conveniently performed on the Wang resin-based solid phase, which may anchor either the reagents or the substrates. This method has been utilized for the preparation of substituted amino acids wherein the -COOH end of the amino acid is first protected by Mitsunobu esterification using a polymer-supported alcohol (Scheme 156a).[1597,1598] In general, only one of the reagents, phosphine or azodicarboxylate, is polymer bound in most of the applications because of solubility problems. The polymer-supported reagents **532**−**533** are soluble in THF but insoluble in ethyl acetate. The byproducts are also insoluble in ethyl acetate, making the separation process much easier (Scheme 156 (b and c)).[1599] Two mole equivalents of each of these reagents were used during the esterification reactions. The authors also reported that their polymer-based phosphine **532** worked better than *JandaJel*-PPh_3 and solid-supported PPh_3 reagents.[1600,1601] A second system wherein both the phosphine and azodicarboxylate are soluble (THF) involves the reagents **534**−**535** (Scheme 157).[1602] Here, the supporting dendritic polymer was prepared by anionic polymerization of glycidol. A chromatography-free protocol in which both the polymeric reagents and byproducts were removed by precipitation cum

Scheme 156



Scheme 157

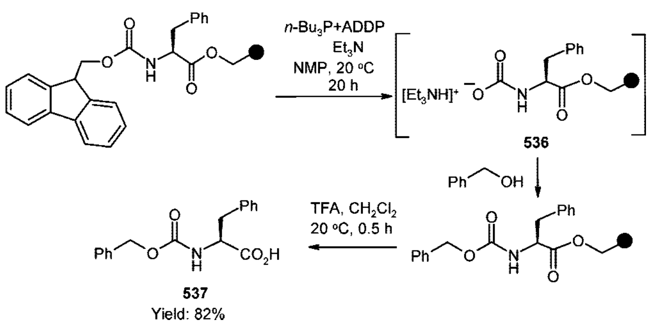


EDCI = *N*-(3-dimethylaminopropyl)-*N*-ethyl-carbodiimide

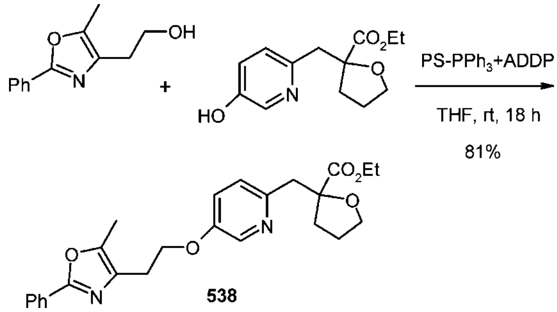
filtration to afford high purity esterified products is reported. In another earlier study, Alexandratos and Miller used benzyldiphenylphosphines derived from copolymers of vinylbenzylchloride and styrene. With an increase in the number of unsubstituted phenyl groups and decreasing the number of ligand sites, the conversion of alcohol to benzylbenzoate ester proceeded better.[1603] They proposed that, in such a system, a nonpolar microenvironment could be used to enhance the reactivity of the intermediates and the rate of product formation. Mitsunobu esterification was also readily conducted (with no interference by other groups present) on a secondary alcohol present in *ortho*-disubstituted polyfunctionalized arene chromium dicarbonyl species immobilized onto a solid support, as demonstrated by Rigby and Kondratenko.[1604]

Zaragoza and Stephensen have reported that fmoc-protected amino acids (e.g. phenyl alanine, proline) esterified with Wang resin (1% cross-linked polystyrene with Wang linker) reacted with aliphatic alcohols in the presence of n-Bu_3P−ADDP/i-Pr_2NEt (or Et_3N) to yield *O*-alkyl carbamates (cf. Scheme 158) that are suitable for robotic synthesizers.[1605] Here the substrate, but not the reagents, was polymer-bound. The authors proposed that the reaction proceeded via *O*-alkylation of an intermediate carbamate anion **536**. They also noted that primary alcohols gave good results, but yields using secondary alcohols were not satisfactory. Tertiary

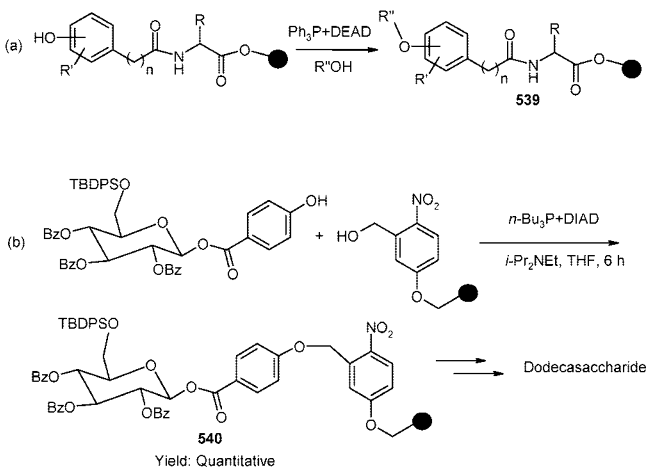
Scheme 158



Scheme 159



Scheme 160



benzylamines could be synthesized readily by first converting the amines to the corresponding ammonium iodides.[1606]

Peroxisome proliferator-activated receptors (PPARs) have great potential as pharmaceutical targets for many applications. In a preliminary communication, Humphries et al. have disclosed a method for the synthesis of PPAR agonists (e.g. **538**) using the PS−PPh_3−ADDP reagent system (Scheme 159).[1607] Here, when DEAD was used in place of ADDP, unwanted substituted hydrazine products were also obtained.

Aromatic hydroxy acids, Ac-Tyr-OH and *N*-(4-hydroxybenzoyl)glycine, were attached to a polymeric solid support, and the phenolic hydroxy groups reacted with a variety of primary and secondary alcohols under Mitsunobu conditions (Ph_3P−DEAD) in THF to give the ethers **539** (Scheme 160a).[1608] One more report by the same group also relates to polymer-bound ethers;[1609] the "one bead−one compound mix and split strategy" was adapted to combine 20 natural amino acids, 10 aromatic hydroxy acids, and 21 alcohols in the library of 4200 products. Nicolaou and co-workers have also utilized a polymeric backbone for the synthesis of a dodecasaccharide (cf. **540**, Scheme 160b) using the Mitsunobu protocol as a primary step.[1610] Use of an additional base (*i*-Pr_2NEt) perhaps had helped in enhancing the yield in this case.

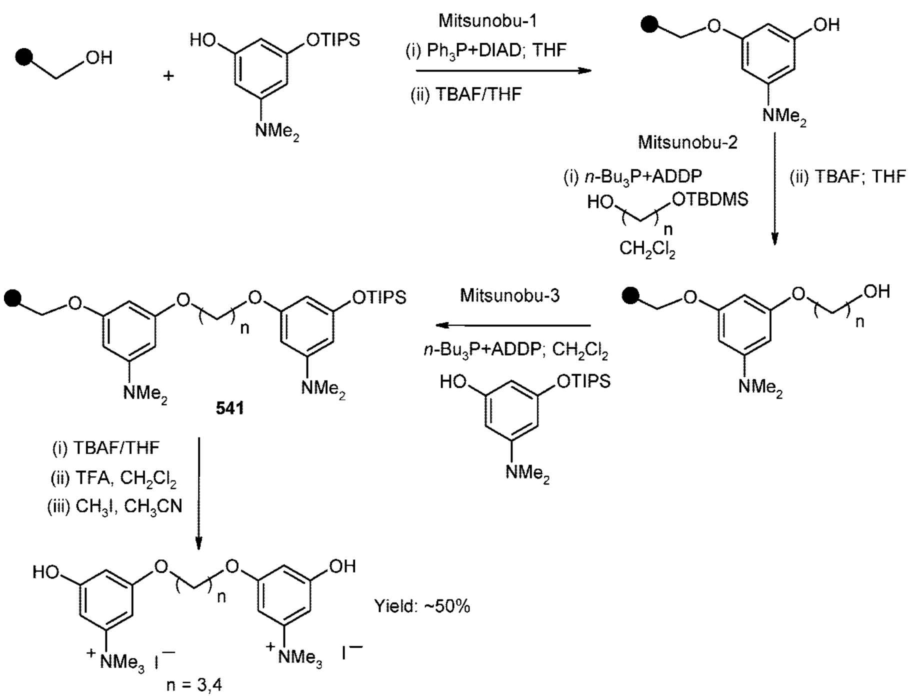
A solid phase synthesis of a number of monoamino and diamino derivatives as potential dual binding site AChE inhibitors was developed by Leonetti et al. (Scheme 161).[1611] The first Mitsunobu reaction was efficiently carried out with Ph_3P−DIAD in THF, whereas the two subsequent reactions, allowing the introduction of an aliphatic spacer linked to a second phenolic moiety and leading to **541**, were more efficiently performed using *n*-Bu_3P−ADDP in CH_2Cl_2. A high-loading soluble star-polymer based on a cyclophosphazene skeleton has been prepared by Reed and Janda.[1612] They have also demonstrated its use in the synthesis of alkyl-aryl ethers. Synthesis of a soluble poly(ethylene glycol)-supported triphenylphosphine conjugate and its utility in the production of alkyl-aryl ethers were also reported earlier by the same group.[1613] The yields were nearly the same as those using the PS-PPh_3 system in most cases.

Although 3-hydroxypyridazine exists predominantly in the oxo form, it does undergo Mitsunobu coupling with polymer bound benzyl alcohols as shown by Salives et al. (Scheme 162).[530] Both the *O*-alkylated (**542**) and the *N*-alkylated (**543**) products [ratio 2:3] were obtained. With an excess of hydroxypyridazine, complete alkylation of the resin-bound alcohol was achieved in 5 h; use of DEAD in place of DIAD reduced the time required to 2 h. In a different report, an interesting concept based on ionic resin-based purification combined with simultaneous cleavage of the protecting group was recently implemented by Meier and Müller.[1614] After the normal Mitsunobu etherification reaction, the products (e.g. **544**) were caught by adding the ionic resin Bondesil SCX, formic acid, water, and methanol and shaking this mixture for 3 days at room temperature. Subsequent washing with MeOH−toluene and MeOH−water followed by treatment with NH_3−MeOH afforded the products in 79−84% yield.

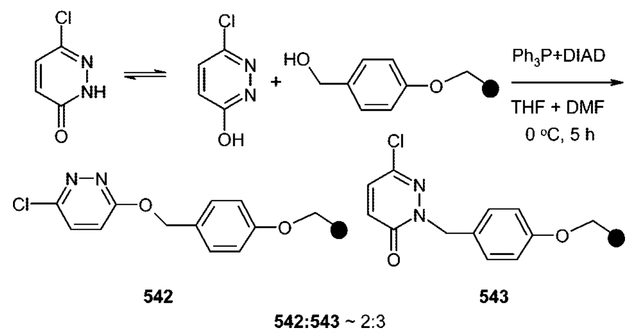
Barrett et al. achieved a chromatography-free Mitsunobu reaction of an alcohol with a carboxylic acid or phthalimide using PS-PPh_3 and bis(5-norbornenyl-2-methyl) azodicarboxylate (DNAD) (Scheme 163).[1593] The purity of the product **545** so obtained was ∼90%. A library of substituted amines, ethers, and esters was readily obtained using a PS−PPh_3−DTBAD reagent system and without using chromatography, by Pelletier and Kincaid.[1594] Recently, a polymer-bound azodicarboxylate and anthracene tagged phosphine for the Mitsunobu reaction leading to phthalimides, esters, as well as ethers has been reported by Lan et al.[1615] The authors pointed out that the azodicarboxylate and its corresponding hydrazine product could be readily separated from the desired products by simple filtration.

The coupling of *N*-Boc-L-tyrosine methyl ester with hydroxymethyl polystyrene resin proceeded in practically quantitative yield in the presence of a tertiary amine under Mitsunobu conditions.[1616] The polymer bound iminodicarbonate (**546**), prepared by the reaction of Wang resin with *N*-(chlorocarbonyl)isocyanate and *tert*-butyl alcohol, acted as a new ammonia equivalent for solid-phase synthesis of primary amines **547** (Scheme 164a).[1617] Oxime resin supports have been useful in the synthesis of sulfahydantoins. The precursors **548** for these sulfahydantoins were prepared by using Mitsunobu *N*-alkylation (Scheme 164b). It may be noted that the *N*-alkylation occurred only at one of the available nitrogen sites.[1618]

