Contribution

Diphenyl Phosphorazidate (DPPA) – More Than Three Decades Later

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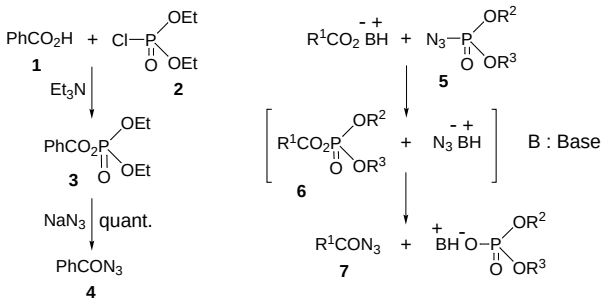
1. Introduction

More than thirty years have already elapsed since we introduced diphenyl phosphorazidate (diphenylphosphoryl azide, DPPA, $(PhO)_2P(O)N_3$) as a reagent for organic synthesis in 1972 (Figure 1).[1,2] During these years, DPPA has been found to be effective for a variety of organic reactions as a versatile synthetic reagent. It is not too much to say that DPPA has secured an established position as a reagent. *SciFinder* will indicate you about 1,000 references about DPPA, and there will be found about 46,000 examples of reactions when you will search for DPPA as "Reaction-Reactant". DPPA is now estimated to be produced over 50 tons per year in Japan and easily available commercially.

This review will first describe why and how the works on DPPA started and then an overview will be made on the utility of DPPA in organic synthesis mainly developed by our group including recent achievements by other groups.[3] A comprehensive review is not intended, but characteristic features of DPPA on organic synthesis will be focused.

2. Why and how has DPPA been developed?

I worked about biosynthetic studies of steroids under the supervision of Professor Sir Derek Barton (1969 Nobel laureate) at Imperial College, London, as a postdoctoral fellow during 1968-1970. I experienced there the Wittig reaction to synthesize some substrates for biosynthetic experiments.[4] The Wittig reaction was not described in any textbooks at that time, and I deeply interested in a behavior of phosphorus reagents. In addition, before this experiment, I had a great interest about serendipitous discovery of polyphosphoric acid (PPA) when I learned it from Professor Shigehiko Sugasawa as an undergraduate student, which drew my interests to synthetic reagents and phosphorus. These experiences and interests led me to investigate organic reactions utilizing phosphorus compounds after return to Japan. When I consulted textbooks at that time from biosynthetic viewpoint, I found that acyl phosphates, $R^1CO_2P(O)(OR^2)_2$, played an important role in biosynthesis of peptides and proteins. Thus my interests were aroused about reactivity of acyl phosphates which are a mixed anhydride from carboxylic and phosphoric acids. I synthesized the acyl phosphate **3** from benzoic acid (**1**) and diethyl phosphorochloridate (**2**) by a known procedure and the reaction of **3** was investigated. As one of several trials, the reaction with sodium azide was found to give benzoyl azide (**4**), as shown in Scheme 1. Although this reaction proceeded in two steps from benzoic acid (**1**), I thought that the acyl phosphate **6** would be temporally formed if the phosphorazidate **5** were used in place of the phosphorochloridate **2**, and the acyl phosphate **6** would react *in situ* with the azide ion giving the acyl azide **7**.



Scheme 1. Formation of acyl azides: practice and hypothesis.

Known diethyl phosphorazidate (**8**) was thus prepared and reacted with benzoic acid (**1**) in the presence of triethylamine. The formation of benzoyl azide (**4**) was detected on a TLC plate, and the reaction with amines proceeded to give the corresponding amide **9** and anilide **10**. Refluxing the mixture in ethanol afforded the ethyl carbamate **11** through the Curtius rearrangement, shown in Scheme 2.[5a] Further, it was found that the same carbamate **11** was directly obtained by refluxing a mixture of benzoic acid (**1**), diethyl phosphorazidate (**8**), and triethylamine in ethanol. However, the yields of the products were moderate in each case. The rate determining step of the reaction was thought to be the stage of the attack of the carboxylate anion to the phosphorus

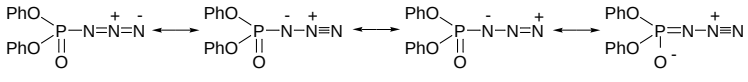
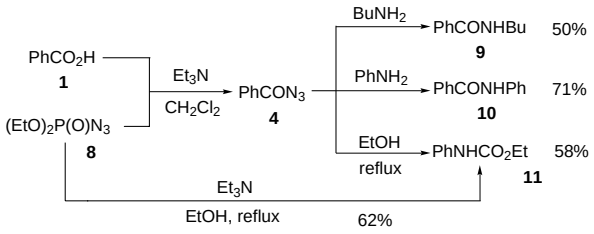


Figure 1. Resonance structures of diphenyl phosphorazidate (DPPA).

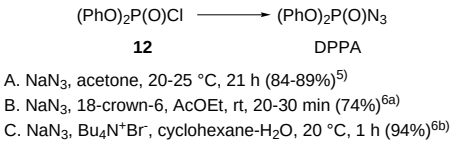
atom of the phosphorazidate. If so, the reaction would proceed more efficiently if the phosphorus atom of the phosphorazidate was attached to more electron-withdrawing functions. These experiments and considerations led me to develop DPPA which has more electron-withdrawing phenyl group. In fact, DPPA was revealed to be much more efficient in the amide synthesis and Curtius rearrangement.



Scheme 2. Reaction of diethyl phosphorazidate with benzoic acid.

3. Preparation of DPPA and its physical properties

DPPA is easily prepared in high yield by the reaction of the corresponding chloride **12** with sodium azide in acetone.[1,5] Combination of sodium azide and 18-crown-6 in the same reaction was reported,[6a] and the use of a quaternary ammonium salt as a phase-transfer catalyst in a biphasic phase of water and an organic solvent was also reported to be effective,[6] as shown in Scheme 3.



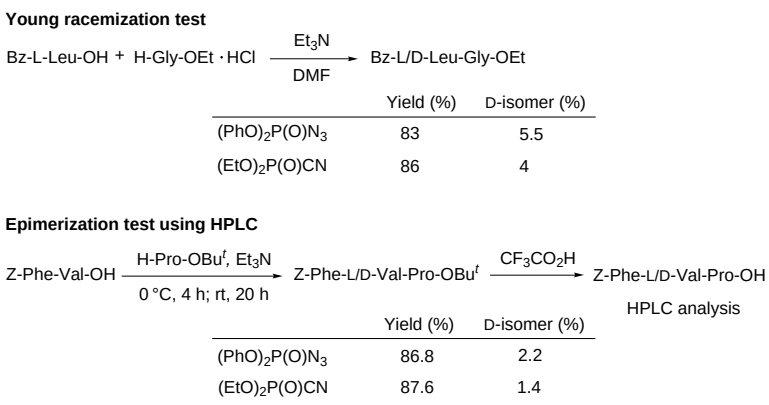
Scheme 3. Preparation of DPPA.

DPPA is a colorless or pale yellow liquid which boils at 134-136 °C/0.2 mmHg, and it will be stable at room temperature under shading. It is non-explosive just like the other phosphorazidate. When DPPA is stored at room temperature for a long time, it might be slowly and partially hydrolyzed with moisture in air to produce diphenyl phosphate and toxic explosive hydrazoic acid. In this case, it will be recommended to use after washing DPPA with aqueous sodium hydrogen carbonate followed by drying.[5b]

4. Peptide synthesis using DPPA

DPPA is useful for amide and peptide bond formation reactions. One of the remained problems in the present advanced peptide synthesis will be epimerization which occurs to some extent at the stereogenic center in the C-terminal amino acids of peptides through activation with the condensing agents during the coupling of the peptide fragments. There will be no coupling reagents and procedures which induce no epimerization. This situation will be quite similar to the coupling of sugars in which α- and β-isomers could not be separately formed at will. Dare I say it, this will be an old but new problem. DPPA is a coupling reagent with little epimerization (and racemization),[1,5a] and inactive to the functional groups in the following amino acids:[1,7,8] serine (Ser), threonine (Thr), valine (Val), asparagine (Asn), glutamine (Gln), histidine (His), pyroglutamic acid (*p*Glu), tryptophan (Trp), methionine (Met), *S*-benzylcysteine (Cys(Bzl)), nitroarginine (Arg(NO_2)). Thus the peptide synthesis using DPPA will proceed without any side reactions for these amino acids. DPPA can be used for both liquid- and solid-phase peptide synthesis,[9] and dimethylformamide (DMF) is a favorable reaction solvent in both cases. In addition, a base such as triethylamine is necessary to generate the carboxylate anion from the carboxyl part.

