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Organic synthesis in an unconventional solvent, 5.0 M lithium perchlorate/diethyl ether

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Dedicated to Professor Paul A. Grieco, a pioneer in the area of highly concentrated solutions of LPDE as a solvent in organic chemistry

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1. Introduction

It is of fundamental importance to be able to predict the course of a chemical process. At least as important as the reactants, for this prediction, are the conditions under which the reaction is carried out. In solution substantial control is provided by the solvent system in which the reaction is run. A large number of reactions are sensitive to the polarity of the solvent.[1] It is well known that one can use solvent effects may be used to alter either the development and course of a reaction (rate, yield, stereochemistry and regioselectivity) or the position of chemical equilibrium. It is, however, additionally possible to produce such change by addition of chemically inert salts to the reaction medium.[2] As early as 1959, Winstein[3] demonstrated that the ionisation rate of

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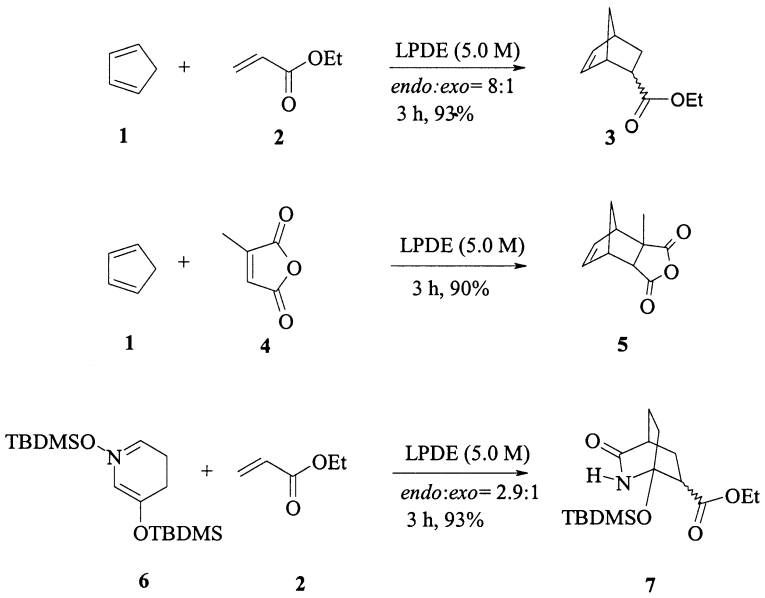


Scheme 1.

p-methoxyneophyl *p*-toluenesulphonate in 0.1 M lithium perchlorate/diethyl ether (LPDE) increased by a factor of 10^5. Similarly, Pocker[4] has observed that 5.0 M LPDE (anhydrous lithium perchlorate is highly soluble in dry diethyl ether and gives a maximum concentration of 6.5 M) increases the rate of ionisation of trityl chloride by 7.0×10^9 compared to diethyl ether alone (the polarity of a 1.5 M LPDE medium on the E_T scale is 53 and is than much higher than of pure diethyl ether, 34.5). In 1986, Sauer had recommended an etheral lithium perchlorate medium for the Diels–Alder reaction.[5] The first publication in which LPDE solutions (5.0 M) were described as new reaction media and catalysts for organic synthesis appeared in 1990.[6] Since then, the scope of this method has been extended to diverse reactions.[7] Some reactions, which usually take place only under rigorous conditions, can occur smoothly under mild conditions at room temperature in this LPDE solvent. In addition, some controversy exists with regard to the reasons underlying this dramatic rate acceleration. Grieco[6] and Kumar[8] have attributed this effect to the high internal pressure generated by the solvent, whereas Forman[9a] Righetti[9b–d] and Kabalka[9e] explained the acceleration in terms of Lewis acid catalysis by the lithium cation.

Caution. Perchlorate salts are of course known to be explosive. It is therefore important that those who wish to use them should be aware of their properties and that appropriate safety precaution should be taken when handling this reagent. The author did not have any accident using LPDE.

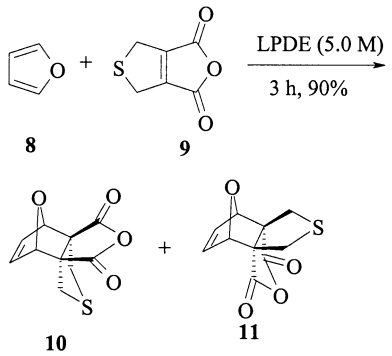
2. Pericyclic reactions

Pericyclic reactions are those that occur by a concerted process through a cyclic transition state and include cyclo-additions, sigmatropic rearrangements and electrocyclisations.