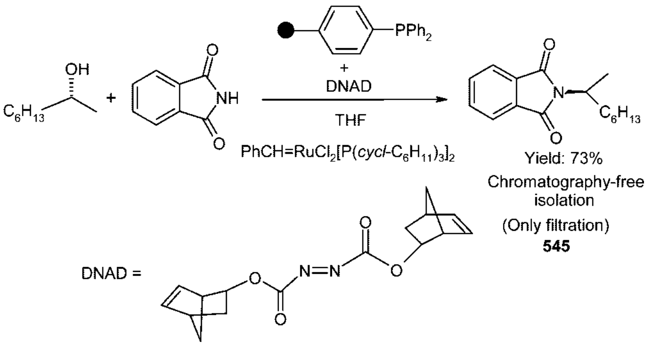
Scheme 161



Scheme 162



Scheme 163



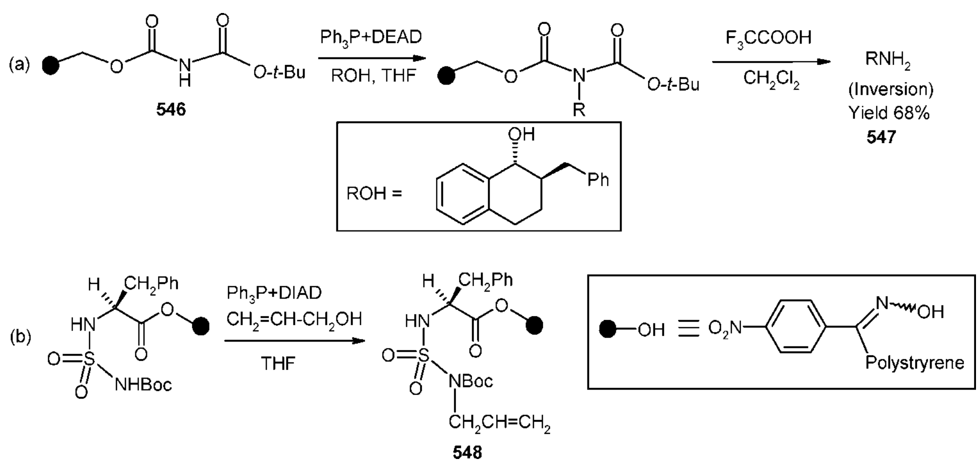
The polymer bound versatile amine releasing *N*-Boc-*o*-nitrobenzenesulfonamide (Boc-ONBS) **549** has been employed in the synthesis of primary and secondary amines by sequential substitution of the sulfonamide moiety using the Mitsunobu reaction.[1619] A large number of amines were prepared by using this linker. Thus, in Scheme 165, step (a) led to (poly)-$ArSO_2N(CH_2CH_2$-2-Np)Boc and then to (poly)-$ArSO_2NH(CH_2CH_2$-2-Np), which in step (b) underwent further alkylation with 4-O_2N-$C_6H_4CH_2OH$ followed by cleavage of the N−S bond to lead to the product **550**. In step (a), instead of removing the Boc group, the sulfonamide group could also be cleaved, which expanded the scope of the reaction further. Alternatively, removal of both the Boc and sulfonamide groups after the first *N*-alkylation led to primary amines. In a different study, Falkiewicz has shown the utility of Merrifield resin-bound *o*-nitrobenzenesulfonylglycine in the synthesis of peptide nucleic acids (PNAs) containing a reduced peptide bond, that involved similar *N*-alkylation.[1620] For subsequent cleavage of the N−S bond, a thiophenol−DBU combination was utilized.

Flynn, Hanson, and their co-workers have developed a capture-ring-opening metathesis polymerization-release (capture-ROMP-release) method for obtaining pure amines and alkylhydrazines and for ring-closing metathesis;[1621,1622] the same methodology was applied to the synthesis of *O*-alkylhydroxylamines using a chromatography-free protocol.[1623] The type of polymer system used in this work has been discussed above (cf. Scheme 156b and c).[1599] Recently, solid phase synthesis of optically pure *N*-aminodipeptide derivatives using a solid-supported α-hydroxy acid and a free phthaloylated α-*Z*-*N*-aminohydrazide has been reported by Jamart-Grégoire and co-workers.[1624]

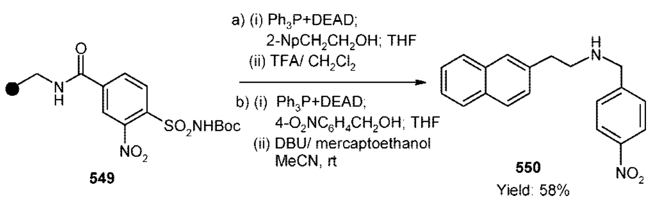
9.2. Other Modified Reagent Systems (Including Fluorous Reagents)

In one study, Jackson and Routledge tagged crown ethers to phosphines and used the resulting compounds (e.g. **551**) for Mitsunobu etherification.[1625] The purification was effected by post-reaction sequestration onto an ammonium functionalized ArgoPore resin. The yield in the reaction of 7-hydroxycoumarin with benzyl alcohol to lead to 7-benzyloxycoumarin was comparable to that using Ph_3P. In another study, Yoakim et al. reported that the use of 4-(diphenylphosphinyl)benzoic acid 2-(trimethylsilyl)ethyl ester [DPPBE, **552**, δ(P) −7.1] greatly facilitated isolation of the desired etherification products.[1626,1627] The ester linkage on the phosphine reagent was cleaved by tetrabutylammonium fluoride or with trifluoroacetic acid/CH_2Cl_2. A subsequent aqueous base wash greatly facilitated the purification of the product. The authors also reported the ^{31}P NMR spectrum

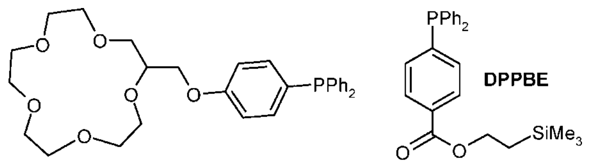
Scheme 164



Scheme 165



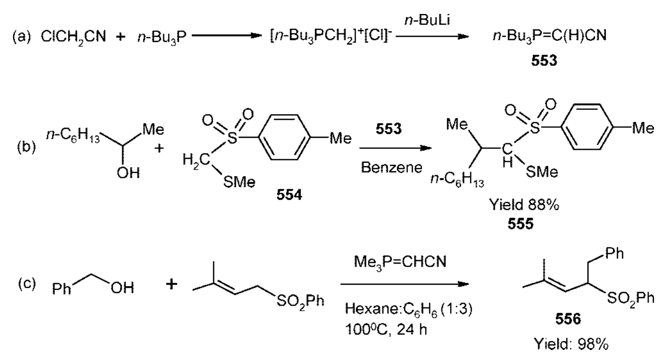
of the corresponding MBH betaine [δ(P) −41.1] that was formed after the addition of DIAD to the phosphine.



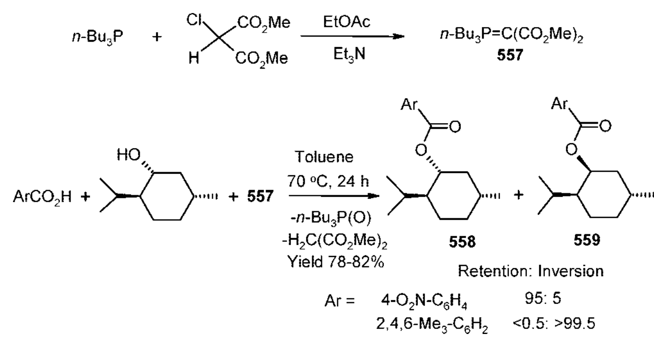
551 552

In contrast to other esterifications, for benzoylation, the Ph_3P-benzoyl peroxide combination also works well, and it may actually be advantageous, since the hydrazine byproduct is avoided.[99,300] While this reaction conducted in DMF using L-menthol as the substrate led to retention, the presence of an additional bulky amine such as *tert*-butylamine favored the inverted product.[99] Another useful system is the cyanomethylene-tri-*n*-butylphosphorane **553** (CMBP), developed by Tsunoda and co-workers, which can be considered to be an equivalent of *n*-Bu_3P−DEAD.[34,57−64,1628] It is prepared by starting with chloroacetonitrile and tributylphosphine. This reagent has been utilized for C−C bond formation even with nucleophiles with pK_a > 20 to give compounds of type **555**. The substrate **554** has a pK_a = 23.4 in DMSO, but the reaction still worked well (Scheme 166a,b).[61,62] It is possible to utilize this reagent in coupling reactions involving unprotected *p*-toluenesulfonamide also. The corresponding methyl analogue cyanomethylenetrimethylphosphorane (Me_3P=CHCN, CMMP) is another valuable reagent.[58,63] The only handicap is that this reagent is sensitive to air and moisture, and hence, care has to be exercised in handling. It has been used in the alkylation of primary and secondary alcohols with prenyl and geranyl phenyl sulfone (Scheme 166c, cf. compound **556**).[1629] Excellent yields of the products were obtained. This reagent and geranyl phenyl sulfone were also utilized for the preparation of norfaranal, an analogue of the pheromone produced by Pharaoh's ant. Earlier, CMMP mediated one pot cyanation of alcohols and efficient alkylation of primary and secondary alcohols with arylmethyl phenyl sulfones were reported by the same group.[1470,1630]

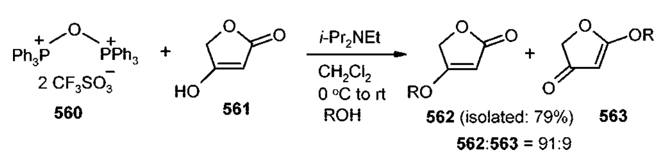
Scheme 166



Scheme 167



Scheme 168

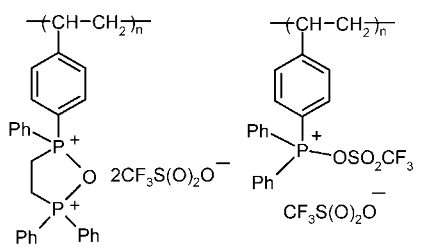


Another alternative to using Ph_3P−DEAD is dimethylmalonyltributylphosphorane (DMTP, **557**) [δ(P) 27.8].[98] This compound can be readily prepared by the reaction of *n*-Bu_3P with dimethyl-2-chloromalonate. It is stable at room temperature under an argon atmosphere. Most of the side products in the esterification, tributylphosphine oxide and dimethylmalonate, can be removed by aqueous base partitioning (0.2 M Na_2CO_3), which simplifies the purification. More importantly, in the esterification of L-menthol, stereochemistry with retention/inversion varied depending on the

acid. Thus, while 4-nitrobenzoic acid gave a 95:5 ratio in favor of retention, 2,4,6-trimethylbenzoic acid gave a 0.5:99.5 ratio in favor of the inverted product (**559**, Scheme 167). The results were rationalized by invoking an alkoxyphosphonium species for inversion and an acyloxyphosphonium intermediate for retention similar to that proposed in normal Mitsunobu esterification.

It can be noted that, in the Mitsunobu reaction, an intermediate alkoxyphosphonium salt (cf. species **18**, Scheme 6) is involved in most of the reactions. Thus, one can think of using phosphonium ions $[R_3POPR_3]^+$ in Mitsunobu type reactions. Hendrickson's reagent $[Ph_3POPPh_3]^{2+}[CF_3SO_3^-]_2$ (**560**) is a compound of that type.[1631] *O*-Alkylation of tetronic acids **561** leading to **562**−**563** was done very efficiently using this reagent (Scheme 168).[1632] The normal Mitsunobu reaction afforded only a hydrazine-substituted product of tetronic acid.

Jenkins and co-workers have developed analogous polymer-supported coupling/dehydrating agents **564**−**565**.[1633,1634] Species **565** was especially useful in ester, amide, anhydride, peptide, ether, and nitrile formation reactions, and it gave high yields. More importantly, this material could be readily recovered and reused several times without loss of efficiency because the product phosphine oxide, upon treatment with triflic anhydride, reverted back to **565**. The tedious step of column chromatography was also avoided because the phosphine oxide was bound to the polymer backbone and easily filtered off. Thus, this reagent offers a lot of scope for further work. In the presence of 4-dimethylaminopyridine (DMAP), esterification of secondary alcohols took place with *retention* of configuration as a result of the formation of the triflate salt of acylated DMAP.

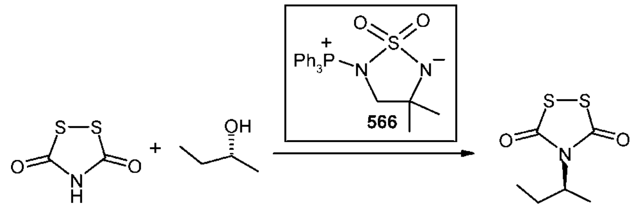


564 **565**

The betaine **566** is another equivalent of the Morrison−Brunn−Huisgen intermediate and can effect Mitsunobu type reactions.[1635] An example of its use in the synthesis of trisubstituted amine **567** is shown in Scheme 169.[1636] The products thus obtained could later be converted to amine derivatives. Dahan and Portnoy have employed compound **566** to obtain poly(aryl benzyl ether) dendrimers on core Wang resin support.[1637] Mukaiyama and co-workers used a reaction of the *in situ* generated $Ph_2P(OR)$ with 1,4-benzoquinone or 2,6-dimethyl-1,4-benzoquinone to obtain an oxophosphonium zwitterion of type $Ph_2P^+(OR)(OAr\text{-}O^-)$ which then reacted with carboxylic acids or phenols to give esters or ethers, respectively.[1638−1641] The reaction worked with tertiary alcohols also. Dialkyl ethers could be obtained in good to high yields *via* fluoranil, alcohols, and alkoxydiphenylphosphine. Likewise, use of Ph_3P/2,4,4,6-tetrabromo-2,5-cyclohexadienone//$Zn(N_3)_2(pyr)_2$ in azidation reactions has also been reported.[1642]

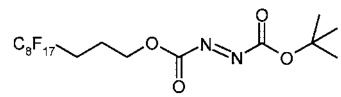
Curran and co-workers have been developing new approaches to circumvent the problem of separation in the Mitsunobu reaction.[35,829,1643−1647] Two new fluorous reagents,

Scheme 169

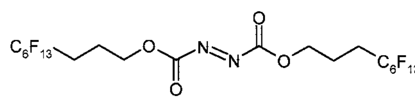


Yield 51% (71% ee)
567

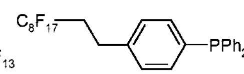
$C_8F_{17}(CH_2)_3O_2CN{=}NCO_2$-*tert*-Bu (F-DEAD-2, **568**) and $C_6F_{13}(CH_2)_3O_2CN{=}NCO_2(CH_2)_3C_6F_{13}$ (F-DEAD-3, **569**), with propylene spacers that help in alleviating the separation problems have been introduced.[1644] These were found to be better than $(C_6F_{13}(CH_2)_2O_2CN{=}NCO_2(CH_2)_2C_6F_{13}$ (F-DEAD-1, **570**) for use with sterically hindered alcohols. They have