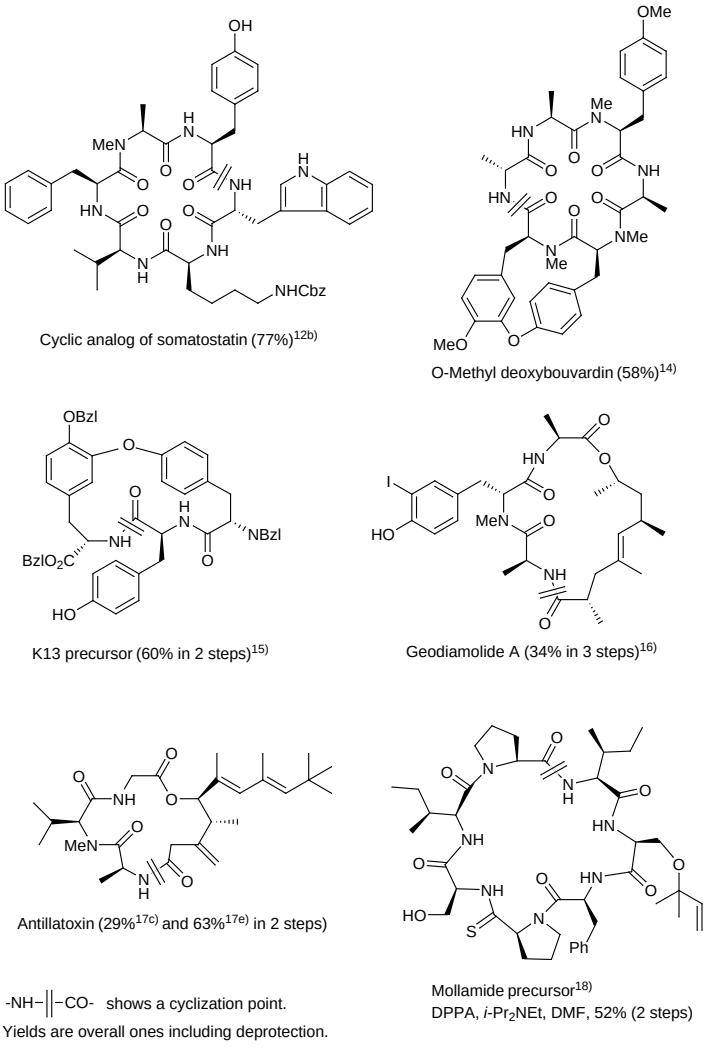
A short while after developing DPPA, we introduced diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$) as another suitable reagent for the peptide bond formation.[10] DEPC proved to be a versatile synthetic reagent quite similar to DPPA.[3b,10] However, DEPC is slightly more active than DPPA and the rate of epimerization (or racemization) will be lower in peptide synthesis. It will be superior to DPPA in the construction of linear peptides. Scheme 4 shows the results of the classical Young racemization test (through the measurement of specific rotation),[1,5a,10a,10b] which is said to be the most stringent test of racemization, as well as the results of our development epimerization test (through HPLC measurement).[11]



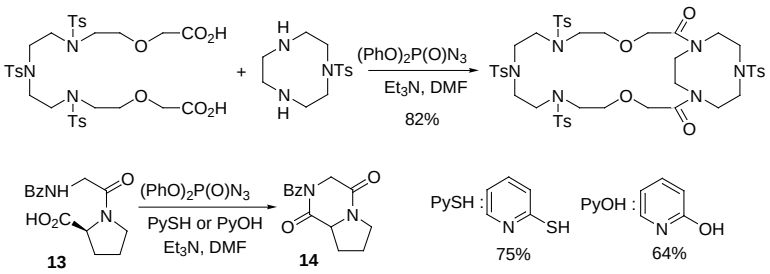
Scheme 4. Racemization and epimerization tests usin DPPA and DEPC.

However, Veber and Merck chemists revealed that DPPA was suitable for macrolactamization of linear peptides.[12] Since then, DPPA is quite often utilized for the synthesis of macrocyclic peptides by macrolactamization.[13] High dilution conditions will be required for the macrolactamization to suppress the intermolecular reaction, and sodium hydrogen carbonate is often employed instead of organic bases such as triethylamine. Scheme 5 shows some examples, most of which employed DPPA-$NaHCO_3$ in DMF under high dilution conditions (*ca.* 5 mM) between 0 °C and room temperature for a longer time (1-3 days).[12-18]

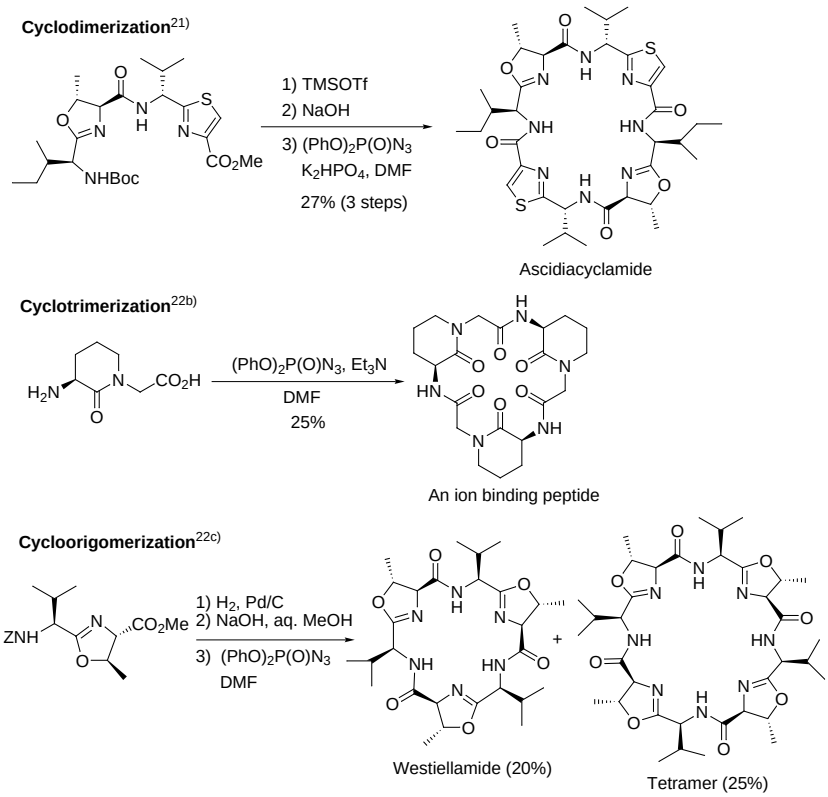
Bislactamization shown in Scheme 6 will be considered to proceed first intermolecular and then intramolecular coupling, and no high dilution conditions are required.[19] Benzoyl-glycyl-L-proline (**13**) affords the corresponding diketopiperazine **14** by reaction with DPPA-triethylamine in the co-existence of 2-mercapto- or 2-hydroxypyridine (PySH or PyOH),[20] shown in Scheme 6.



Scheme 5. Cyclic peptides obtained by macrolactamization with DPPA.



Scheme 6. Lactamization using DPPA.

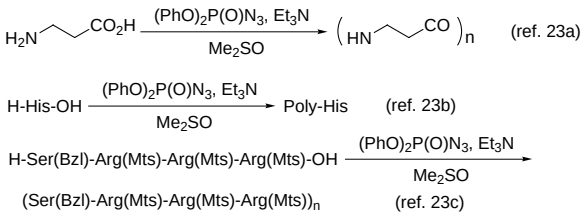


Scheme 7. Cycloorigomerization using DPPA.

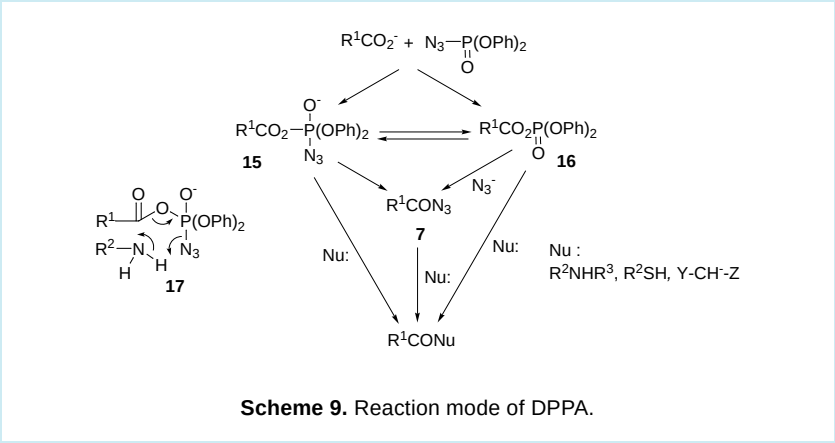
In addition, DPPA proved to be useful for cyclodimerization,[21] cyclotrimerization,[22] and so on, as shown in Scheme 7.

Nishi and co-workers developed a convenient polymerization method for the preparation of polypeptides from amino acids or monomer peptides which were unprotected at both N- and C-terminals.[23] The DPPA method is simple in the work-up, and useful for the synthesis of sequential polypeptides (Scheme 8).