2.1. Intermolecular Diels–Alder reactions

Since the discovery of the cycloaddition between cyclopentadiene and *p*-benzoquinone by Diels and Alder in 1928,[10] the Diels–Alder reaction has become one of the most important reactions in organic synthesis, and has been utilized for the synthesis of six-membered carbocycles and heterocycles by the combination of various 1,3-dienes and dienophiles. Some Diels–Alder reactions are unsuccessful because of the low reactivity of the reaction system and changing the conditions, for example, by using higher temperature, Lewis acid catalysts, high pressures and different solvents, can sometimes accelerate the reaction. High temperatures, however, usually accelerate cycloreversion more than cycloaddition, thereby shifting the equilibrium towards the starting materials and causing side reactions which are also caused by Lewis acids. Highly negative activation volumes (-25 to -45 cm^3 mol^{-1}) for Diels–Alder reactions indicate that high pressures may accelerate the rates of these reactions without the disadvantage of raising the temperature and the use of this technique has been studied widely in the last three decades. An outstanding discovery in cycloadditions was made in 1990, when Grieco et al.[11] reported high rate acceleration of Diels–Alder reactions in 5.0 M LPDE solutions. In this study, different dienophiles, dissolved in a 5.0 M solution of LPDE, were treated with 1.0 equiv. of a diene or azadiene (Scheme 1) at ambient temperature and pressure, and good yields of cycloadducts possessing a high *endo*/*exo* ratio were obtained. In a preliminary study, cyclopentadiene **1** was treated with ethyl acrylate **2** in 5.0 M LPDE solution. After 3 h, a 93% isolated yield of cycloadduct **3** possessing and *exo*/*endo* of 8:1 was obtained. The formation of Diels–Alder adducts, such as **5** normally requires ultra-high pressure and is accompanied by copious amounts of dicyclopentadiene. Interestingly, during the formation of **5**, the rate of dimerization of cyclopentadiene is not affected. In the case of the sensitive diene **6**, reaction with ethyl acrylate **2** was complete in 3 h, and good yields of cycloadducts **7** were obtained. In contrast, the reaction of **6** with **2** in benzene required 72 h at 60°C to completion.

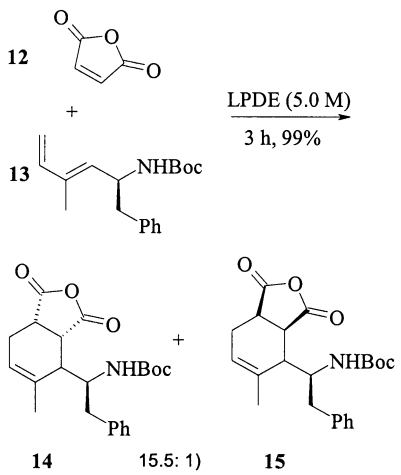
Furan is a poor Diels–Alder diene due to its aromaticity and



Scheme 2.

generally requires pressures in the range of 10–20 kbar to effect cycloaddition. Dauben[12] found that the reaction of furan with the dienophile **9** in methylene chloride required 6 h under 15 kbar pressure in order to realise an 85:15 mixture of the cycloadducts **10** and **11**. The Diels–Alder reaction between furan and the dienophile **9** in 5.0 M LPDE proceeded at ambient temperature and pressure, giving rise (70% after 9.5 h) to the cycloadducts **10** and **11** in an 85:15 ratio. [4+2]-Cycloaddition reactions confirmed a direct correlation between the reaction rate and molarity, with the rate increasing on going from 1.0 to 5.0 M LPDE (Scheme 2).

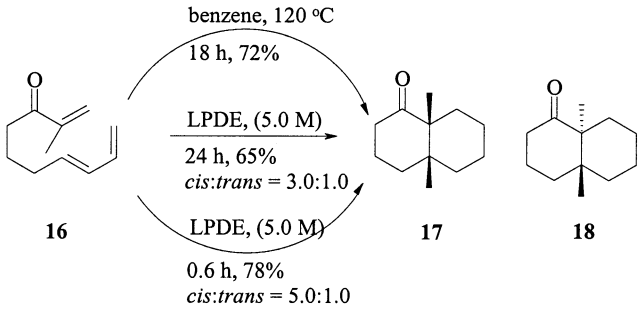
In addition Grieco et al.[13] reported that performing the Diels–Alder reaction in 5.0 M LPDE could enhance the diastereofacial selectivity which is observed during the formation of the cycloadducts **14** and **15** from maleic anhydride **12** an diene **13** in conventional hydrocarbon solvents (Scheme 3).



Scheme 3.

2.2. Intramolecular Diels–Alder reactions

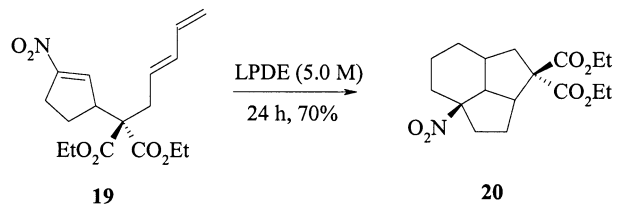
Intramolecular Diels–Alder reactions of the type illustrated in Scheme 4 are often carried out at relatively high temperatures (sealed tubes, and benzene or toluene as solvents). Whereas the yields of the cycloadducts obtained are good, the diastereoselectivity is modest. When 5.0 M LPDE is employed as the medium, the reaction of **16** proceeds at ambient temperature over a 24 h period, giving rise to a comparable yield of **17** and **18** but with an improved



Scheme 4.

diastereoselectivity of 3:1.[14] The intramolecular Diels–Alder reaction of **16** can be dramatically accelerated further by the addition of 1.0–10 mol% of camphorsulphonic acid[15] to the solution of LPDE. Similar results were obtained with a number of other trienones.