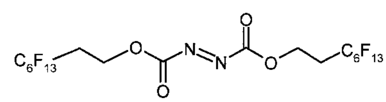
(F-DEAD-2, **568**)



(F-DEAD-3, **569**)



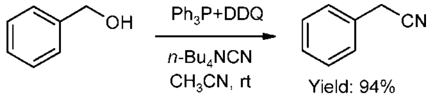
(F-TPP, **571**)



(F-DEAD-1, **570**)

also introduced fluorous phosphine like $C_8F_{17}(CH_2)_2C_6H_4-PPh_2$ (F-TPP, **571**) for use in the Mitsunobu reaction. The byproducts could be separated either by fluorous flash chromatography or fluorous solid-phase separation.[1644,1645] Other useful phosphines introduced by the same research group are $[RfCH_2CH_2-C_6H_4]_2PPh$ [Rf = C_6F_{13} and C_8F_{17}].[1646] A simple chromatography-free fluorous Mitsunobu protocol using a highly fluorinated substituted benzoic acid has also been developed by Dembinski and co-workers.[1648,1649] Dobbs and McGregor-Johnson also have independently developed the fluorous reagent **570** and effectively utilized it in the *O*-alkylation of *N*-hydroxyphthalimide.[1650] Separation of the fluorous byproducts was easily achieved by fluorous liquid extraction, using a perfluoro solvent. Thus, this procedure offered an easy method for the purification of the hydrazine byproduct from the Mitsunobu reaction. Synthetic routes to the reagents **568**−**569**[1644] and **570**[1650] have also been described in detail. For the microwave (MW) assisted esterification of pharmacologically important dihydropyrimidine C^5 acids, Kappe and co-workers employed the fluorous phosphine F-TPP (**571**) and the fluorous azodicarboxylate **569**.[1651] The best conditions were THF as solvent, 1.8 equiv each of the alcohol, F-TPP (**571**), and F-DEAD-3 (**569**), and microwave irradiation at 110 °C for 10 min for a conversion of ∼80% (HPLC). However, it was found that the classical reagent system Ph_3P−DIAD was better than the fluorous one in these cases. Use of the same fluorous phosphine was also reported by Zhang and Lu in the same year for automatic (96 parallel reactions) fluorous solid phase extraction in Mitsunobu esterification/etherification/*N*-alkylation.[1652,1653] In the alkylation of various 2-nitrobenzenesulfonyl-substituted sulfonamides (using PS−PPh_3−DTBAD), use of a fluorous scavenger

Scheme 170



Yield: 94%
572

$C_8F_{17}CH_2CH_2CH_2I$ has been reported by Baslé et al. to facilitate the isolation of amine products.[1654] A nice review by Zhang and Curran on fluorous solid-phase separation has also appeared recently.[1655] The new greener reagent, t-$C_4F_9O(CH_2)_3$-OC(O)-N=N-C(O)O-$(CH_2)_3O$-t-C_4F_9, has also been reported recently by Curran's group.[829]

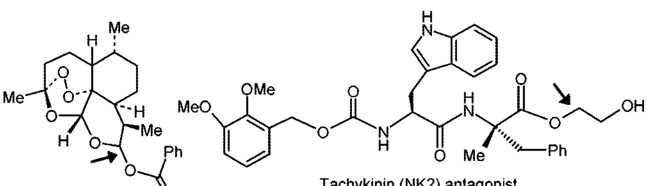
Firouzabadi and co-workers have been looking at alternative systems with phosphine as one of the components.[1656−1658] Thus, they found that 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), when used in place of DEAD for the conversion of an alcohol or a thiol to a cyano compound (e.g. **572**), was quite effective (Scheme 170).[1644] In a competitive reaction, primary alcohols reacted much faster than secondary alcohols. Using a Ph_3P−DDQ combination, it was also possible to convert α-hydroxyphosphonates to α-thiocyanatophosphonates.[1657] Facile conversion of alcohol ethers to bromides could also be effected by the same combination along with a bromide source.[1658] In a different type of reaction, Zhang et al. used n-Bu_3P-ArSeCN to convert an alcoholic −OH to −SeAr (Ar = o-nitrophenyl) group in their synthesis of absinthin.[1659]

10. Patented Literature

A sizable number of patents (>150) subsequent to the year 1996 make use of the Mitsunobu reaction explicitly. Although essentially no new insight into the mechanistic aspects is offered in a majority of cases, the efforts are directed toward the pharmaceutical industry or materials and hence this literature is of practical significance. A large number of applications involve ether formation or N-alkylation reactions. In the presentation below, where multistep syntheses are involved, the connectivity resulting from the Mitsunobu reaction is shown by an arrow for the reader's convenience.

10.1. Esterification

A normal Mitsunobu protocol has been utilized in the synthesis of the artemisinin derivative **573** and the tryptophan amide **574**.[1660,1661] A publication related to dihydroartemisinin has also appeared.[249] While former compound **573** is claimed to be particularly effective for the treatment of malaria and neosporosis, the latter compound **574** is useful as a tachnykinin (NK2) antagonist. Mitsunobu esterification with inversion of configuration at the secondary alcoholic carbon

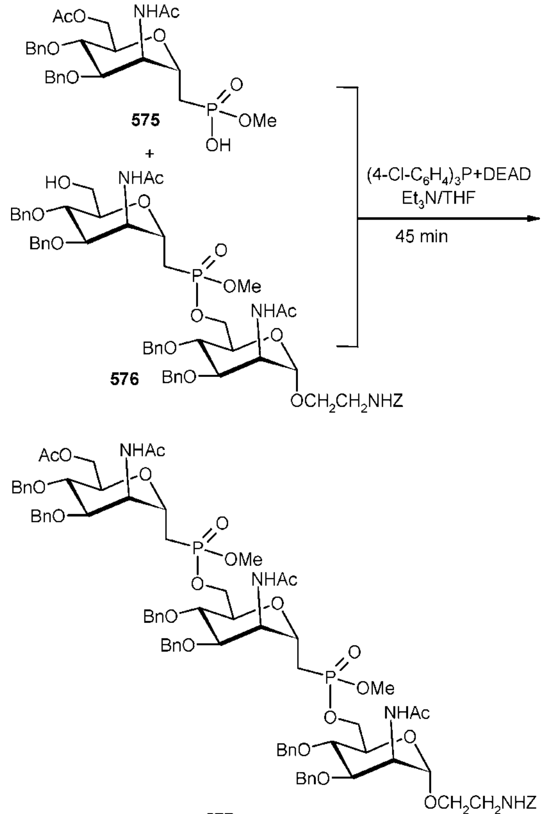


573 Effective against malaria and neosporosis

Tachykinin (NK2) antagonist **574** IC_{50} (for NK2 recptors of hamster urinary bladder membrane): 150 nM

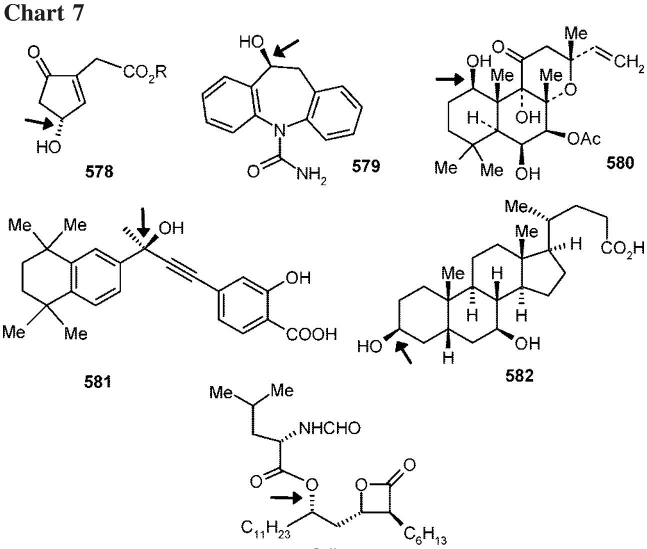
has been employed in the synthesis of losartan (antihypertensive), calanolide (antiviral), and analogues of leucascandrolide A (antitumor active) derivatives.[1662−1664] Pertinent