The reaction mechanism of the peptide (or amide) synthesis using DPPA would be as shown in Scheme 9. The carboxylate anion would attack to the phosphorus atom in DPPA to give the acyl phosphates **15** and **16**. The acyl azide would be formed by S_Ni type rearrangement of **15** or S_N2 type reaction of **16** with the azide anion. Reaction of the amine with the acyl phosphates **15** and **16** as well as the acyl azide **7** would form the amide or peptide bond. Each route would respectively contribute more or less, and the Young racemization test (cf. Scheme 4) was adopted to find out which route would be predominant. Thus, the acyl phosphate **16** and acyl azide **7** were prepared from benzoyl-L-leucine (Bz-L-Leu-OH), and reacted with glycine ethyl ester (H-Gly-OEt) to check the rate of racemization and chemical yield. The most favorable result was obtained by the addition of triethylamine to a mixture of Bz-L-Leu-OH, H-Gly-OEt, and DPPA followed by the reaction in both racemization rate and chemical yields of the dipeptide, Bz-L-Leu-Gly-OEt, which proved to be superior to the acyl phosphate (**16**) and azide (**7**) methods. These experiments would suggest the concerted transition state shown in **17** in which **15** is first formed and then the amine will come to react.[1,7a] This amide bond formation is the N-acylation of the amine as a nucleophile. When the nucleophile is replaced with the thiol or active methylene anion,



Scheme 8. Polymerization of amino acids and peptides using DPPA.



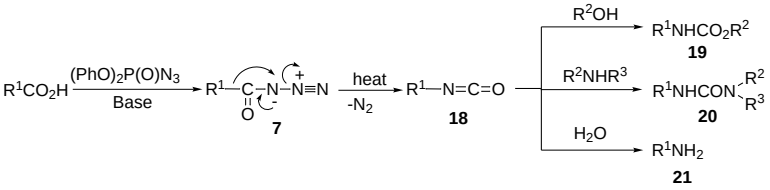
Scheme 9. Reaction mode of DPPA.

S-acylation or C-acylation will occur, as described later. If there is no nucleophile, the reaction will stop at the stage of the acyl azide, which thermally undergoes the Curtius rearrangement to furnish the isocyanate.

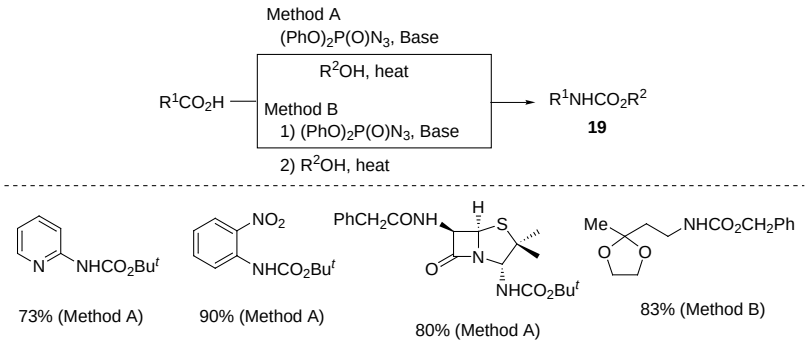
5. The Curtius rearrangement using DPPA

Hofmann, Curtius, Schmidt, and Lossen rearrangements are well-known as a useful method to convert carboxylic acids or derivatives to amines or derivatives having one less carbon unit, whose key step is the transfer of a carbon atom to an electron deficient nitrogen atom.[24] DPPA is also quite useful for the Curtius rearrangement (cf. Scheme 2). Carboxylic acids react with DPPA in the presence of bases such as triethylamine to give acyl azides, which thermally undergo the Curtius rearrangement accompanied with expulsion of nitrogen. The isocyanate **18** thus formed will react with alcohols, amines, water, and other nucleophiles to produce carbamates **19**, ureas **20**, amines **21**, and so on (Scheme 10). The intermediates, acyl azides or isocyanates, could be isolated if they are thermally stable.

The carbamate **19** will be obtained by the one-pot procedure (method A) in which a mixture of carboxylic acids, DPPA, and triethylamine is directly refluxed in a solvent, *e.g. tert*-butanol, inert to DPPA.[1,25] In some cases, addition of alcohols followed by thermal treatment is better after the formation of acyl azides, shown in Scheme 11. When alcohols are reactive and will easily react with DPPA, the carbamates will be efficiently prepared by the two reactions-in-one pot (two-in-one) procedure (method B) in which the reaction of carboxylates with DPPA and thermal treatment are conducted in an inert solvent, and then alcohols are added to isocyanates. Method B is suitable for the preparation of ureas and amines.



Scheme 10. The Curtius rearrangement using DPPA.



Scheme 11. Two procedures for the Curtius rearrangement with DPPA.

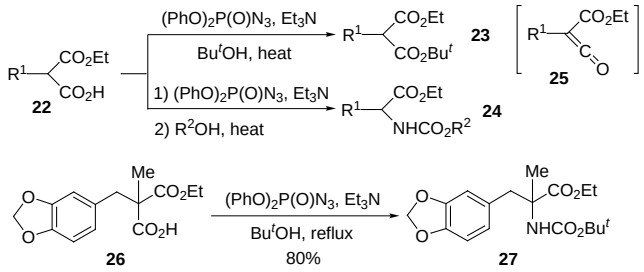
The application of method A using *tert*-butanol with alkylmalonic acid half esters **22** afforded the corresponding diesters **23**, as shown in Scheme 12. In contrast, method B in which the half esters **22** were first converted to the isocyanates followed by heating the whole mixture after addition of alcohols afforded α-amino acid derivatives, the products by the Curtius rearrangement. In method A, the half esters will first afford the acyl azides which will be in equilibrium with the ketenes **25** formed by elimination because of the high acidity of α-hydrogen. Alcohols will irreversibly add to the ketenes **25** to give the diesters **23**. The malonic acid half ester **26** which would not undergo the ketene formation, because they have no α-hydrogen, smoothly afforded the α-amino acid derivative **27** by method A.[26] The above esterification using DPPA commonly occurs in the case of $RCH(X)CO_2H$ (X=electron-withdrawing functions such as CO_2Et, CN, $CONH_2$, *etc.*)

The analogous α-amino acid synthesis from the cyclopentanedicarboxylic acid **28** efficiently afforded the carbamate **29** by method B, as shown in Scheme 13.[27]

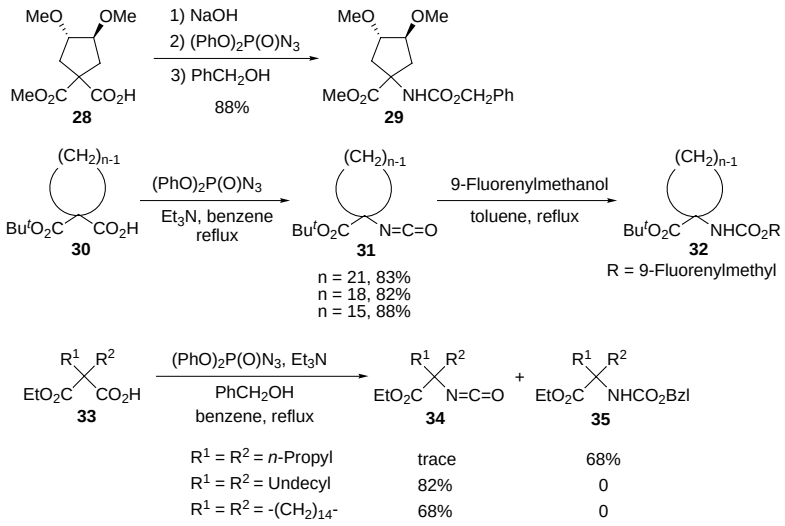
However, the reaction with the macrocyclic dicarboxylic derivatives **30** stopped at the isocyanates **31** stage in refluxing benzene even in the presence of benzyl alcohol due to the possible steric hindrance.[28] The isocyanates **31** were stable and could be isolated. Conversion of the isocyanates **31** to the carbamates **32** required more forcing conditions such as refluxing toluene in the presence of 9-fluorenylmethanol.

The non-cyclic alkyl malonic acid half ester **33** having shorter alkyl group such as the propyl function afforded the carbamate **35** while the half ester **33** having longer alkyl side chain, *e.g.* the undecyl function, stops at the stage of isocyanate **34** (Scheme 13).

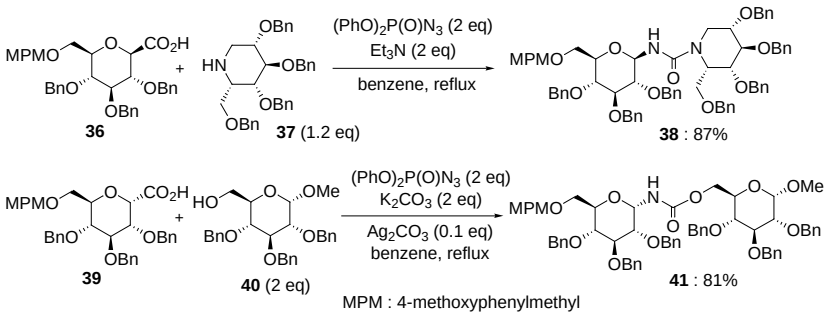
The urea synthesis from sugar carboxylic acids by the Curtius rearrangement with DPPA smoothly proceeds in good yields when using triethylamine, a common base, *e.g.* **36**+**37**→**38**.[29] However potassium carbonate proved to be a better base in the carbamate synthesis using alcohols as a nucleophile, as shown in Scheme 14. The addition of a catalytic amount of silver carbonate to triethylamine or potassium carbonate is often effective to conduct the reaction, *e.g.* **39**+**40** → **41**.