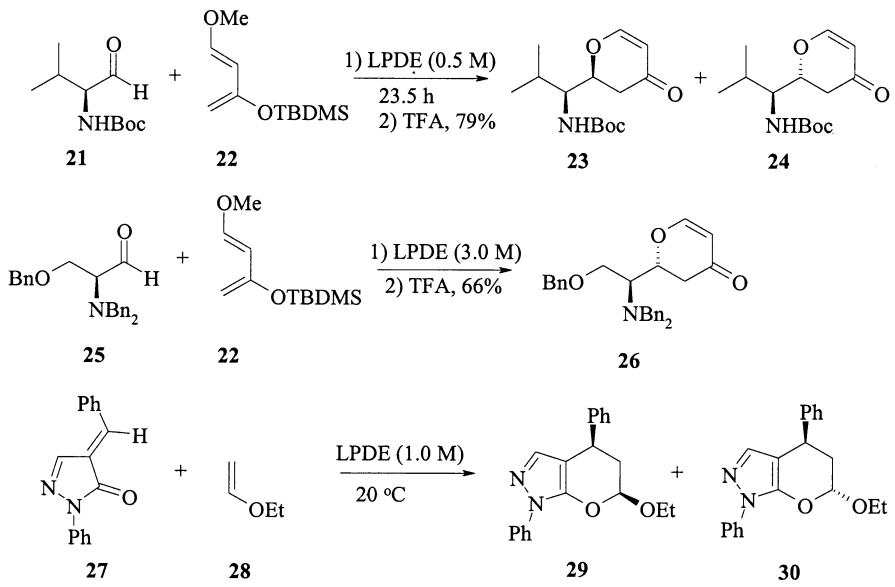
There are few reports in the literature on the catalysis of the Diels–Alder reaction of nitroalkenes.[16] In the presence of classical Lewis acids, it is known that nitroalkenes act as heterodynes, giving rise to cyclic nitronates.[17] The presence of catalytic quantities of $TiCl_2(O\text{-}i\text{-}Pr)_2$ causes exclusive polymerisation of the nitroalkenes. Guy[16] has reported successful results on the catalysis of the intramolecular Diels–Alder reaction of nitrotrienes **19** with a concerted solution of LPDE (5.0 M). Only one *anti* stereoisomer **20** (from *endo* selectivity) was obtained. This remarkably mild intramolecular Diels–Alder reaction proceeds exclusively via an *anti* transition state controlled by electronic and steric effects (Scheme 5).



Scheme 5.

2.3. Hetero-Diels–Alder reactions

For the synthesis of heterocyclic compounds, hetero-Diels–Alder reactions with nitrogen- or oxygen-containing dienophiles are particularly useful. The [4+2]-cycloadducts derived from the cyclocondensation of *N*-protected α-aminoaldehydes with Danishefky's diene represent useful building blocks for the construction of complex aminosugar antibiotics. In 1993, Grieco[18] reported the first example of hetero-Diels–Alder reactions between *N*-Boc-protected α-aminoaldehyde **21** and the *trans*-1-methoxy-3-silyloxy-1,3-butadiene **22**, leading to the formation of dihydropyrones **23** and **24** (after exposure to acid) possessing the *threo* configuration, in LPDE solution. The *threo* configuration is consistent with a chelation-controlled process. The *threo* diastereofacial selectivity could be reversed to *erythro* by changing the nature of the protecting group on nitrogen.[19] The best results were obtained with *N*,*N*-dibenzyl-α-aminoaldehyde **25**. The corresponding *threo* diastereomer could not be detected. α,β-Unsaturated carbonyl compound **27** can serve as the diene component in



Scheme 6.

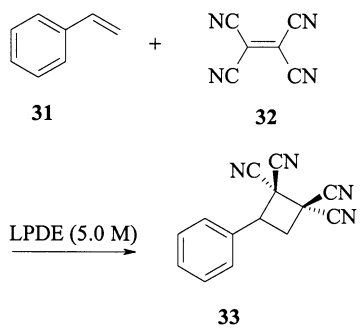
Diels–Alder reaction with ethyl vinyl ether **28** to give 3,4-dihydro-2*H*-pyrans **29** and **30** in LPDE solution (Scheme 6).[20]

2.4. [2+2]-Cycloadditions

The formal [2+2]-cycloaddition is a useful method for cyclobutane, oxetane and azetane synthesis. Thermal concerted [2+2]-cycloadditions are disallowed by orbital symmetry. The photochemical [2+2]-cycloaddition of olefins or the thermal stepwise [2+2]-cycloaddition between electrophilic and nucleophilic olefins has generally been employed for the construction of cyclobutane rings. Lewis acids have occasionally been employed to catalyse [2+2]-cycloadditions.[21] The application of LPDE as a solvent for these cycloadditions has been reported by Huisgen[22] who showed that 2 M LPDE can be used for the synthesis of the [2+2]-cycloadducts of propenyl ethers and tetracyanoethylene.