Scheme 171



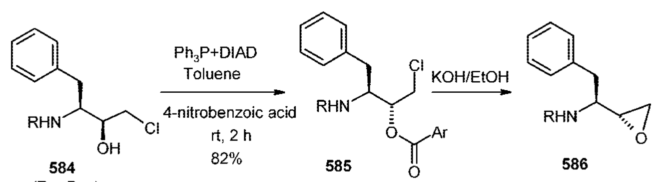
Z = carboxybenzyl
92% yield

Chart 7



578 **579** **580** **581** **582** Orlistat **583**

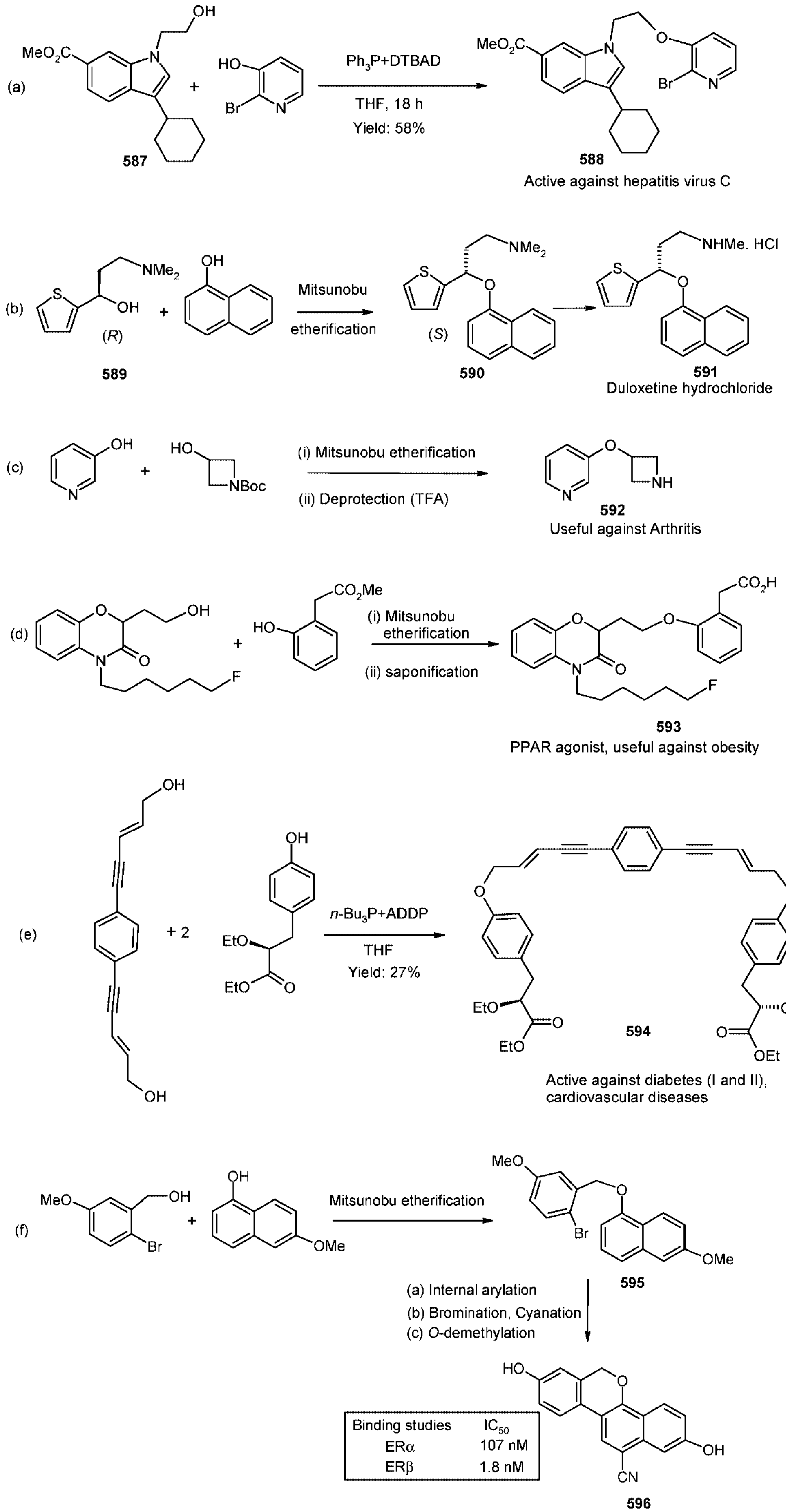
Scheme 172



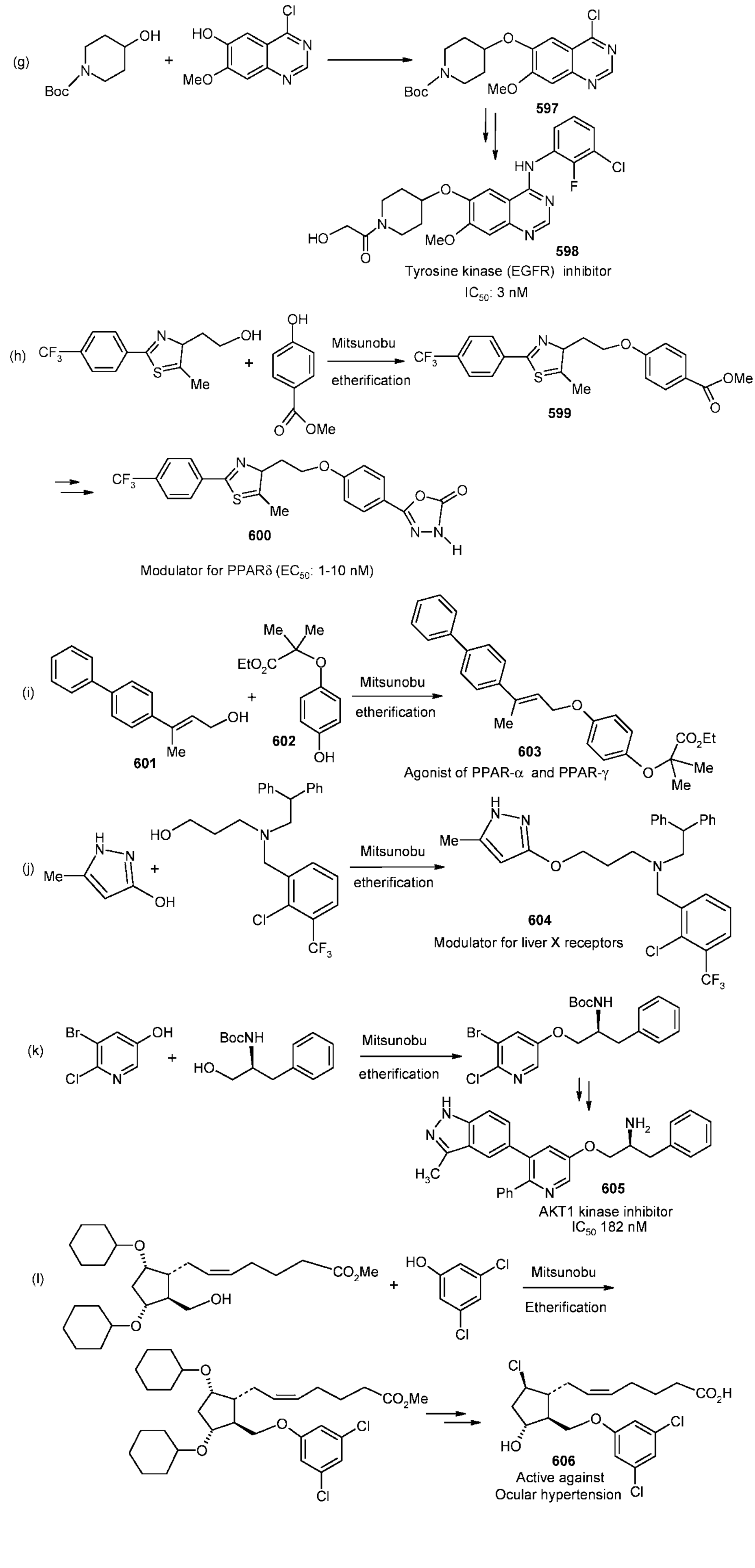
584 (R = Boc) **585** Ar = -C_6H_4-4-NO_2 **586**

publications on leucascandrolide A have been discussed above.[173,174,385−387] In the preparation of oligosaccharides conjugated with proteins, esterification of the phosphonates

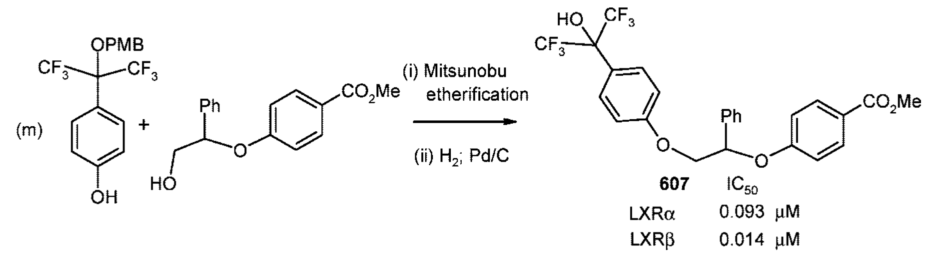
Scheme 173


(a)
587
Ph3P+DTBAD
THF, 18 h
Yield: 58%
588
Active against hepatitis virus C
(b)
589
Mitsunobu
etherification
590
591
Duloxetine hydrochloride
(c)
(i) Mitsunobu etherification
(ii) Deprotection (TFA)
592
Useful against Arthritis
(d)
(i) Mitsunobu
etherification
(ii) saponification
593
PPAR agonist, useful against obesity
(e)
+ 2
n-Bu3P+ADDP
THF
Yield: 27%
594
Active against diabetes (I and II),
cardiovascular diseases
(f)
Mitsunobu etherification
595
(a) Internal arylation
(b) Bromination, Cyanation
(c) O-demethylation
Binding studies IC50
ERα 107 nM
ERβ 1.8 nM
596

Scheme 173. (Continued)



Scheme 173. (Continued)



was required (Scheme 171).[407,1665] In these cases, it is claimed that the use of tris(4-chlorophenyl)phosphine and a large excess of triethylamine in place of just triphenylphosphine increased the yield to nearly two-fold. Derivatives of the product **577**, after deprotection, were claimed to be useful as Meningitidis A vaccines. Normal esterification was also employed in the synthesis of (i) ethyl 4-cyano-3-hydroxybutyric acid,[1666] (ii) (*S*)-α,4-dimethyl-2-(4-trifluoromethylphenyl)-5-thiazolemethanol,[1667] (iii) intermediates for the preparation of halichondrin B,[1668] (iv) hexahydrofurofuranols,[1669,1670] (v) 12-aryl prostaglandin analogues as antiglaucoma agents,[1671] and (vi) fluorinated polymers and membranes containing a 4-phenolsulfonic acid residue.[1672]

Inversion of configuration at the secondary alcoholic carbon site has been reported in the synthesis of (i) cyclopentenone derivatives **578** (intermediates for prostaglandins),[1673] (ii) hydroxydibenzazepinecarboxamides **579**,[1674] (iii) epicoleonol **580**,[1675] (iv) (*R*)-propargylic alcohol **581**,[1676] (v) isoursodeoxychloic acid **582** (a bile acid),[1677] (vi) orlistat **583** (a drug designed to treat obesity),[1678] (vii) dehydroepiandrosterone derivatives for use in cosmetics,[1679] (viii) chiral propargylic alcohol and ester intermediates of himbacine analogues,[1680] (ix) paclitaxel, docetaxel, and taxol (partial synthesis),[1681,1682] (x) hydroxyvitamin D,[131,1683] and (xi) *trans*-(+)-sobrerol.[1684] The structures of compounds **578**−**583** are shown in Chart 7. It is interesting to note that isoursodeoxychloic acid **582** is almost completely converted back to its epimer, ursodeoxychloic acid, in rat livers. Orlistat **583** is claimed to be useful against type II diabetes. With a halide (X) present as C*(OH)-CH_2X, a convenient route to optically pure epoxides **586** has been developed as shown in Scheme 172.[1685] Some details on the esterification of thiophosphate salts which were patented earlier are now published and have been discussed already.[459,1686]

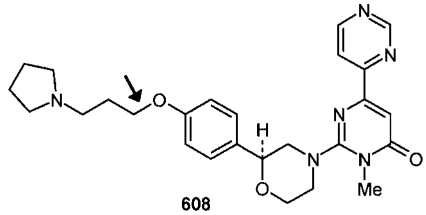
10.2. Ether Formation

10.2.1. Etherification without Cyclization

Numerous reports on etherification on pharmaceutically important compounds exist in the patented literature. The indole carboxylic acid derivatives **588** that are active against hepatitis C virus have been prepared in decent yields (Scheme 173a) with the use of DTBAD in place of the usual DEAD or DIAD.[1687] The thienyl derivative **590**, an intermediate in the synthesis of duloxetine hydrochloride **591** (cymbalta; used for major depressive disorder), was prepared by starting with the appropriate chiral secondary alcohol and 1-naphthol (Scheme 173b).[1688] This method had the advantage that no racemic product was formed. The pyridyl ethers **592**, that are useful in the treatment of Alzheimer's disease, memory loss, or dementia and analgesia, have been obtained via pyridinols as shown in Scheme 173c.[1689] The benzooxazinones **593**, that are active as PPARγ agonists/antagonists, have been prepared by Mitsunobu etherification followed by saponification (Scheme 173d).[1690,1691] In an agonist intrinsic activity assay for induction of aP2 mRNA production, compound **593** was reported to give a 64.9-fold increase over control. For the synthesis of the diether **594** (Scheme 173e), even with the stronger reagent system n-Bu_3P-ADPP, the yield was only moderate. However, a large number of applications, that included treatment of type I and II diabetes, cardiovascular diseases including atherosclerosis, and hypercholesterolemia, are claimed for this compound.[1692] In the synthesis of estrogen receptor modulator **596**, Mitsunobu etherification was one of the key steps (Scheme 173f).[1693] Compound **596** bound to ERα and ER*β* human recombinant estrogen receptors in vitro with IC_{50} values of 107 nM and 1.8 nM, respectively. The tyrosine kinase inhibitor piperidyl-quinazoline derivative **598** was prepared using Mitsunobu etherification as a primary step (Scheme 173g).[1694] It showed inhibition against EGFR and erbB2 tyrosine kinases with IC_{50} values of 3 nM and 59 nM, respectively. Compound **600**[1695] showed PPAR*δ* whereas derivative **593** showed PPAR*γ* activity. The PPARα and PPAR*γ* activities are also exhibited by the 1,4-dioxyphenyl ether **603**, which was prepared by reacting the allyl alcohol **601** with the phenol **602** (Scheme 173i).[1696] Looking at the structures of **600** and **603**, it appears that molecular modeling could be of some help to have a more active compound for PPAR activity. Compound **604** is claimed to be useful in the treatment of cardiovascular diseases, atherosclerosis, and inflammation.[1697] Here, the key connectivity with 5-methyl-1H-pyrazol-3-ol was made via Mitsunobu etherification (Scheme 173j). Starting with a pyridinol and protected phenylalaninol, compound **605** has been prepared in several steps (Scheme 173k);[1698] it is claimed to be useful for treating cancer and arthritis. Multisubstituted cyclopentane derivative **606** with an ether linkage to a 2,4-dichlorphenolic residue has been prepared as a therapeutic agent for treating hypertensive conditions. The ether linkage here was provided by a simple Mitsunobu protocol (Scheme 173l).[1699] The trifluoromethyl-substituted phenolic ether **607**, claimed to be useful for treatment of diseases modulated by LXRα and LXR*β* agonists, was prepared in two steps by etherification of the appropriate protected phenol with the required alcohol followed by deprotection (Scheme 173m).[1700]

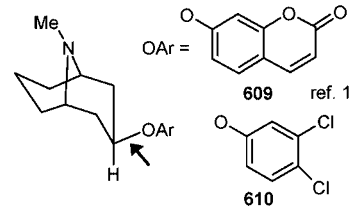
In addition to the above, there are several other pharmaceutically important derivatives wherein Mitsunobu etherification−connectivity played a key role. Chart 8 shows some of these.[1701−1746] The bond at which ether formation is effected is shown by an arrow mark in each case. Wherever possible, the pharmacological activity of the compound is indicated. In the synthesis of **628**, the reaction mixture was treated with $MgCl_2$ and Celite twice and then distilled with isopropanol to remove toluene; no chromatography was used.[1723] The product was claimed to have no detectable $Ph_3P(O)$. For **633**, diphenyl(2-pyridyl)phosphine (**1**) was used in place of Ph_3P.[1728] In the synthetic route given for **638**,

Chart 8



608

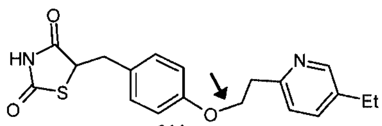
(Active against Alzeimer's disease)
Inhibition of bovine cerebral TPK1
IC_{50} 0.43 nM ref. 1701



609 ref. 1702

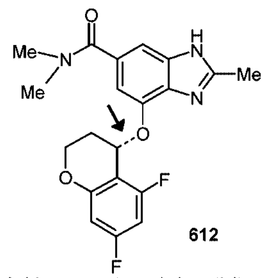
610

Inhibitor of monoamine neurotransmitters
ref. 1703



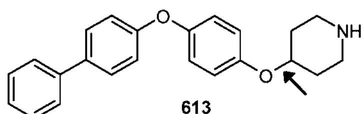
611

Pioglitazone (insulin sensitizing agent)
ref. 1704



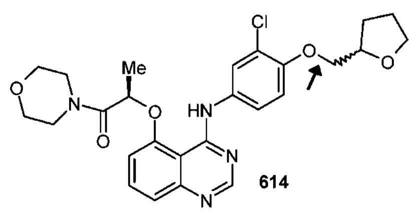
612

Acid pump antagonistic activity
(claimed uses: peptic/gastric/duodenal ulcers
hearburn, hypersalivation etc.)
ref. 1705



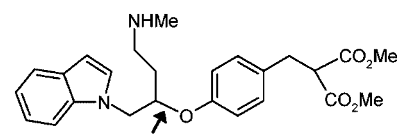
613

(treatment of inflammatory diseases)
ref. 1706



614

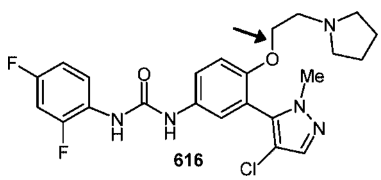
Inhibition of erbB2 receptor tyrosine kinase
ref. 1707



615

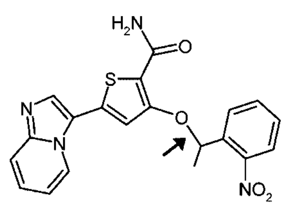
(treatment of type II diabetes)

ref. 1708



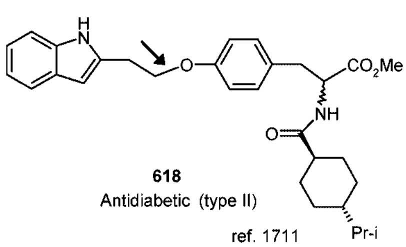
616

Treatment of 5-HT2A mediated disorders
and platelet aggregation related conditions
ref. 1709