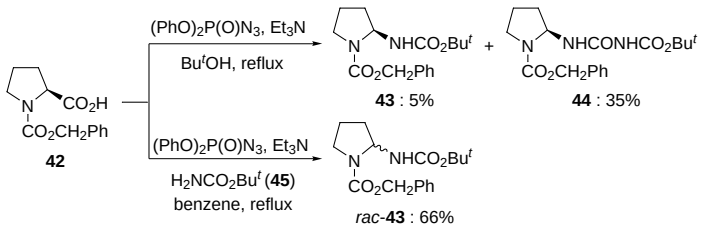
Scheme 12. Reaction of ethyl hydrogen malonates with DPPA.



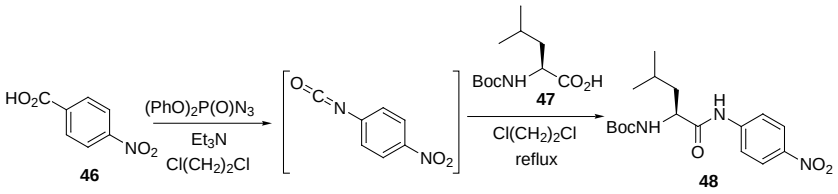
Scheme 13. The Curtius rearrangement of cyclic and dialkyl malonic acid half esters with DPPA.



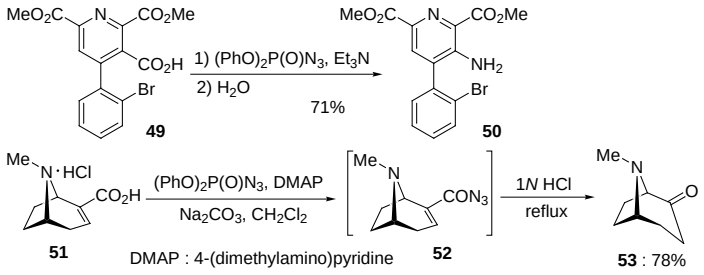
Scheme 14. The Curtius rearrangement of sugar carboxylic acids using DPPA.



Scheme 15. The Curtius rearrangement of carbobenzoxy-L-proline with DPPA.



Scheme 16. Preparation of amino acid amides of aromatic amines using DPPA.



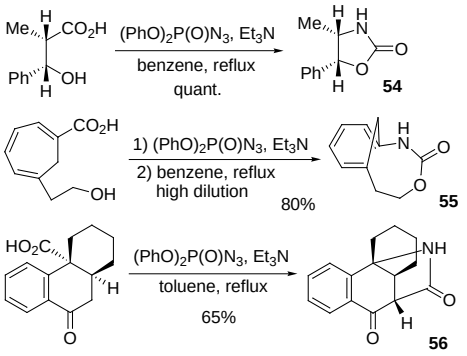
Scheme 17. Preparation of amines and ketones by the Curtius rearrangement with DPPA.

As an unusual example, the proline derivative **42** afforded the allophanate **44** as the main product rather than the carbamate **43**. However, co-existence of *tert*-butyl carbamate (**45**) afforded the carbamate **43** as the major product though racemization occurred (Scheme 15).[30]

Anilines, in general, have weak nucleophilicity and coupling with carboxylic acids does not smoothly proceed to give the corresponding anilides using DPPA. In contrast, anilides will be prepared in good yields by use of a two-in-one procedure: (1) conversion of aromatic carboxylic acids to isocyanates by the DPPA method and then (2) addition of the other carboxylic acids.[31] Scheme 16 shows the preparation of the anilide 48 from *tert*-butoxycarbonyl-L-leucine (Boc-L-Leu-OH, **47**) and 4-nitrobenzoic acid (**46**).

Similarly to the above, carboxylic acids are first converted to isocyanates using DPPA, and then hydrolysis under aqueous or acidic conditions affords amines, *e.g.* **49** → **50**.[32] In the case of the reaction of the α,β-unsaturated carboxylic acid **51** with DPPA, the ketone **53** was obtained from the intermediate acyl azide **52** through thermal rearrangement to the isocyanate and then acidic hydrolysis to the amine (Scheme 17).[33]

Carboxylic acids having hydroxyl or active methylene functions in the same molecules, as shown in Scheme 18, afford the cyclic carbamates, **54**[34a] and **55**,[34b] and the lactam **56** through intramolecular cyclization by use of the DPPA method.



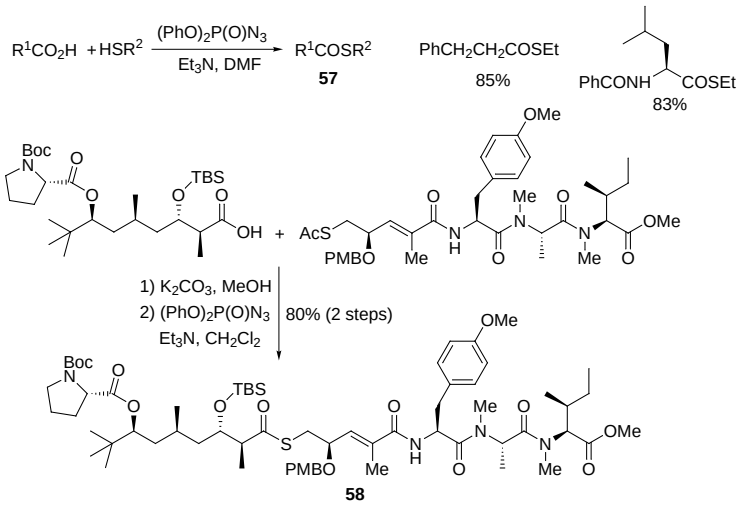
Scheme 18. Intramolecular cyclization of isocyanates.

The Curtius rearrangement utilizing DPPA proceeds under mild reaction conditions by simple procedure in comparison with the usual Curtius, Hofmann, Schmidt, and Lossen rearrangements. The DPPA method will have a wider applicability in synthesis, and will be the first choice in the conversion of carboxylic acids to amines and derivatives having one less carbon.

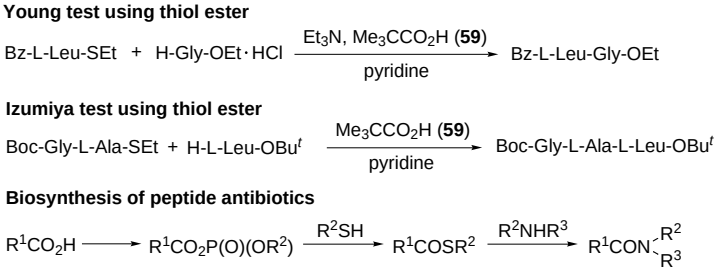
6. Thiol ester synthesis using DPPA and peptide synthesis from thiol esters

Thiol esters (thioesters) **57** will be easily obtained by S-acylation of thiols with carboxylic acids using DPPA in the presence of triethylamine in DMF under similar reaction conditions to the amide or peptide bond formation, as shown in Scheme 19.[36] Direct conversion of carboxylic acids to thiol esters without the intermediacy of acid chlorides was first explored by our group in 1974. DEPC can be also used for thiol synthesis. One of the representative examples in the application of the DPPA method to natural product synthesis will be the synthesis of the thiol ester **58** which is an intermediate in the total synthesis of apratoxin A, a macrocyclic depsipeptide.[37]

We further found that thiol esters react with amines in the presence of pivalic acid (**59**), a bifunctional catalyst, in DMF to give amides or peptides.[38] As shown in Scheme 20, the reaction proved to proceed without any racemization (or epimerization) in the Young racemization test as well as the Izumiya test. Peptide synthesis from carboxylic acids via thiol esters will be the same as the biosynthesis of peptide antibiotics, and regarded as organic chemical realization of *in vivo* reactions. Pivalic acid is a sort of organic catalysts[39] equivalent to enzymes.



Scheme 19. Preparation of thiol esters using DPPA.