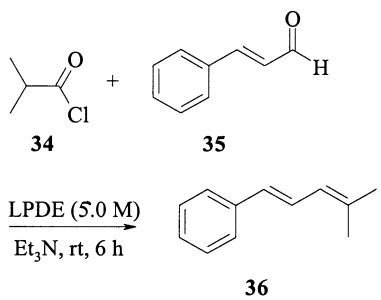
The reaction of phenyl vinyl sulfide with dimethyl cyanofumarate, dimethyl 2-cyano-ethylene-1,1-dicarboxylate, trimethyl ethylene-tricarboxylate and methyl α-cyanoacrylate has been run in 5.0 M LPDE, with efficient [2+2]-cycloaddition taking place at room temperature in near-quantitative yield.[23] For the four electrophilic olefins used in this study, the inverse electron demand [4+2]-cycloaddition is observed with phenyl vinyl sulfide in acetonitrile at room temperature, and no cyclobutane is formed.[24]

Another group of [2+2]-cycloadditions made possible by the use of 5.0 M LPDE as the solvent are the reactions of non-nucleophilic donor olefins, such as styrene **31**, with highly electrophilic olefins such as tetracyanoethylene **32** (TCNE). According to the literature, TCNE and styrene only react at high pressures to give a rather unstable 1:1 Diels–Alder adduct.[25] The use of LPDE 5.0 M as the reaction medium makes cyclobutane formation possible, the desired cyclobutane **33** being obtained in 67% yield (Scheme 7).



Scheme 7.

In 1996, Gossio et al.[26] found that 5.0 M LPDE promotes the direct conversion of ketones and aldehydes into alkenes. This reaction is formally conceived as a tandem [2+2]-cycloaddition–cycloreversion between the aromatic or α,β-unsaturated aldehyde **35** and the in situ-formed ketene (from acyl chloride **34** in the presence of a *tertiary* amine). The substituted alkene **36** was obtained by thermal decarbonylation of the intermediate 2-oxetanone (Scheme 8).

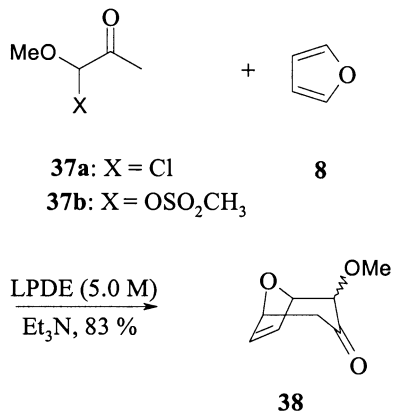


Scheme 8.

2.5. [2+3]-Cycloadditions

Five-membered ring systems are rapidly emerging as important structural features in a large number of natural products and theoretically interesting molecules. One particularly attractive and logical approach to a

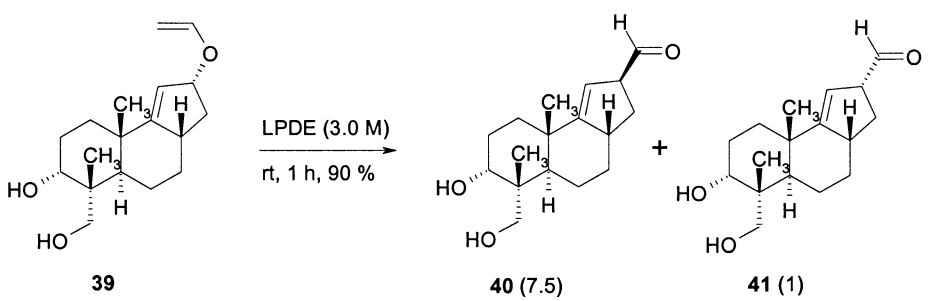
five-membered ring is the [3+2]-cycloaddition. This reaction couples a three-carbon 4π unit directly with a two-carbon 2π unit, forming two C–C bonds in one operation. The success of using the [3+2] methodology in a synthetic sequence depends critically on the effective generation, reactivity and selectivity of the C3 synthon; dimethylenemethane, 2-oxyallyl and trimethylenemethane. 2-Oxyallyl is a useful C3 synthon in [3+2]-cycloadditions because it generates a five-membered ring containing a carbonyl moiety. Although oxyallyl zwitterions can be generated from the ring-opening reaction of cyclopropanones, they have only limited synthetic utility. 2-Oxyallyl can be generated in situ from readily-accessible organic precursors, and these provide an alternative approach. An electrophilic version of the 2-oxyallyl synthon derived from 1-chloro-1-methoxy-2-propanone **37a** or 3-methoxy-2-oxopropyl mesylate has been developed by Foelisch et al.[27] in $LiClO_4/Et_2O/Et_3N$. The oxyallyl intermediate can be trapped by furan in a [3+2]-cycloaddition reaction to provide 8-oxa-bicyclo[3,2,1]oct-en-3-ones **38** (Scheme 9).