617

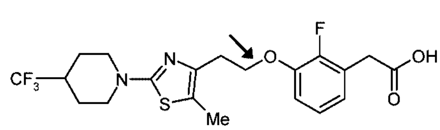
(oncolytic drug)
PLK1 inhibitor/anticancer drug ref. 1710



618

Antidiabetic (type II)

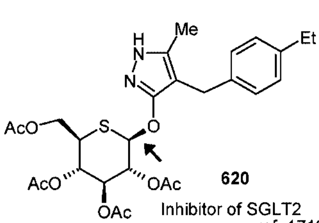
ref. 1711



619

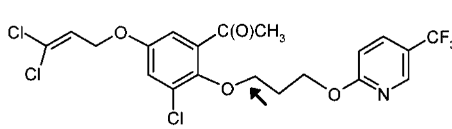
PPARδ agonist (treatment of obesity, hyperlipidemia)

ref. 1712



620

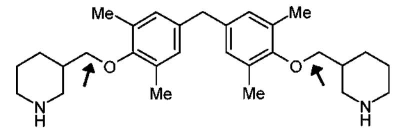
Inhibitor of SGLT2
ref. 1713-1714



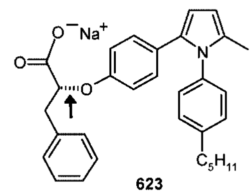
621

Pest control agent ref. 1715

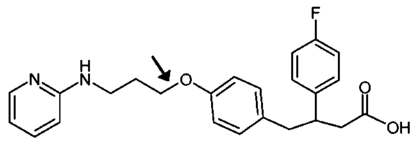
Chart 8. (Continued)



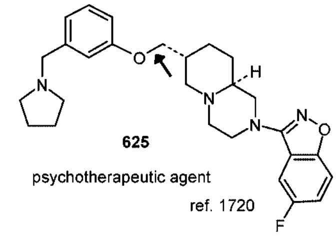
622
sodium channel modulator
ref. 1716



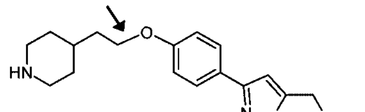
623
Tyrosinase phosphatase inhibitor
(treatment of diabetes)
ref. 1717



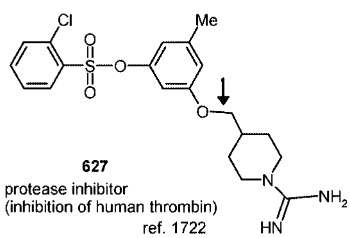
624
claimed uses: treatment of thromboses, tumors, osteoporosis etc.
refs. 1718-1719



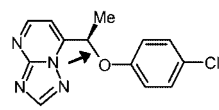
625
psychotherapeutic agent
ref. 1720



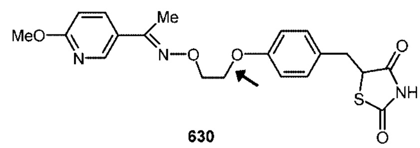
626
Inhibitor of platelet aggregation
ref. 1721



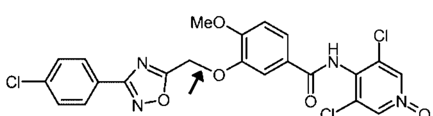
627
protease inhibitor
(inhibition of human thrombin)
ref. 1722



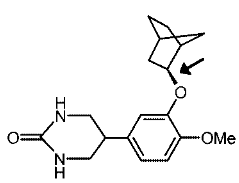
628
Anticonvulsant, neuroprotectant
ref. 1723



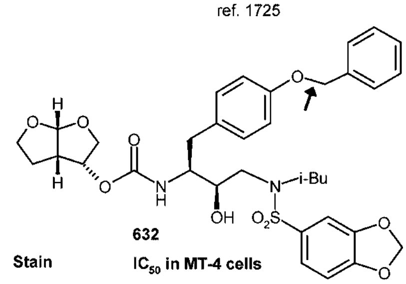
630
Active against hyperlipidemia, obesity, IGT, diabetic complications, fatty liver etc
ref. 1725



629
inhibitor of TNF and PDE IV
ref. 1724



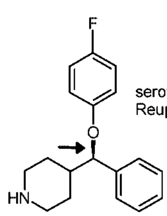
631
antidepressant/antiinflammatory agent
ref. 1726



632

Stain	IC_{50} in MT-4 cells
mutant HIV-1 EP13	<0.001μM
D545701-14 HIV	0.01-0.001μM

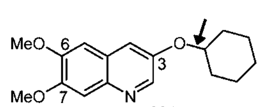
ref. 1727



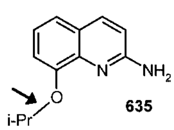
serotonin, noradrenaline and dopamine Reuptake inhibitory activity K_1 values

serotonin	0.45
noradrenaline	111.44
dopamine	821.04

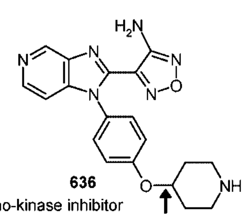
633 ref. 1728



634
Inhibitor of platelet-derived growth factor
ref. 1729

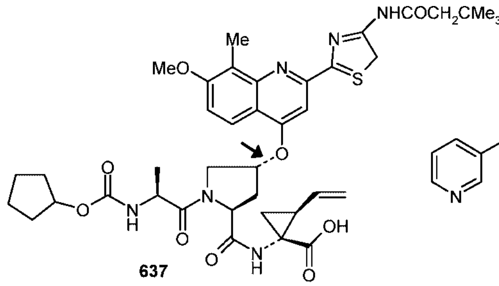


635
claimed utility:
abnormaility in reproduction, sexual behavior,thyroid hormone secretion etc
ref. 1730



636
Rho-kinase inhibitor
ref. 1731

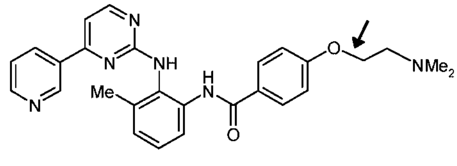
Chart 8. (Continued)



637

Hepatitis C inhibitor

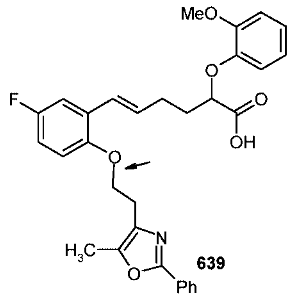
ref. 1732



638

tyrosine kinase inhibitor

ref. 1733

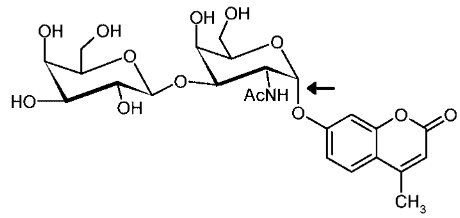


639

PPARγ–Gal4 Activity 5.8 at 10μM

Treatment of dyslipidemia, diabetes etc

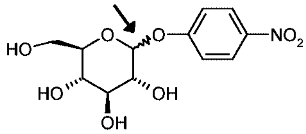
ref. 1734



640

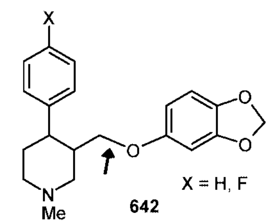
Useful in screening of endo-galactosaminidase by enzyme assays

ref. 1735



Yield 50% using unprotected D-Glucose

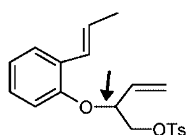
641 ref. 1736



642

(3*S*,4*R*) Yield: 52%

ref. 1737-1738

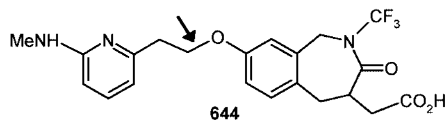


(*R*) **643**

(inversion)

Yield: 64% (97% ee)

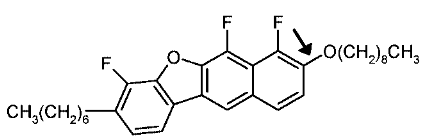
ref. 1739



644

(protected acid in *t*-butyl methyl ether was used)

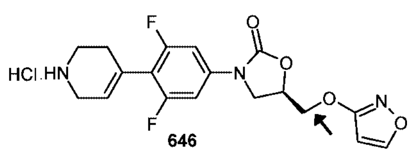
Etherification yield: 56% ref. 1740



645

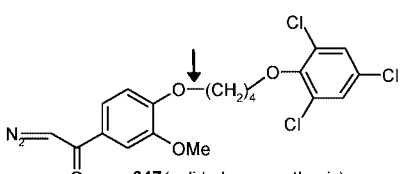
Liquid crystal formulation

ref. 1741



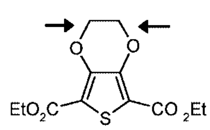
646

ref. 1742



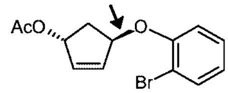
647 (solid phase synthesis)

ref. 1743



648

ref. 1744

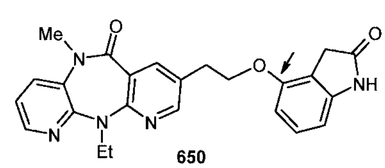


(with inversion)

(used for cycloalkabenzo-furan synthesis)