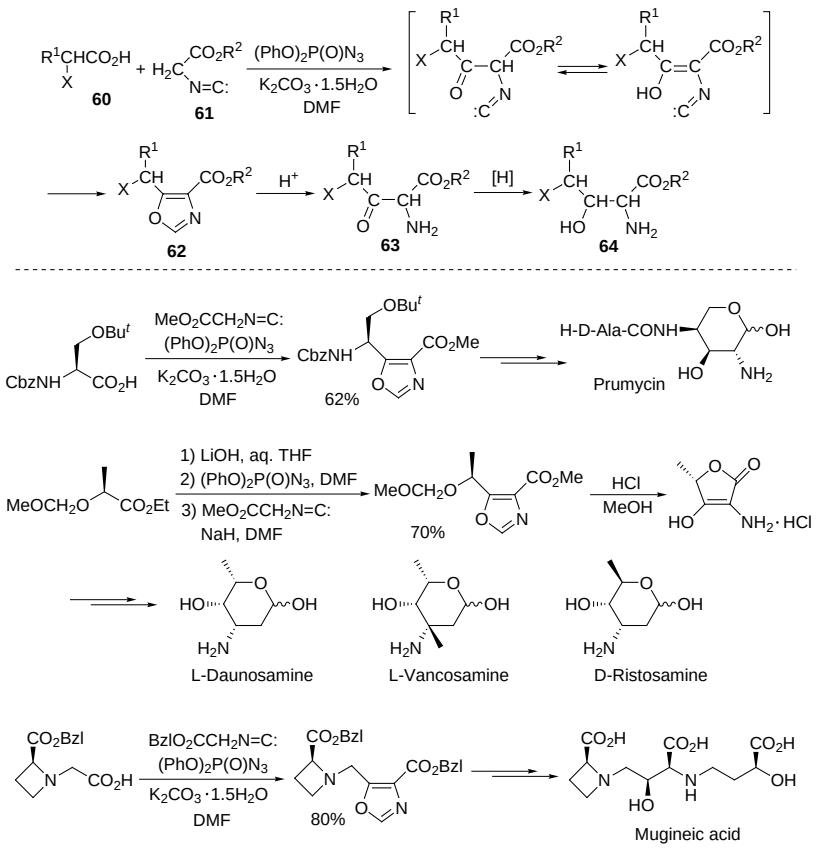
Scheme 20. Peptide synthesis from thiol esters.

7. Oxazole synthesis by C-acylation

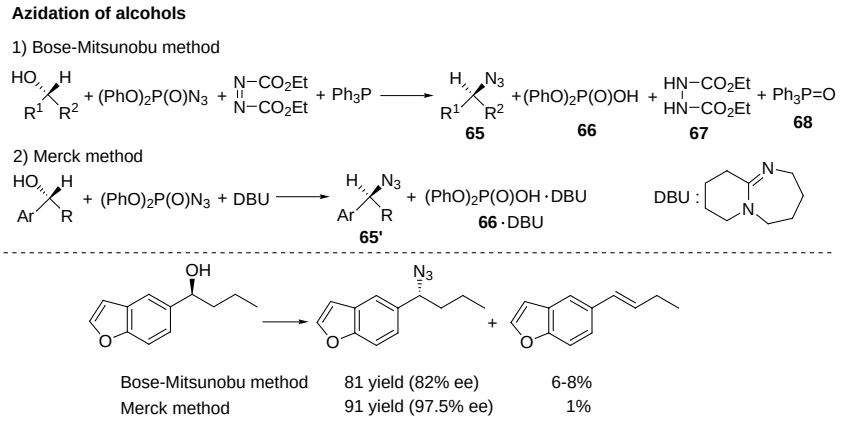
DPPA can be applied to direct C-acylation of active methylene compounds with carboxylic acids just like S-acylation. Treatment of carboxylic acids **60** and isocyanoacetic esters **61** with DPPA-base affords oxazole derivatives **62** having ester functions at the C4 position by C-acylation followed by cyclization, as shown in Scheme 21.[40] The oxazole derivatives **62** undergo acidic hydrolysis to give β-keto-α-amino acid derivatives **63**, whose carbonyl group is reduced to furnish β-hydroxy-α-amino acid derivatives **64**. The C-acylation conveniently proceeds by use of a combination of DPPA and potassium carbonate sesquihydrate while use of sodium salts of isocyanoacetic esters is also effective. No or little racemization at the α-position was observed in the C-acylation with α-amino or α-oxy acids **60**. Utilizing this series of reactions as a key step, various amino sugars such as prumycin,[41a] L-daunosamine,[41b] L-vancosamine,[41c] and D-ristosamine[41d] were conveniently synthesized, and the synthesis of mugineic acid,[41e] a phytosiderophone, was accomplished by this procedure.[41f]

8. Azidation of alcohols and phenols

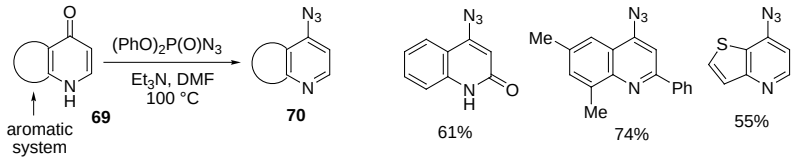
The conversion of alcohols to azides is quite useful since azides can be easily converted to amines by a reductive process. Generally, the two step process is employed to convert alcohols to azides: transformation of alcohols to halides, mesylates, or tosylates followed by reaction with the azide anion. There are not so many procedures of one step conversion of alcohols to azides. The Mitsunobu reaction using DPPA (Bose-Mitsunobu method)[42] and the DPPA-DBU (18-diazabicyclo[5.4.0]-7-undecene) method (Merck method)[43] shown in Scheme 22 will be representative, and both methods proceed with inversion of configuration to azides **65** or **65′**. The Bose-Mitsunobu method utilizes safe DPPA in place of dangerous hydrazoic acid and is useful for the preparation of various azides. However, it is not so easy to remove hydrazino esters **67** and phosphine oxides **68** formed in the reaction. On the other hand, the DBU salt of diphenyl phosphate **66** formed in the Merck method is easily removed by washing with water hence work-up after the reaction is simple. In addition, the Merck method proceeds to a lesser extent of racemization than the Bose-Mitsunobu method for the substrates which easily racemize.[43] However,



Scheme 21. Oxazole synthesis using DPPA.



Scheme 22. Azidation of alcohols.



Scheme 23. Azidation of 4-pyridone derivatives.

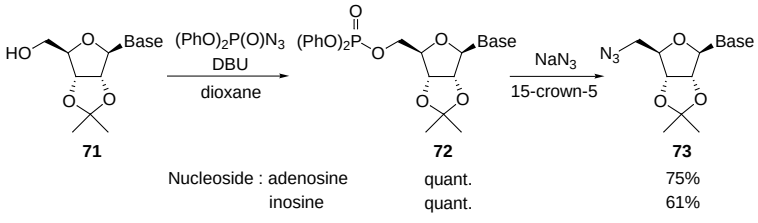
only reactive alcohols such as benzyl type alcohols and α-hydroxycarboxylic acid esters smoothly undergo the azidation by the Merck method. In contrast, a combination of DBU and bis(*p*-nitrophenyl) phosphorazidate (*p*-NO_2DPPA, (p-$NO_2C_6H_4O)_2P(O)N_3$), which was also developed by our group,[7a] proved to be much more effective for the azidation of a wide range of alcohols.[44] Azidation using both DPPA and *p*-NO_2DPPA will proceed through the formation of the phosphate esters followed by S_N2 type reaction with the azide anion.

Quinolines, pyridines, and quinazolines **69** having the keto group at the C4 position can be converted to the corresponding azides **70** in moderate yields by heating at 100 °C with DPPA-triethylamine in DMF.[45] The reaction will proceed by enolization (phenolization), formation of phosphate esters, addition of the azide anion, followed by elimination of the phosphate group to give the azides **70**, as shown in Scheme 23.

9. Synthesis of phosphate esters and phosphoramidates

Interestingly, the application of the above Merck method using DPPA-DBU to 2′,3′-*O*-isopropylidenenucleosides **71** furnished not the azides but the phosphate esters **72** at the C5 position, which were converted to the azides **73** by further treatment with sodium azide, as shown in Scheme 24.[46] The reason why the reaction stops at the phosphate esters step is due to the mild reaction conditions at room temperature. Heating in this reaction will cause side reactions.

Treatment of DPPA with water, butanol, ammonia, and amines affords diphenyl phosphate, butyl diphenyl phosphate, diphenyl phosphoramidate, and diphenyl *N*-alkylphosphoramidate, respectively.[47]



Scheme 24. Phosphorylation with DPPA.

10. Ring opening of epoxides using DPPA

The epoxides **74** regioselectively produce β-azido phosphates **75** by the reaction with DPPA in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP) and lithium perchlorate in DMF.[48] The reaction will proceed through the formation of the pyridinium azides **76** from DPPA and DMAP followed by the ring opening of the epoxide **74** activated with lithium perchlorate, giving the β-azidophosphate **75**, as shown in Scheme 25. The α,β-epoxyketone **77** affords the α-azido vinylketone **78** which will be formed by elimination of diphenyl phosphate from the azido phosphate once generated.