Scheme 9.

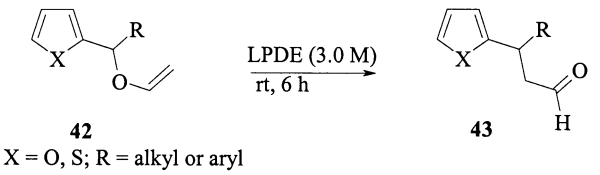
2.6. [1,3]-Sigmatropic rearrangement of allyl vinyl ethers

The thermal rearrangement of allyl vinyl ethers to γ,δ-unsaturated carbonyl compounds was first described by Claisen in 1912.[28] The intervention of the [1,3]-sigmatropic rearrangement during the Claisen rearrangement is a rare event,[29] since a typical [3,3]-sigmatropic rearrangement is energetically and/or sterically unfavourable. In 1991, Grieco[30] reported that allyl vinyl ether **39** undergo unprecedented [1,3]-sigmatropic rearrangement at ambient temperature in 3.0 M LPDE solution. After 1 h, a 90% yield of rearrangement product **40** and **41** was obtained in 7.5:1 ratio (Scheme 10).



Scheme 10.

The [1,3]-sigmatropic rearrangement of allyl vinyl ethers in LPDE solution is applicable to a variety of substrates. [1,3]-Rearrangement is always the major reaction pathway, but traces of products arising from [3,3]-sigmatropic rearrangement and, less commonly, elimination with the formation of dienes have been observed. In 1995, Palani and Balasubramani,[31] described a facile [1,3]-rearrangement of 2-furylmethyl and 2-thienylmethyl vinyl ethers **42** in LPDE. After 6 h at ambient temperature, in modest yield aldehydes **43** were obtained (Scheme 11).



Scheme 11.

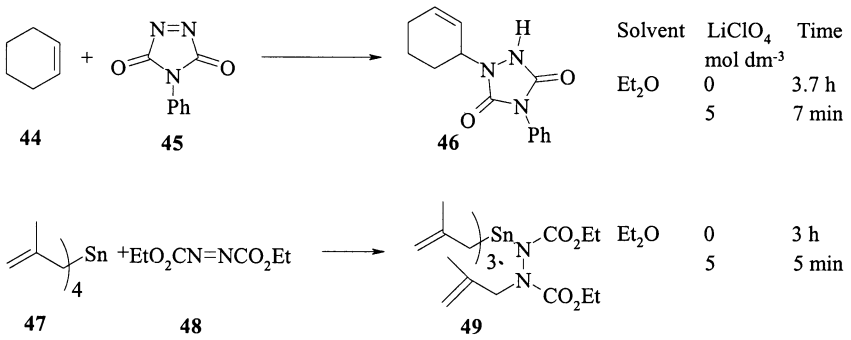
2.7. Ene reactions

The thermal reaction of an alkene having allylic hydrogen (an ene) with a compound containing a double or triple bond (enophile) to form a new bond, with migration of the ene double bond and a 1,5-hydrogen shift, is referred to as the ene reaction. Pioneering studies by Davies and Kinart[32] demonstrated that the ene reactions of allylic hydrocarbons, and metalloene reaction of some allyltin compounds, with 1,3,4-triazole-2,5-dione **45**, or diethyl azodicarboxylate **48** as the enophiles, in diethyl ether are strongly accelerated by lithium perchlorate (Scheme 12).

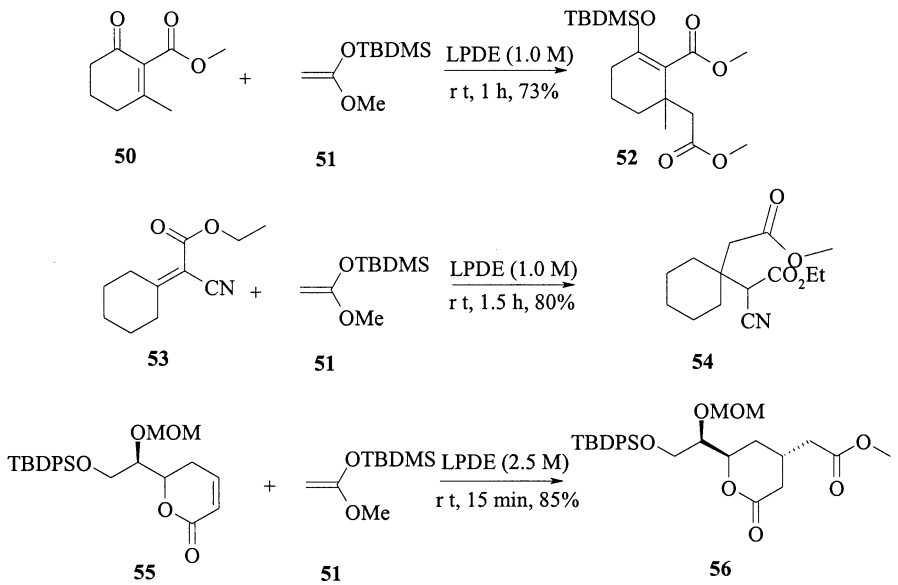
The triazoledinone **45** gave hydrogen-ene product **46** with the cyclohexene **44**, whereas diethyl azodicarboxylate **48** gave only the metalloene product **49** with tetrakis-(2-methylprop-2-en-1-yl)tin **47**.