649

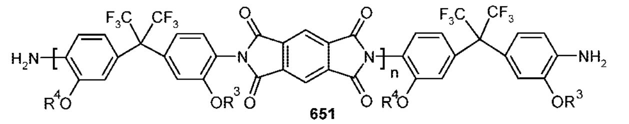
ref. 1745



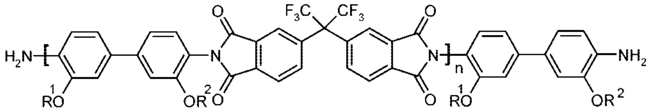
650

Inhibitor against HIV-1RT

ref. 1746



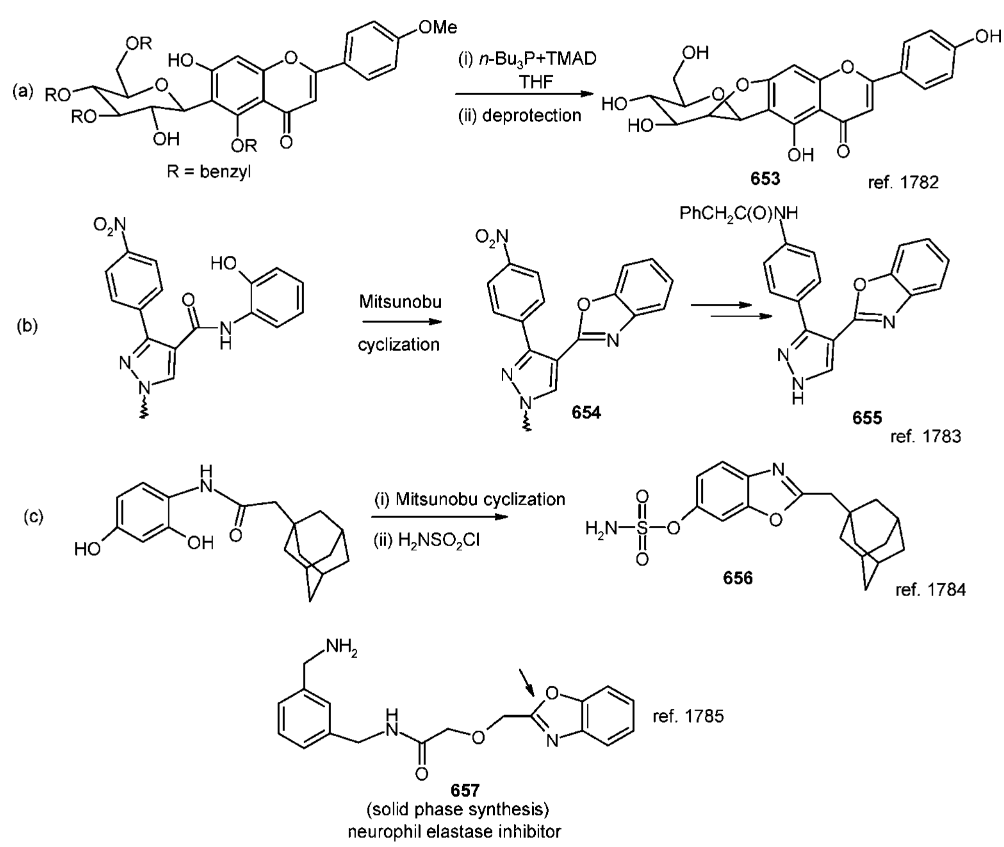
651



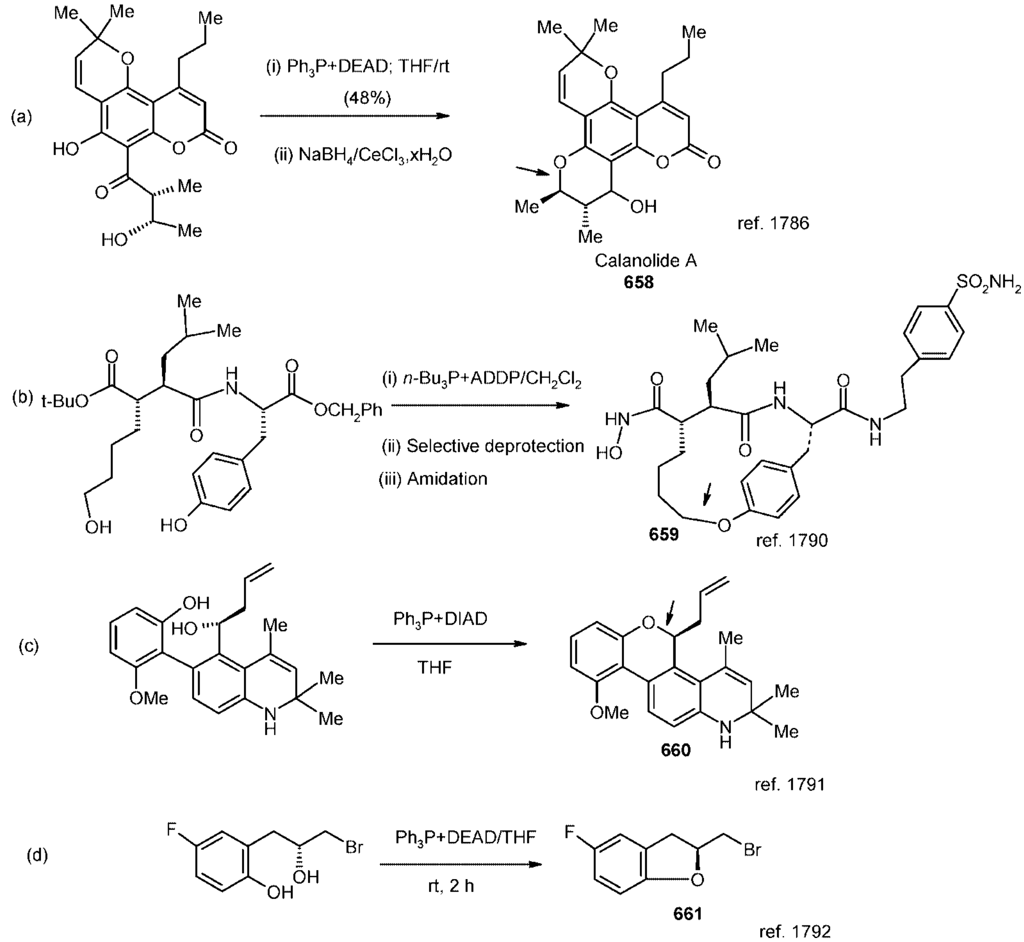
652

the phosphine appears to be missing in the reaction sequence.[1733] In the case of **641**, unprotected D-glucose was used with methyl cyanide as the solvent.[1736] Details on patented compounds of type **648** (compound **236** above, R = R′ = H) have been published as full papers.[755,757] Other patents that make use of the simple Mitsunobu etherification pertain to (i) polyimides from 3,6-dialkyloxypyromellitic dianhydrides,[1747] (ii) 3,3′-bis((4-R-4-stilbenyl)oxyalkyloxy)-biphenyl-4,4′-diamine (R = Cl, CN, etc.) for liquid crystal applications,[1748] (iii) 2,3′-anhydro-5′-*O-tert*-pentanol deoxythymidine,[1749] (iv) antimitotic agents,[1750] (v) 3-indolyl-4-phenyl-1H-pyrrole-2,5-dione derivatives,[1751] (vi) solid support based on selenium useful in solid phase reactions,[1752] (vii) fluoxetine,[1753] (viii) acyclic hydrazides for use as cannabinoid receptor modulators,[1754] (ix) 1H-quinolin-2-one derivatives as antagonists of gonadotropin releasing hormone (GnRH),[1755] (x) indanyloxy-substituted pyridine derivatives and analogues, useful as phosphodiesterase inhibitors,[1756] (xi) benzoxazinone and benzopyrimidinone piperidinyl tocolytic oxytocin receptor antagonists,[1757] (xii) dihalopropene compounds as insecticides/acaricides, and intermediates for their production,[1758] (xiii) cyclic guanidine derivatives for treatment of thromboembolic disorders,[1759] (xiv) tricyclic spiro compounds (5-HT1D receptor antagonists),[1760] (xv) bridged biaromatic and triaromatic ring compounds,[1761] (xvi) heterocyclic ethers as neuronal nicotinic receptor ligands,[1762] (xvii) 5-[(4-piperidinyl)methoxy]-2-indolecarbonyl-2(*S*)-phenylsulfonylamino-*β*-alanine as a fibrinogen receptor antagonist,[1763] (xviii) oxazolylethyltyrosine and oxazolylethoxyarylserine derivatives as hypoglycemic and hypolipidemic agents,[1764] (xix) phenalkyloxy phenyl derivatives for use in conditions associated with insulin resistance,[1765] (xx) aminoindazole derivatives active as kinase inhibitors,[1766] (xxi) 11a-aza-11a-homoerythromycin compounds as antibacterial agents,[1767] (xxii) substituted 3-phenyl-2-alkoxypropanoic acids and analogues as modulators of peroxisome proliferator activated receptors,[1768] (xxiii) phenylalkanoic acid derivatives as preventive or remedial agents for digestive tract diseases,[1769] (xxiv) aza-ring derivatives and their use as monoamine neurotransmitter re-uptake inhibitors,[1770] (xxv) substituted 3-phenylpropionic acid derivatives with PPARα and PPAR*δ* modulatory activities,[1771] (xxvi) 4-substituted pyrrolidine-2-carboxylic acid derivatives,[1772] (xxvii) 3-aryl-3-heteroaryloxy-1-propanamine derivatives useful as serotonin and norepinephrine re-uptake inhibitors,[1773] (xxviii) prolines/proline analogues for preventing neuropathic pain and as acromelic acid analogues/allodynia inducers,[1774,1775] (xxix) triazolyl thiophenecarboxamides as inhibitors of polo-like kinases,[1776] (xxx) retinoid-based polyunsaturated compounds,[1777] (xxxi) oxazoles and thiazoles as PPAR modulators,[1778] and (xxxii) duloxetine (using HF elimination from 1-fluoronaphthalene).[1779] An interesting class of polyimide derivatives, **651**−**652**, useful in nematic liquid crystal devices, with chromophores attached via ether linkages by the Mitsunobu reaction, has also been patented.[1780] Synthesis of a nonlinear optical (NLO) polymer using a similar reaction is also claimed.[1781]

Scheme 174



Scheme 175

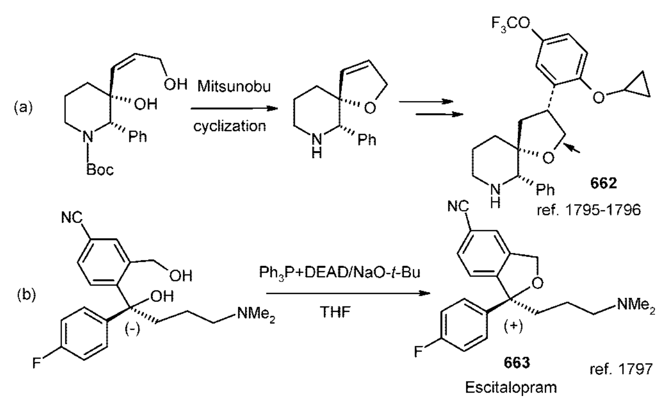


10.2.2. Etherification with Cyclization

The flavone *C*-glycoside, an antiallergy agent, was prepared by a novel cyclization reaction as shown in Scheme 174a;[1782] a related publication has also appeared.[709] A more active reagent system, *n*-Bu_3P−TMAD, was utilized for this purpose. In the cyclization shown in Scheme 174b, tautomerization of NHC(O) to N=C(OH) could precede oxazolyl ring formation. These compounds (e.g. **655**) have been claimed to be good protein kinase inhibitors;[1783] intermediates of type **654** (cf. species **251**) have already been mentioned above.[774] This type of cyclization is quite common, and two more examples, **656**−**657**, are depicted in Scheme 174c.[1784,1785] Compound **656** is an inhibitor of steroid sulfatase and is claimed to be useful against acne, seborrhea, androgen-dependent cancer, inflammatory or autoimmune diseases, etc.[1784]

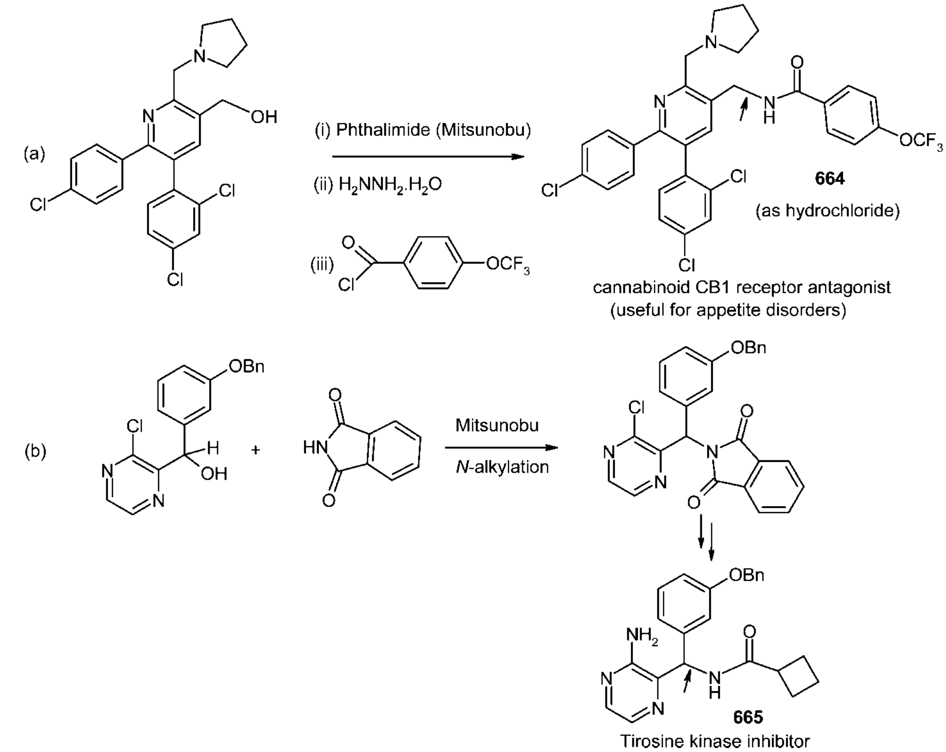
As mentioned above, (+)-calanolide A (**658**) is a potent HIV reverse transcriptase inhibitor. This compound and its analogues have been claimed to be useful in treating tuberculosis. Mitsunobu ether formation cum cyclization prior to reduction of a keto group was one of the key steps in the synthetic strategy, as shown in Scheme 175a;[1786−1789] related work has been published earlier.[732−734] The macrocyclization in the case of **659** was also accomplished by a Mitsunobu etherification as shown in Scheme 175b.[1790] Some of these cyclized peptide derivatives are inhibitors of matrix metalloproteinases and tumor necrosis factor α secretion. Species of type **660** are glucocorticoid receptor agents; their single biaryl atropisomers were readily prepared in high yields with high stereoselectivity via a Mitsunobu procedure (Scheme 175c).[1791] Asymmetric dihydrobenzofuran derivative **661** has been obtained through internal cyclization in good yields (76%) as shown in Scheme 175d.[1792] Derivatives of this compound are claimed to be useful for treating schizophrenia, psychotic disorder, etc. Several indole-based multiring compounds as inhibitors of HCV replication have been prepared recently through a multistep procedure. In some of these, a seven-membered ring containing both nitrogen and oxygen have been generated via Mitsunobu etherification.[1793,1794]

Scheme 176



The cyclization shown in Scheme 176a for the synthesis of NK-1 receptor antagonist **662** is slightly different from previous ones in the sense that no phenolic −OH is involved.[1795,1796] Citalopram and escitalopram (**663**, Scheme 176b) are known active ingredients commonly used for

Scheme 177

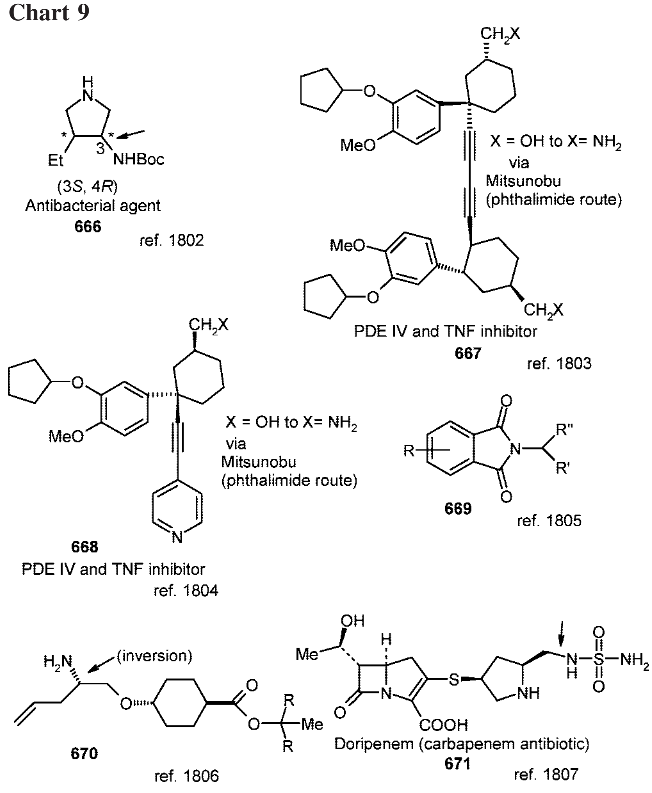


the treatment of depression. Both of these have been prepared via Mitsunobu cyclization.[1797] In particular, it has been claimed that this process is particularly advantageous for escitalopram, since it permits cyclization of the diol with high stereoselectivity. The preferred molar ratio of the phosphine, DEAD, and the substrate was 3:5.3:1 in the presence of the strong base sodium *tert*-butylate with THF as the reaction medium (60% yield). Here also, no phenolic −OH was involved in the cyclization process. Other patents wherein cyclization is involved are (i) NK-1 receptor antagonists for treating sexual dysfunction[1798] and (ii) isoflavan/isoflavene derivatives.[1799]