11. DPPA as a 1,3-dipole

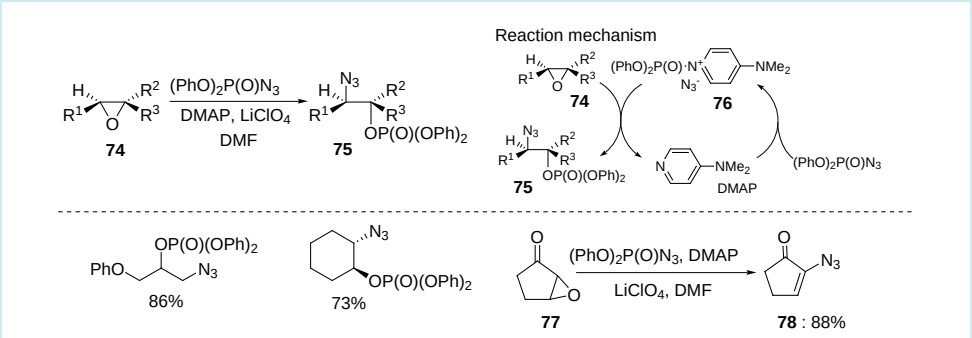
DPPA works as not only the azide anion equivalents already described but also a 1,3-dipole.

We have explored the ring contraction of cyclic enamines **84** using DPPA as a 1,3-dipole.[49] Thus, the pyrrolidine enamines **80** obtained from the cyclic ketones **79** react with DPPA to give the ring-contracted phosphoryl amidines **81** through the 1,3-dipolar cycloaddition followed by ring contraction accompanied with evolution of nitrogen. The phosphoryl amidines **81** are hydrolyzed with potassium hydroxide to produce the ring-contracted carboxylic acids **82**, as shown in Scheme 26.

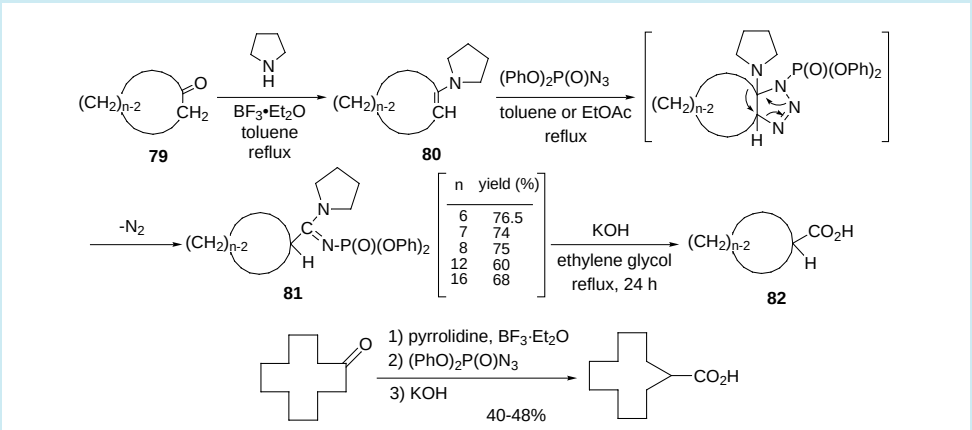
Analogously, the reaction of DPPA with the pyrrolidine enamines **84** derived from aromatic ketones **83** followed by the alkaline hydrolysis of the resulting phosphoryl amidines **85** affords α-alkylarylacetic acids **86** in good yields (Scheme 27).[50] Especially, better results are obtained by the successive treatment without the isolation of any intermediates. The method will be a general method for the synthesis of α-alkylarylacetic acids **86** from alkylarylketones **83**. Utilizing this method, nonsteroidal antiinflammatory agents having the α-alkylarylacetic acid skeleton such as *rac*-naproxen, ibuprofen, ketoprofen, and flurbiprofen can be conveniently synthesized.[50c]

L'abbé and co-workers first clarified the action of DPPA as a 1,3-dipole,[2] and reported that the reaction of DPPA with carbethoxymethylenetriphenylphosphorane (**87**) afforded a mixture of ethyl diazoacetate (**89**) and the iminophosphorane **90**. The intermediate would be the triazoline **88** which undergoes 1,3-dipolar elimination to yield **89** and **90**, shown in Scheme 28.

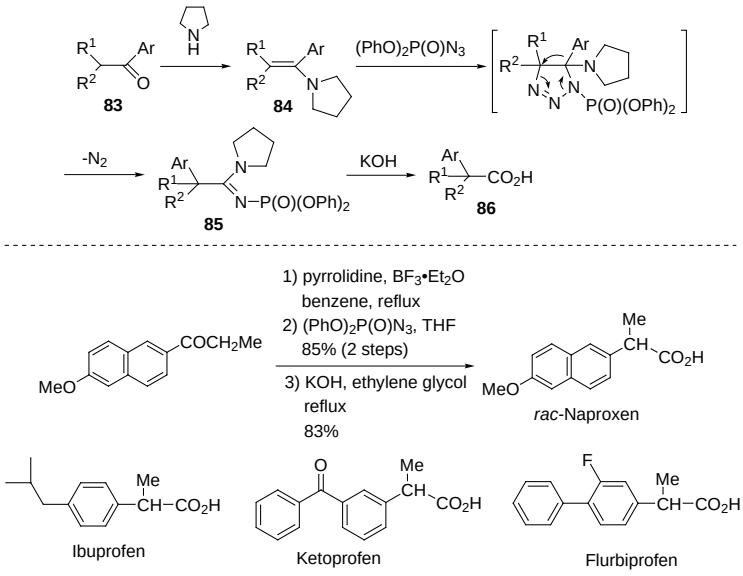
The bicyclic lactams, 2-substituted 2-azabicyclo-[2.2.1]hept-5-en-3-one **91**, react with DPPA under high pressure reaction conditions to give two triazoline derivatives **92** and **93** different from each other about the addition mode.[51a] Irradiation of a mixture of **92** and **93** affords the aziridine derivatives **94**. However, heating under microwave reaction conditions instead of high pressure directly gives the same aziridines **94**, as shown in Scheme 29.[51b]



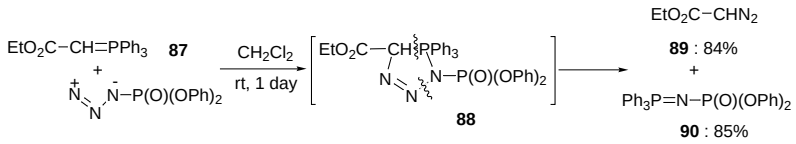
Scheme 25. Ring opening of epoxides with DPPA.



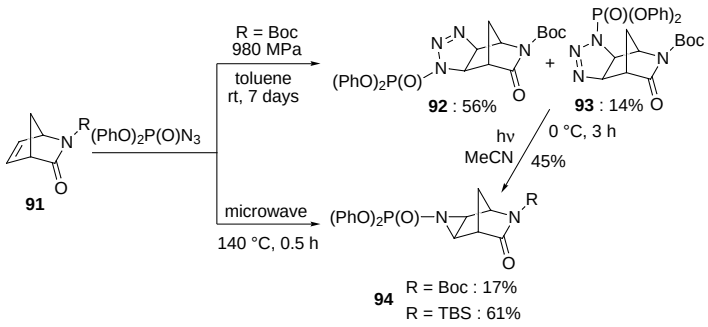
Scheme 26. Ring contraction of enamines of cyclic ketones with DPPA.



Scheme 27. Synthesis of α-arylacetic acids using DPPA.



Scheme 28. Reaction of carbethoxytriphenylphosphorane with DPPA.

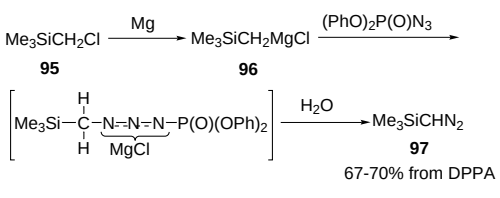


Scheme 29. High-pressure and microwave assisted cycloaddition with DPPA.

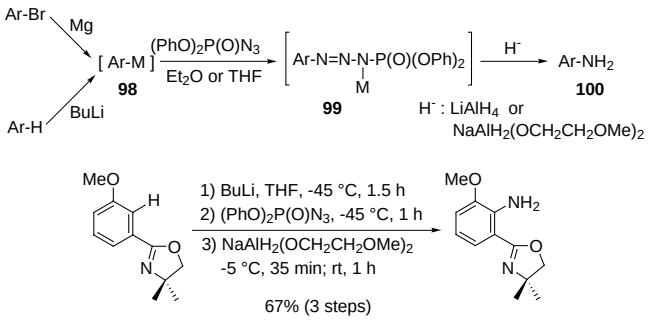
12. Reaction of DPPA with organometalic reagents

DPPA is useful as a diazo-transter reagent just like other azides. Reaction of DPPA with the Grignard reagent **96** prepared from trimethylsilylmethyl chloride (**95**) gives trimethylsilyldiazomethane (**97**), a diazo-transter product, after aqueous work-up, as shown in Scheme 30.[52] The other silyldiazomethanes can be prepared by the same procedure.[53]