3. Nucleophilic additions and substitutions

Nucleophiles are molecules or ions with non-bonded pairs of electrons. These species are electron-rich and can react with electron-poor ions or molecules (electrophiles). For nucleophilic additions involving anionic nucleophiles, either bases or acids can often catalyse the reaction. An acid catalyses the reaction through complexation with the polar group of the reactant, further polarising the electrophile and lowering the activation energy of the reaction. Only acids will therefore catalyse the use of neutral nucleophiles for additions.



Scheme 12.



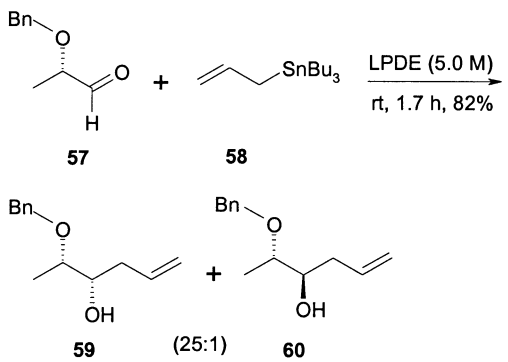
Scheme 13.

3.1. Addition of *O*-(trialkylsilyl)ketene acetals to α,β-unsaturated carbonyl compounds

The lithium perchlorate-catalysed Michael reaction has been conducted on a number of substrates, including sterically demanding, β,β-disubstituted, α,β-unsaturated carbonyl compounds. Treatment of enone **50** in 1.0 M LPDE with 1-methoxy-1-(*t*-butyldimethylsiloxy)ethylene **51** for 1 h gave the 1,4-addition product **52** in 73% yield. Lithium perchlorate has also been used to catalyse the conjugate addition of silyl ketene acetals to α,β-unsaturated δ-lactones. Treatment of the δ-lactone **55** in 2.5 M LPDE with ketene acetal **51** gave Michael-product **56** in 85% yield. In general, the reactions are conducted at ambient temperature and pressure (Scheme 13).[33]

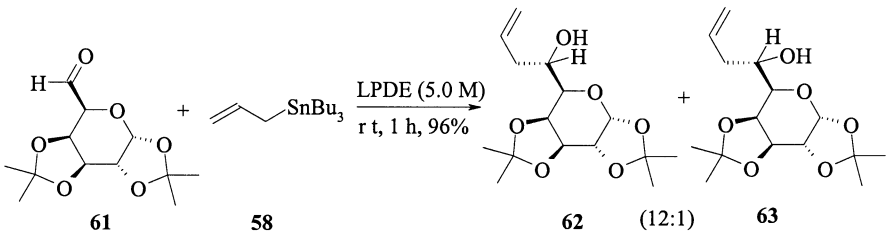
3.2. Addition of allylmetals to aldehydes

The addition of allylmetals such as allylsilanes, allylboranes or allylstannanes to aldehydes and ketones is a highly efficient and widely used method for the synthesis of homoallylic alcohols. The addition of allylstannanes to aldehydes has been shown to proceed in the presence of conventional Lewis acids such as titanium tetrachloride, zinc iodide and magnesium bromide.[34] In the absence of Lewis acids, allylstannanes do not react with aldehydes at ambient temperature and pressure.[35] In 1992, Grieco et al.[36a] have reported that the addition of tri-*n*-butylallylstannane **58** to α-benzyloxyaldehyde **57** proceeds rapidly in 5.0 M LPDE, providing high yields of the chelation-controlled products.[36b] After 1.7 h, at ambient temperature, the alcohols **59** and **60** were obtained in a ratio of 25:1 (Scheme 14).



Scheme 14.

The reaction of tri-*n*-butylallylstannane **58** with the galactose derivative **61** proceeds similarly, with high diastereofacial selectivity in 5.0 M LPDE via chelation-controlled catalysis by the lithium ion. After 1 h, a



Scheme 15.

96% yield of **62** and **63** were obtained in a ratio of 12:1 (Scheme 15).