10.3. *N*-Alkylation

In the synthesis of aminomethylpyridine derivatives (e.g. **664**) that are useful as CB1 receptor antagonists, *N*-alkylation via phthalimide and a benzylic alcohol was utilized (Scheme 177a).[1800] The phthalimide residue was subsequently removed by hydrazine hydrate in most cases. Compound **664** was shown to have very good in vitro affinity for the cannabinoid CB1 receptor, with $IC_{50} \leq 5 \times 10^{-7}$ M, and claimed uses include treatment or prevention of appetite disorders, metabolic disorders, gastrointestinal diseases, inflammatory phenomena, immune system disorders, psychotic disorders, etc. Introduction of nitrogen by means of phthalimide was again a key step in the synthesis of the imidazo-pyrazine **665**, a tyrosine kinase inhibitor (Scheme 177b).[1801] Compounds **666**−**670** have also been synthesized via phthalimide,[1802−1806] but in the case of **671**[1807] the species of interest was the *N*-substituted phthalimide itself (Chart 9). Compound **670** was a precursor to other *trans*-cyclohexane derivatives that were intermediates for VLA-inhibitors.[1806] This method of converting −OH to an $-NH_2$ group was found to be quite convenient and hence was adapted for synthesizing oligoamines that were useful as antineoplastic and anticancer agents.[1808] A synthetic route to ultrabroad-

Chart 9



spectrum injectable antibiotic doripenem **671** involved this inexpensive phthalimide protocol with no necessity for column chromatography purification.[1807]

As discussed in the earlier sections, the amino nitrogen can be activated by having a sulfonyl group attached to it. Thus, optically pure **672** (Scheme 178) has been obtained.[1809] Interestingly, many such sulfonamides themselves are of significant pharmaceutical interest. Chart 10 shows compounds **673**−**678**, wherein *N*-alkylation has been

Scheme 178

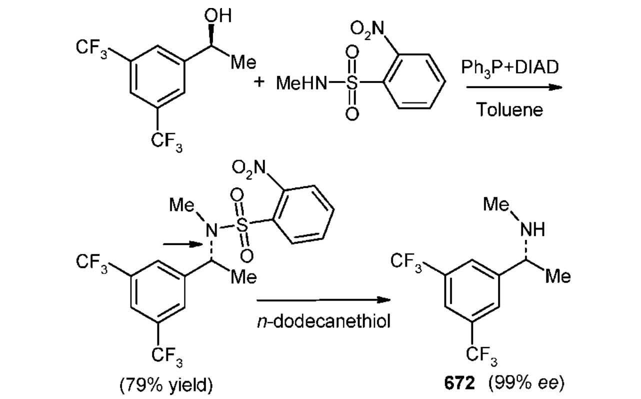
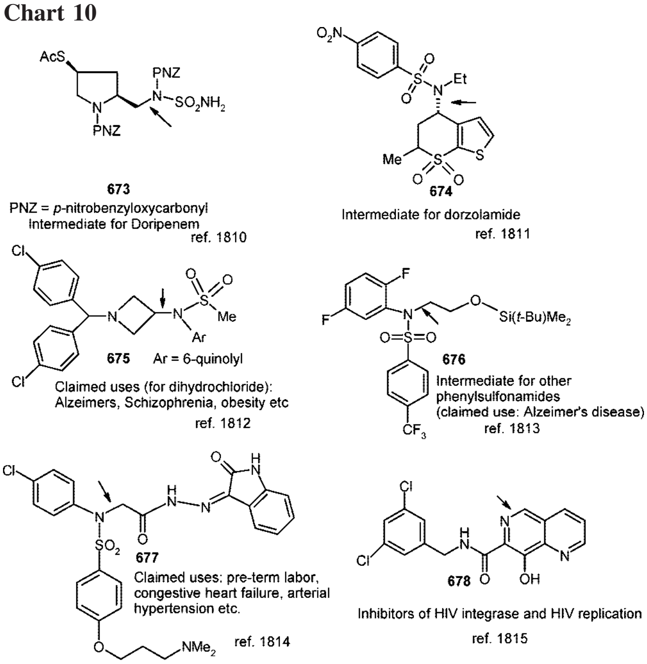
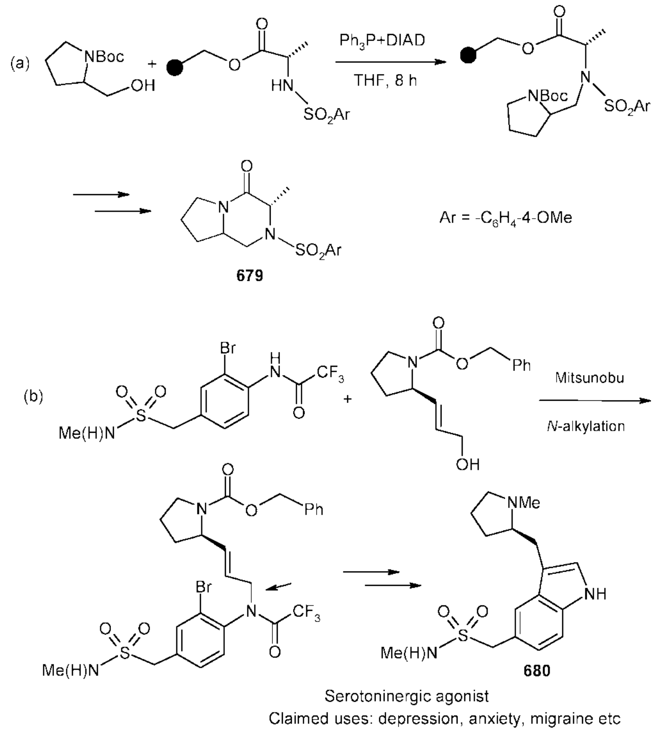
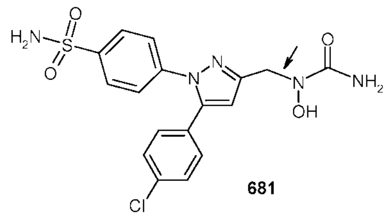


Chart 10



Scheme 179





681

(antiinflammatory agent)

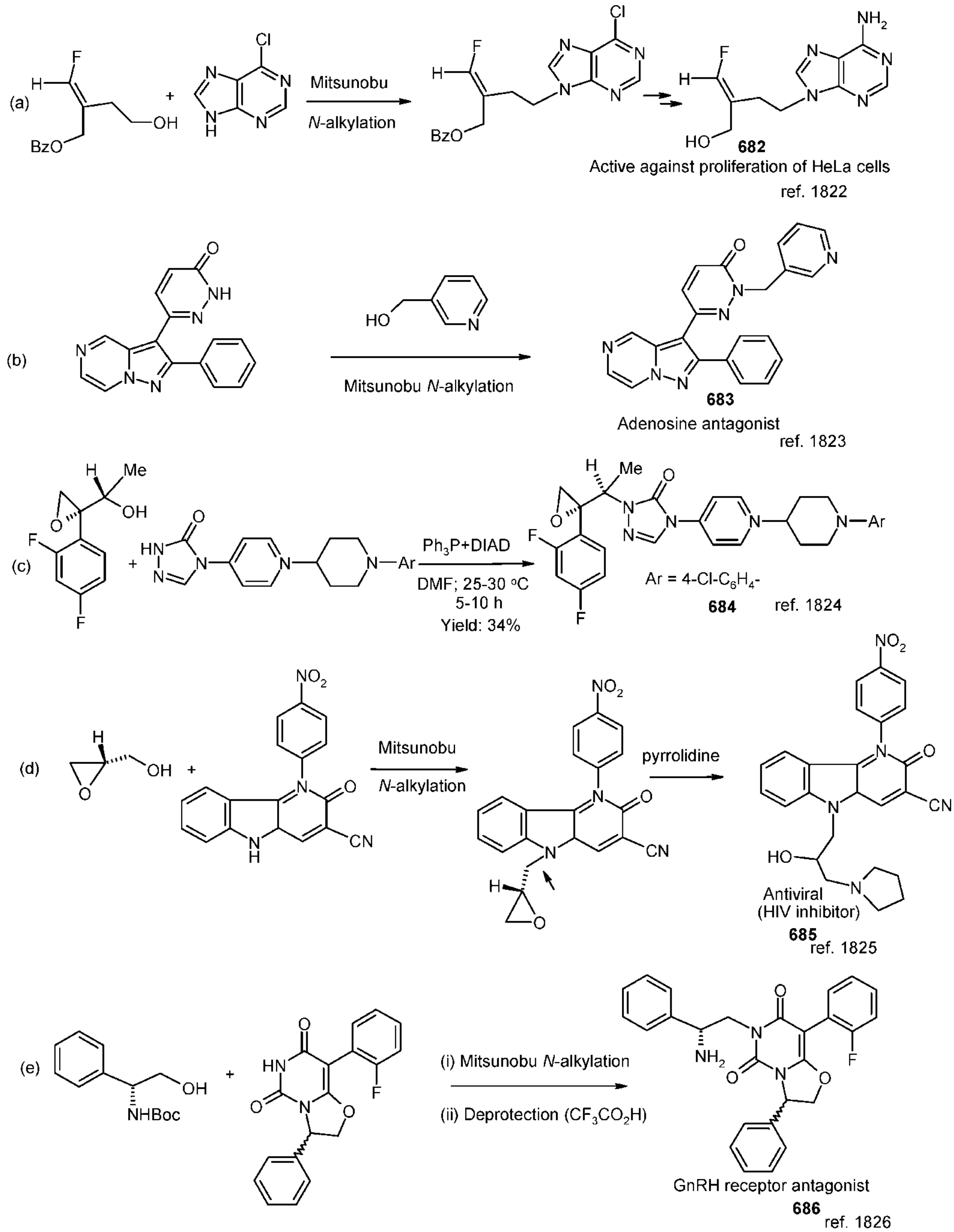
	IC_{50}
Enzyme COX-1	53.5μM
Enzyme COX-2	6.6μM
Enzyme 5-LO	12.3μM

performed. These were intermediates for doripenem (doribax),[1810] dorzolamide,[1811] substituted azetidines,[1812] and phenylsulfonamides (the $OSiR_3$ group was later replaced by a $OC(O)NR_2$ group),[1813] respectively. Compound **675** was obtained in a decent yield (45%) without performing chromatography. In the synthesis of the target sulfanilide **677**, Mitsunobu *N*-alkylation was a key step.[1814] A large number of (poly)azanaphthalenyl carboxamides of type **676** as HIV integrase inhibitors have been prepared by starting with Me-*N*-[(4-methylphenyl)sulfonyl]glycinate and related compounds.[1815] A solid-supported synthesis of sulfonated 2-oxopiperazines **679**, shown in Scheme 179a, involved an initial Mitsunobu alkylation.[1816] Trifluoroacetamide NH appears to be more reactive than sulfonamide, as exemplified by the synthesis of the indole derivative **680**, which is claimed to be useful as a psychotherapeutic agent (Scheme 179b).[1817] In one case, bis(*tert*-butoxycarbonyl) imide $(Boc)_2NH$ was used as the nitrogen source to build an oligomeric peptide nucleic acid (PNA) combinatorial library.[1818,1819] In another, $PhOCONHOCO_2Ph$ was utilized for the synthesis of a hydroxamic acid derivative of cyclohexygenase-2 and 5-lipoxygenase inhibitors (**681**, anti-inflammatory agent).[1820,1821]

The ring NH moiety in purines, pyrimidines, pyrimidones, imidazoles, etc. is amenable to Mitsunobu *N*-alkylation. Five reactions of this type leading to compounds **682**−**686** are shown in Scheme 180.[1822−1826] Chart 11 presents a few more compounds (**687**−**691**) where this type of *N*-alkylation has been utilized.[1827−1831] In the example leading to **690**, though, the cyclic 1,4-diamino precursor itself was sufficiently reactive. Finally, one patent dealing with the synthesis of carbamate esters using the Mitsunobu protocol has been recently awarded.[1832] This type of reaction has been described in section 8 above. Other examples of *N*-alkylation involve the synthesis of (i) taxane intermediates,[1833] (ii) substituted purine heterocyclics,[1834−1836] (iii) 5′-nor-1-homo-*N*-carbonucleosides as antiviral and antitumor agents,[1837] (iv) N^3-aminoalkyl derivatives of (*Z*)-5-arylidenehydantoin,[1838] (v) tetrahydrocarbazole and cyclopentanoindole derivatives as antagonists of the prostaglandin D2 receptor,[1839] (vi) *N*-(3-amino-2-hydroxypropyl)benzenesulfonamide derivatives as GlyT1 transporter inhibitors,[1840] and (vii) polymer conjugates of therapeutic agents and food additives.[1841]

Intramolecular *N*-alkylation has led to the formation of many important cyclic amines such as **692**−**695** (Scheme 181).[1842−1847] In compound **692** (claimed to be anticonvulsant), a new benzodiazepine ring was generated via the hydrazino residue.[1842−1844] Rings of several sizes could be generated employing this approach. Chemistry analo-

Scheme 180



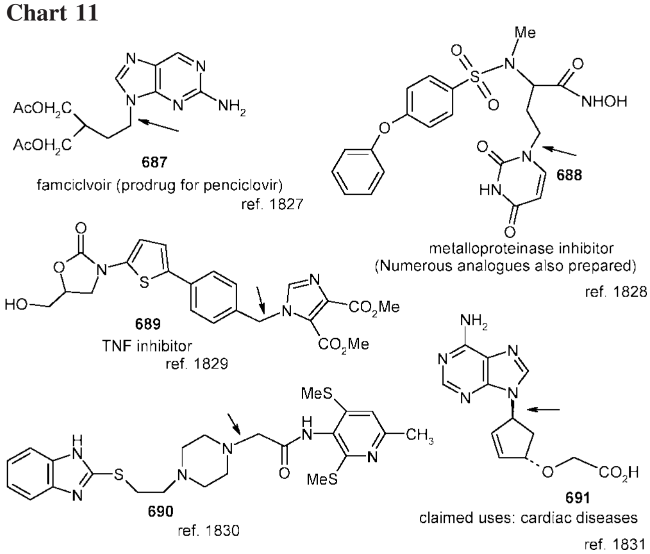
gous to that for the synthesis of **693** has been published.[1083,1084]

As mentioned earlier, the nucleophilic partner in the Mitsunobu reaction can be HN_3 (via Me_3SiN_3). Azidation using this nucleophile and subsequent reactions can be done on a NHC(O) group that can tautomerize to N=C(OH). This is shown in Scheme 182, wherein a formation of tetrazole is shown;[1848] a similar cyclization with the NHC(S) group is discussed above.[1526] These reactions probably involve 1,3-dipolar cycloaddition of Me_3SiN_3 to an intermediate nitrilium ion. The final target molecule, phosphonate **696**, is an ECE inhibitor. Relatively speaking, compared to C−O, C−N, or C−S bonds, C−C bond formation by the Mitsunobu protocol is difficult. In one such rare example, a solid-supported reagent of the type $RNHCOC_6H_4(CH_2OH)$-4 (R = resin) was condensed with diethyl malonate (in solution) in the presence of Ph_3P/$Me_2NCON{=}NCONMe_2$.[1849] Subsequent cleavage of the resin led to 4-$(H_2NCO)C_6H_4CH_2CH(CO_2Et)_2$.