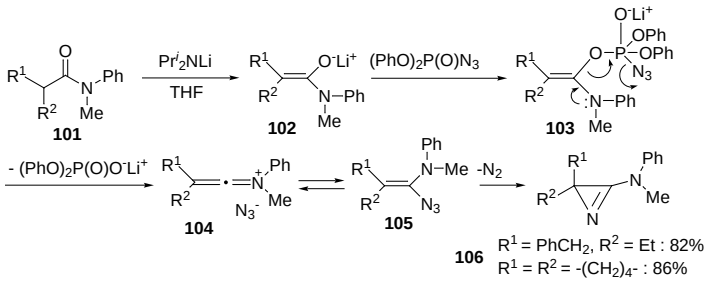
Trimethylsilyldiazomethane, now commercially available, is a stable and safe ("green") substitute for hazardous and labile diazomethane which should be prepared just before its use. Trimethylsilyldiazomethane proved to be a useful and versatile synthetic reagents as a C1 unit introducer, a [C-N-N]azole synthon, and an alkylidene carbene generator.[54]



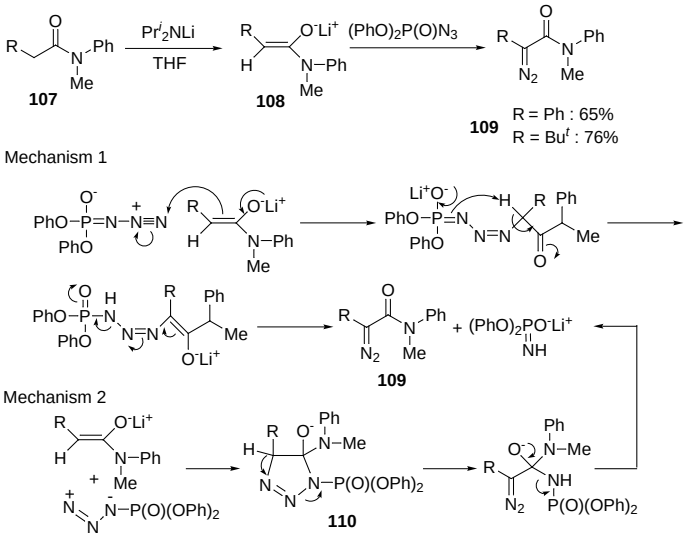
Scheme 30. Preparation of trimethylsilyldiazomethane.



Scheme 31. Conversion of aromatic organometallics to aromatic amines.



Scheme 32. Synthesis of 2*H*-azirines using DPPA.

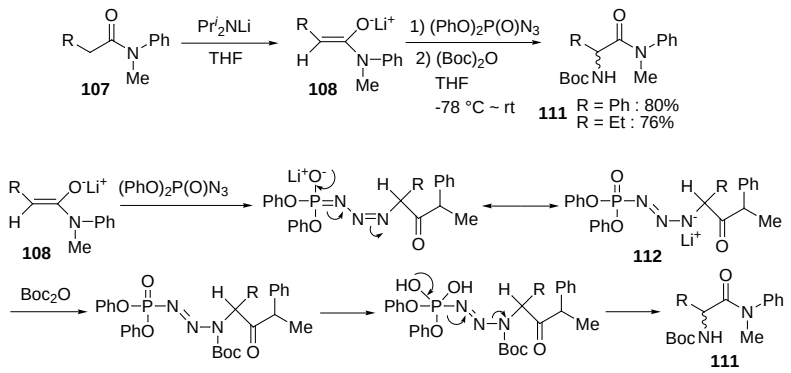


Scheme 33. Diazo-transfer reaction with DPPA.

DPPA reacts with aromatic Grignard or lithium reagents **98** to give the phosphoryltriazene derivatives **99**, which undergo reduction with a hydride reductant such as lithium aluminum hydride or sodium bis(2-methoxyethoxy)-aluminum hydride to give aromatic primary amines **100**, as shown in Scheme 31.[55] Hydrogen chloride in methanol could be used in place of hydride reductants though with less efficiency.[55b] This is an amino-transfer reaction in which DPPA works as a $^{+}NH_2$ synthon. The intermediary phosphoryltriazenes could be isolated but labile. Consequently, successive reactions will give better results. The method is useful for the preparation of a wide variety of both aromatic and heteroaromatic primary amines.

Interestingly, the lithium enolates of *N*-methylanilide derivatives react with DPPA to give three different type products according to reaction substrates or reaction conditions. Reaction of DPPA with lithium enolates **102** derived from the α,α-dialkyl-*N*-methylacetanilides **101** affords 2*H*-azirine derivatives **106**.[56a] The proposed mechanism of the reaction is shown in Scheme 32. The first products by the reaction of DPPA with the enolates **102** will be the phosphate **103**, from which lithium diphenyl phosphate will be eliminated to give the ketenimminium azides **104**. Attack of the azide anion to the ketenimminium cation will furnish the azide enamines **105**, and then finally the 2*H*-azirines **106** will be formed by loss of nitrogen and cyclization. The process is a sort of azide-transfer reaction from DPPA.

On the other hand, lithium enolates **108** from α-monoalkyl-*N*-methylacetanilide **107** react with DPPA under the analogous reaction conditions as above, giving the α-diazo anilides **109** but not the 2*H*-azirines **106**.[56a]



Scheme 34. Amination with DPPA.

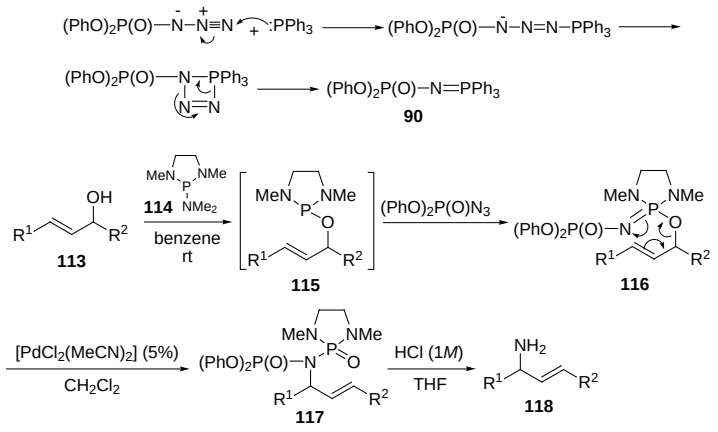
α-Diazo compounds are also formed from *N,N*-dimethylphenylacetamide, methyl phenylacetate and benzyl phenyl ketone though in low yields. The reaction will be a diazo-transfer reaction initiated by attack of the lithium enolates to the terminal nitrogen of DPPA, or a 1,3-dipolar cycloaddition of the enolates **108** to DPPA by which the triazolines **110** will be formed, as shown in Scheme 33.

In contrast, the lithiation of α-monoalkyl-*N*-methylacetanilides **107** and addition of DPPA followed by di-*tert*-butyl dicarbonate (Boc_2O) furnished α-Boc-amino derivatives **111** in good yield, as shown in Scheme 34.[56b] In this reaction, the lithium enolates **108** will react with DPPA to give the phosphoryltriazene anions **112**, to which *tert*-butoxycarbonylation will occur, and then a fragmentation reaction will give the Boc-amino derivatives **111**. DPPA acts as a $^{+}NH_2$ synthon and the amino-transfer reaction occurs just like the reaction of DPPA with the aromatic Grignard or lithium reagents.

13. The Staudinger reaction of DPPA

The well-known Staudinger reaction is a formation reaction of iminophosphoranes having a pentavalent phosphorus atom from azides and trivalent phosphorus compounds. Since the hydrolysis of iminophosphoranes affords amines, iminophosphoranes are a useful intermediate for the transformation of azides to amines. In addition, they are used for the aza-Wittig reaction with various carbonyl compounds. DPPA also reacts with triphenylphosphine, a representative trivalent phosphorus compound, to give the iminophosphorane **90**, shown in Scheme 35.[2]

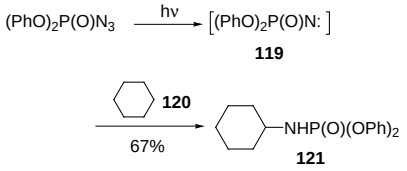
Utilizing the Staudinger reaction of DPPA, an efficient conversion of allylic alcohols to allylic amines accompanied with rearrangement was developed.[57] After the reaction of the allylic alcohols **113** with the phospholidine **114**, the resulting phosphoramidites **115** were successively treated with DPPA to give the phospholidines **116**, a Staudinger reaction product, in an efficient manner. Treatment of the phospholidines **116** with the palladium catalyst $PdCl_2(MeCN)_2$ induced the [3,3]-sigmatropic rearrangement to give the phosphoramides **117**, which were hydrolyzed with hydrochloric acid to the allylic amines **118**. Tosyl azide can be used analogously to DPPA, but the final hydrolysis products were the tosyl amides.



Scheme 35. Staudinger reaction of DPPA.