Optically active α,β-epoxyaldehydes are readily available via Sharpless epoxidation of allyl alcohols followed by oxidation. The additions of allylmetals to *trans*- or *cis*-α,β-epoxyaldehydes have been investigated and have revealed moderate to good diastereoselectivities, with the *anti* adducts always predominating, regardless of the degree of selectivity.[37] The Felkin–Anh model (Fig. 1A) would account for these *anti* selectivities. *Syn* selectivity should stem from the chelation-controlled addition of nucleophiles to α,β-epoxyaldehydes (Fig. 1B) and a Lewis acid having a strong coordinating ability seems to improve the *syn* selectivity. This route to *syn* selectivity cannot, however, be applied to α,β-epoxyaldehydes, because the strong coordination of a metal cation to an epoxide moiety will result in its destruction via ring opening.[38]

Studies by the author's group[39] on the addition of tri-*n*-butylallylstannane to α,β-epoxy aldehydes have shown that the reaction of *trans*-substituted α,β-epoxyaldehydes **64** with allylstannanes provides a general method for the synthesis of the corresponding *syn*-alcohols **65** with high selectivity. When *cis*-epoxyaldehyde **67** was treated with allylstannane **58**, *syn*-alcohol **69** was produced as the major component of an 86:14 mixture. For *cis*-substituted α,β-epoxyaldehydes, the selectivity depends on the size of the substituents (Scheme 16).

Quinones are excellent Michael acceptors and, due to their low reduction potential, they also undergo electron transfer-mediated reactions with nucleophiles. The allylation of quinones is an important reaction for the preparation of biologically active isoprenoid quinones, for which a series of synthetic methods already exists. The allylation of quinones with allylsilanes have been reported in 5.0 M LPDE solution.[40] When 1,4-benzoquinone **71** was used, the allylation reaction with allylsilane **72** produced the corresponding coupling product **73** in 75% yield and reductive product **74** in 12.5% yield (Scheme 17).

4. Mannich-type reactions

Mannich-type reactions (three-component condensation reactions) are interesting and important, not only because two bonds are formed in one-pot, but also because the methodology would be useful for making a broad variety of compound libraries.[41] The classical intermolecular three-component Mannich reaction is, however, plagued by a number of serious disadvantages.[42] Due to the drastic

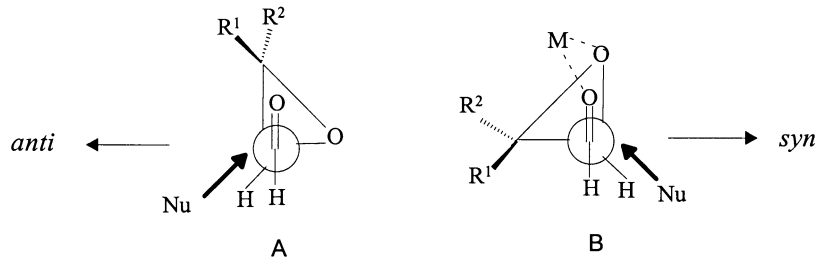
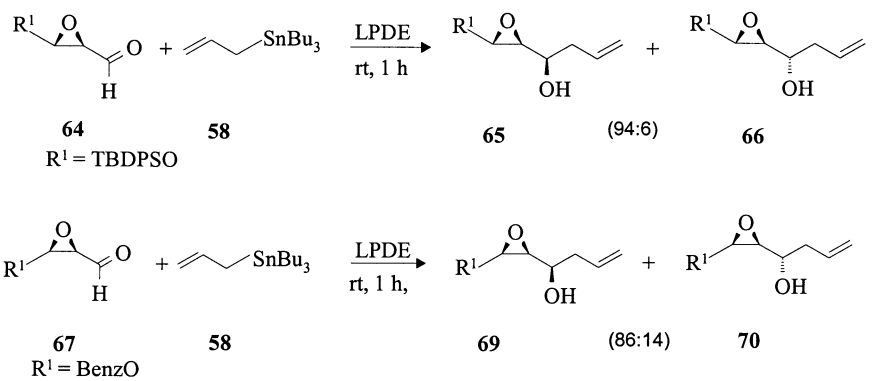
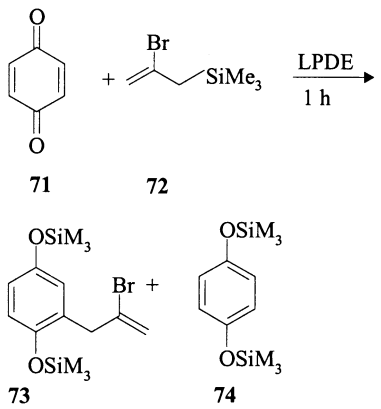


Figure 1.



Scheme 16.