10.4. Other Reactions

As discussed in section 8, the Mitsunobu protocol offers a simple route to thiols from alcohols. Thus, the LTA4 hydrolase-inhibiting compound **698** (K_i = 62 nM) was synthesized by esterifying the precursor alcohol **697** with thioacetic acid followed by hydrolysis (Scheme 183a).[1850] In the synthesis of mercaptobenzene sulfonamide **699** (Scheme 183b; claimed uses: rheumatoid arthritis, osteoarthritis, tumor metastasis)[1851] and *N*-(mercaptoethyl) amino acid derivative **700** (active against neutral endopeptidase),[1852] a similar thioacylation was utilized. This *S*-alkylation reaction may be contrasted with that for the thiophosphate salt shown in Scheme 36 (compound **147** above) where *O*-alkylation

Chart 11



was reported. In the preparation of thioethers **701** and **702**, the unprotected amino functionalities did not interfere in the process.[1853,1854] Mercaptans such as **703** that are intermediates for antibacterial agents have also been synthesized using similar procedures.[1855]

Parts of the patents on three of the phosphine modifications, by Charette and co-workers,[50−52] Tavonekham and co-workers (compound **536** above),[1626,1627] and Curran's group, have been published[1643−1647] and hence are not discussed further.

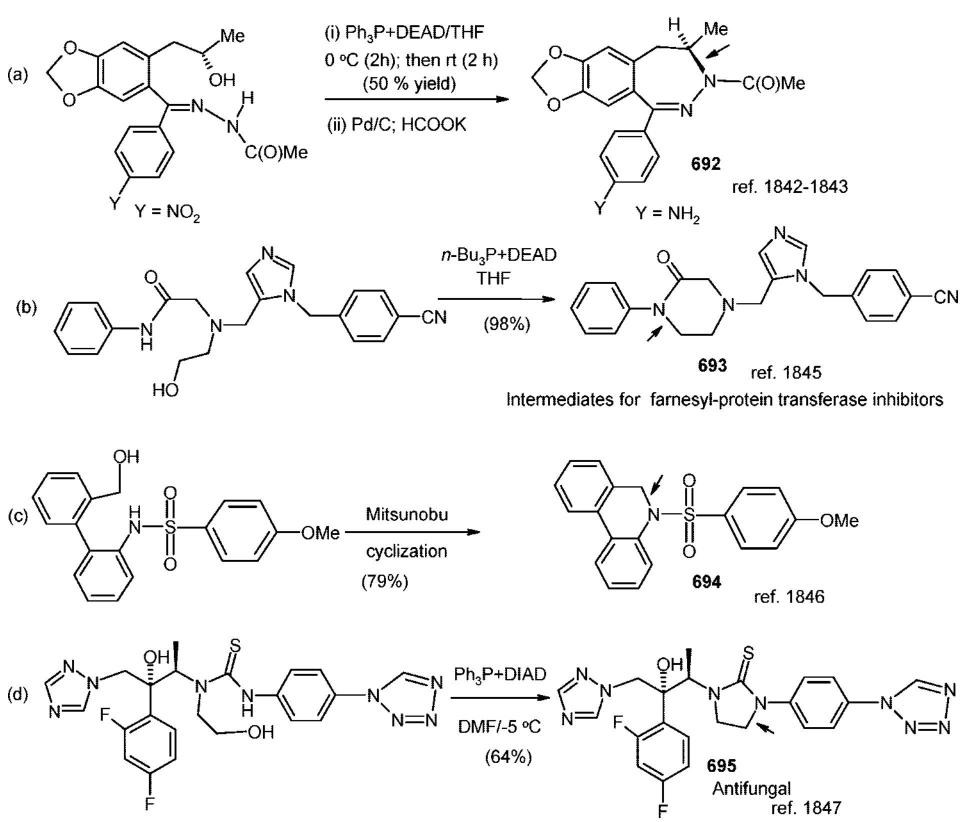
11. Summary and Outlook

As mentioned in the Introduction, the Mitsunobu reaction, along with its modifications, has been versatile and applicable for a variety of organic transformations. The ease with which stereochemistry at the chiral secondary alcohol can be reversed is a valuable asset. The large number of publications, particularly in the area of nucleobase alkylation, reflects its popularity, mainly as a result of the mild conditions employed during the reaction. It is expected that this aspect is going to be much sought after, particularly by the pharmaceutical industry. Synthetic chemists tend to rely on its various facets, be it natural product synthesis or nucleobase alkylation or etherifcation. As far as the future of this reaction is concerned, an efficient and inexpensive way to recycle the reagents or to make the reaction fully catalytic is desirable. Another aspect worth looking into would be to synthesize a water soluble but degradable phosphine/phosphite of low toxicity, to simplify the purification process. The aforesaid points become important if we desire to employ the Mitsunobu route for large scale synthesis. Recoverable polymer bound phosphonium salts of type **565** that avoid the wastage of phosphine as well as azodicarboxylate, and hence make the system more atom economical and greener, also need to be considered in the future. Finally, although a major part of the mechanistic pathways is fairly well understood, the complexity of the initial steps when different P^{III} precursors are used is intriguing. This could also be a fruitful area for a physical organic chemist to probe in detail.

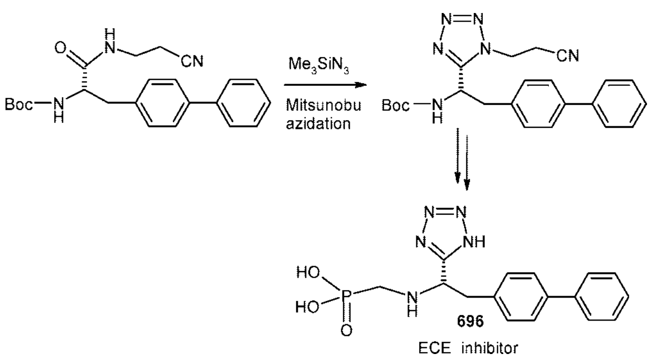
12. Note Added in Proof

Since the number of articles htat appeared after the first submission of this review is large (>100), inclusion of these would require another review process, and hence, these are not added. Also, despite our (unbiased) attemt to be as comprehensive as possible in this review utilizing *SciFinder* search, we might have missed some articles.

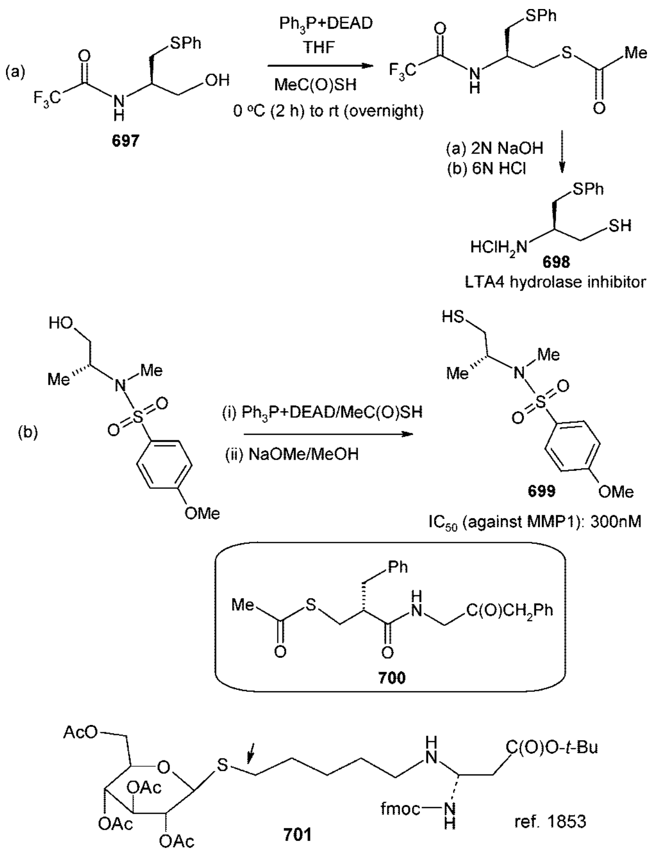
Scheme 181

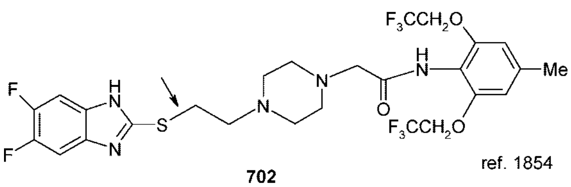


Scheme 182

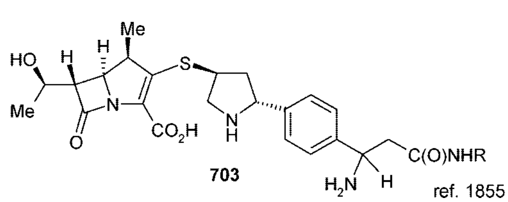


Scheme 183





Claimed use: treatment of hyperlipidemia, arteriosclerosis



13. Abbreviations Used in This Review

ADDP	1,1′-(azodicarbonyl)dipiperidine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
CMBP	(cyanomethylene)tributylphosphorane
CMMP	(cyanomethylene)trimethylphosphorane
m-CPBA	*m*-chloroperbenzoic acid
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCAD	di-*p*-chlorobenzyl azodicarboxylate
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DDQ	5,6-dicyanobenzoquinone
DEAD	diethyl azodicarboxylate
DEPC	diethyl pyrocarbonate
DHTD	4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione
DIAD	diisopropyl azodicarboxylate
DMAP	dimethylaminopyridine
DMB	dimethoxybenzyl
DMEAD	di-2-methoxyethyl azodicarboxylate
DMSO	dimethyl sulfoxide
DMTP	dimethylmalonyltributylphosphorane
DMTr	dimethoxytrityl
DNAD	bis(5-norbornenyl-2-methyl) azodicarboxylate
DPPA	diphenylphosphoryl azide
DPPE	1,2-diphenylphosphinoethane
DTBAD	di-*tert*-butyl azodicarboxylate
DTT	dithiothreitol
EDCI	*N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide
fmoc	9-fluorenylmethoxycarbonyl
HMPB	4-hydroxymethyl-3-methoxyphenoxybutyric acid
MOM	methoxymethyl
Ms	methanesulfonamide
NBSH	*o*-nitrobenzenesulfonylhydrazine
NMP	*N*-methylpyrrolidinone
o-Ns	*o*-nitrobenzenesulfonyl
p-Ns	*p*-nitrobenzenesulfonyl
PhF	phenylfluorenyl
PMB	*p*-methoxybenzyl
Pmc	2,2,5,7,8-pentamethylchroman-6-sulfonyl
SES	trimethylsilylethylsulfonyl
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsiloxy (see also TBS)
TBDPS	*tert*-butyldipheylsilyl
TBP	tri-*n*-butylphosphine
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEMT	triethylmethanetricarboxylate
TES	triethylsilyl
TFA	trifluoroacetic acid
THP	tetrahydropyranyl
Thy	thyminyl residue
TIPS	triisopropylsilyl
TMAD	*N*,*N*,*N*′,*N*′-tetramethyl azodicarboxamide
TMBMS	trimethyl(2,6-dibromo-4-(*N*-maleimido)phenoxy)silane
TMS	trimethylsilyl
Troc	*N*-2,2,2-trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl
Ziram@	*N*,*N*-dimethyldithiacarbamate [$(Me_2NCS_2)_2Zn$]

14. Acknowledgments

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checking the contents of the manuscript. We also thank Dr. Nune Satish Kumar for providing some useful references.

15. Supporting Information Available

Tables containing structures of additional compounds (with references cited in the main text) wherein the Mitsunobu reaction is utilized (Tables S1−S9; 67 pages). This information is available free of charge via the internet at http://pubs.acs.org/.

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