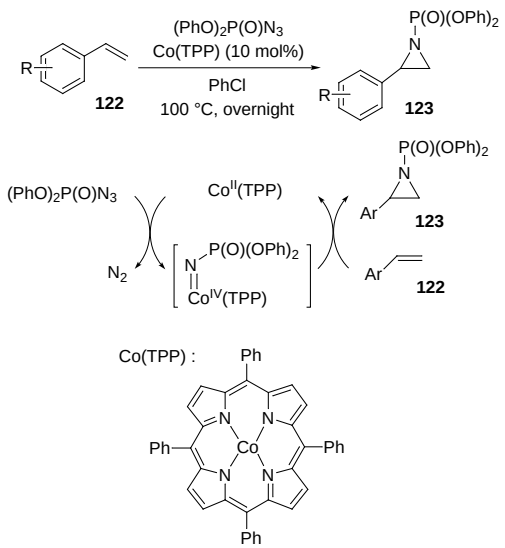
14. DPPA as a nitrene source

Nitrenes are formed by photolysis of various azides, and DPPA also generates the phosphoryl nitrene **119**.[58] The nitrene **119** is reactive and undergoes the C-H insertion reaction with a variety of hydrocarbons. Cyclohexane (**120**) used for a solvent reacts with DPPA to give the cyclohexylamine derivative **121**, as shown in Scheme 36.



Scheme 36. Phosphoryl nitrenes generated from DPPA.

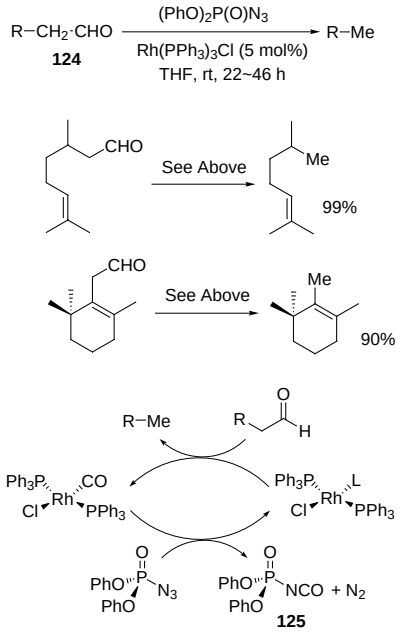
DPPA reacts with styrene derivatives **122** by the catalytic action of cobalt(II) porphyrin complex (Co(TPP)) at 100 °C in chlorobenzene to yield the *N*-phosphorylated aziridines **123** in moderate yield.[59] As shown in Scheme 37, the reaction of DPPA with Co(TPP) affords a cobalt-nitrene intermediate which undergoes the aziridination of the styrene derivatives **122**. Chlorobenzene is the solvent of choice for the aziridination, and the other metals except cobalt are not effective at all. Further, it is necessary to use 5 equivalents of the styrene derivatives.



Scheme 37. Cobalt-catalyzed aziridination of styrene derivatives with DPPA.

15. Decarbonylation using DPPA

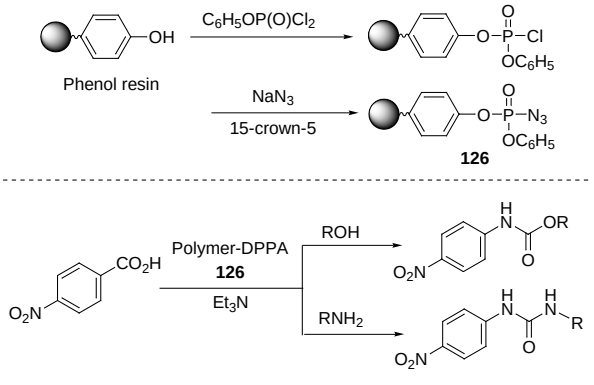
DPPA can be used for the decarbonylation of aldehydes, which smoothly occurs at room temperature by slow addition of an equivalent amount of DPPA to aldehydes **124** in the presence of a catalytic amount of triphenylphosphine rhodium chloride ($Rh(PPh_3)_3Cl$) in THF.[60] The decarbonylation will be considered to proceed as shown in Scheme 38: carbon monooxide will migrate from the aldehydes **124** to the rhodium catalyst and then DPPA will catch the carbon monooxide from the catalyst to give the isocyanate **125** accompanied with loss of nitrogen.



Scheme 38. Decarbonylation of aldehydes using DPPA.

16. DPPA analogs

One of the disadvantages of DPPA from the viewpoint of green chemistry will be the formation of diphenyl phosphate as a waste after reactions using DPPA as an azide equivalent. Thus the polymer-supported DPPA **126** was prepared, and the Curtius rearrangement using **126** was exploited, as shown in Scheme 39.[61] Diphenyl phosphate bounded to the polymer will be easily recovered, and can be recycled by conversion to the azide **126**.



Scheme 39. Polymer-supported DPPA.

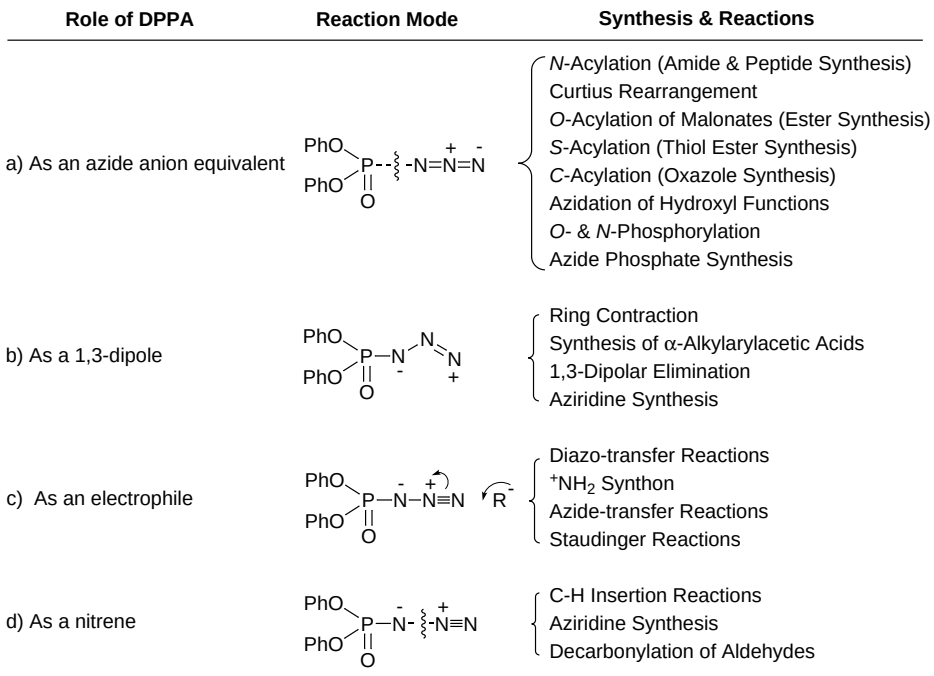


Figure 2. Role of DPPA in organic synthesis.

As described in the one-pot azidation of alcohols, DPPA is slightly less active and the reaction subtrates will be restricted to active alcohols, while *p*-NO_2DPPA prepared easily by nitration of DPPA is much more reactive and can be applied to a wide range of alcohols.[44] The future development of *p*-NO_2DPPA in organic synthesis will be expected because it is now commercially available and a crystalline solid more easily usable than oily DPPA.

17. Conclusion

Various reactions using DPPA can be classified by the reaction modes as shown in Figure 2.

Presumably, the Curtius rearrangement reaction with DPPA will be used most frequently. The one-pot conversion of alcohols to azides by the Bose-Mitsunobu method will also be used quite often, especially in laboratories. Anyway, as you will see here, exploitation of a new synthetic reagent will open the frontier of synthetic organic chemistry. Again, according to *SciFinder*, reaction examples utilizing DPPA are increasing especially from 2000, and there are more than 5,000 examples of the uses of DPPA in 2002, 2004, and 2005. I believe that DPPA will be used more and more in the future, and that new useful reactions utilizing DPPA will be developed hereafter.

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Introduction of the authors

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Education:
B. S. and M. S. University of Tokyo
Ph. D. University of Tokyo
Professional Experiences:

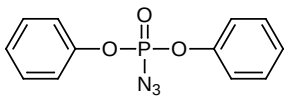
1962-1977	Assistant Professor, University of Tokyo
1968-1970	Postdoctoral Fellow, Professor D. H. R. Barton (1969 Nobel Laureate) at the Imperial College
1977	Associate Professor, University of Tokyo
1977-2001	Professor, Nagoya City University
2001	Emeritus Professor, Nagoya City University
2002-2007	Professor, Graduate School of Environmental and Human Sciences, Meijo University
1990-2007	Regional executive editor of Tetrahedron
2000-2002	President of the Japanese Peptide Society
2001-present	President of the Japanese Society for Process Chemistry

Honor:

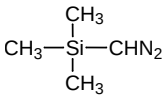
1974	Pharmaceutical Society of Japan Award for Young Scientists
1978	Abbott Prize, Pharmaceutical Society of Japan
1981	Aichi Pharmaceutical Association Encouragement Award
1993	Pharmaceutical Society of Japan Award
1999	Japanese Peptide Society Award

Expertise and Speciality:
Organic Synthesis

TCI Related Compounds



Diphenylphosphoryl Azide (DPPA)
250g, 25, 5g [D1672]



Trimethylsilyldiazomethane
(*ca.* 10% in Hexane, *ca.* 0.60 mol/L)
25ml, 10ml [T1146]