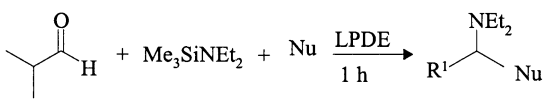


Scheme 17.

reaction conditions, unwanted side reactions often take place and the major problems here are deamination and the formation of methylene bisketones. If a primary amine is used, the reaction can continue until all of the hydrogen atoms on the nitrogen are replaced. Additionally, and with very few expectations, only formaldehyde (and non-enolizable aldehydes) can be used.

4.1. Aminoalkylation of aldehydes

Due to the very attractive nature of the Mannich bases, there have been many attempts to find alternative synthetic routes to β-aminocarbonyl compounds which do not suffer the severe drawbacks of the classical procedure. Modern versions of the Mannich reaction usually allow a distinctly simpler entry into β-aminocarbonyl compounds through the use of preformed electrophiles (e.g. iminium salts or imines) or nucleophiles (enolates, enol ethers and enamines). In this way, the reaction is not restricted to aminomethylation, and aminoalkylation is also possible. In this context, Mannich products have been synthesised from enolisable aldehydes in good to excellent yields by the addition of nucleophiles to benzotriazole derivatives,[43] as well as by the three-component addition of C-nucleophiles such as diethylzinc **76a**, (trimethylsilyl)methyllithium **76b** and *O*-(trimethylsilyl)ketene acetal **76c**, to (trimethylsilyl)diethylamine **75** and aldehyde **74** in concentrated etheral $LiClO_4$ solution[44] led to the corresponding amine **77**. The formation of iminium intermediates has been postulated without real investigation (Scheme 18).

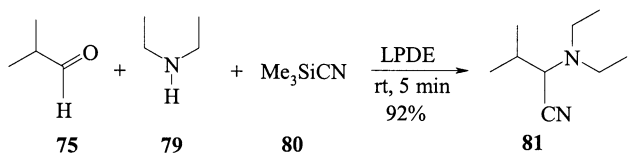


	Nucleophile	Yield (%)
a	Et_2Zn	95
b	$LiCH_2SiMe_3$	83
c	$CH_2C(OPh)(OSiMe_3)$	95

Scheme 18.

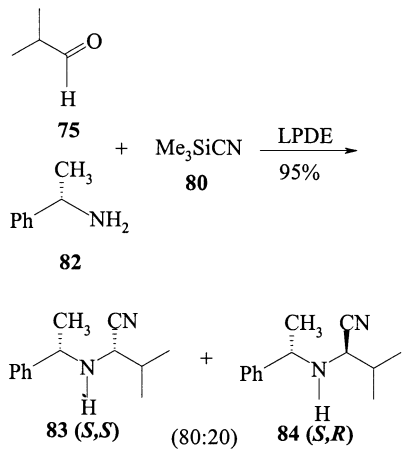
4.2. Aminocyanation of aldehydes

α-Aminonitriles are important intermediates in the preparation of many α-amino acids. Numerous methods describing the preparation of α-aminonitriles are reported in the literature. Most of these reactions, however, involved lengthy reaction conditions and tedious work up. In studies by the author and his co-workers on the Mannich reaction, a very mild, convenient, simple, one-pot and fast procedure for the preparation of α-aminonitriles has been developed from aldehydes+amines+trimethylsilyl cyanide in LPDE.[45] Aminocyanation of isobutyraldehyde **74** with diethylamine **78** and trimethylsilyl cyanide **79** in 5.0 M LPDE solution gave the corresponding α-aminonitrile **80** in excellent yields (Scheme 19).



Scheme 19.

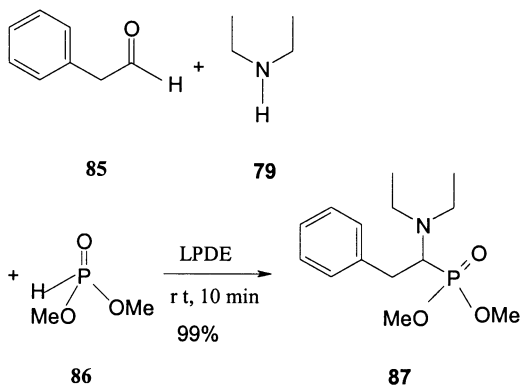
Optically active α-aminonitriles **82** and **83** were synthesized by using (*S*)-(−)- or (*R*)-(+)-α-methylbenzylamine **81**, (*S*)-(−)-α-methylbenzylamine affording predominantly (*S*)-aminonitriles and (*R*)-(+)-α-methylbenzylamine leading to the (*R*)-aminonitriles. This reaction with (*S*)-**82** and (*R*)-**82** always gave similar enantiomeric results. In addition, Ojima and Stout obtained similar stereochemical results in their studies of TMSCN or potassium cyanide addition to chiral Schiff bases when the bases are prepared from (*S*)-**82** and (*R*)-**82**.[46] The diastereoselectivity achieved in the author's method can be explained on the basis of the aza analogue of the Anh–Eisenstein hypothesis (Scheme 20).[47]



Scheme 20.

4.3. Aminophosphonation of aldehydes

α-Aminophosphonic acids and their diesters exhibit a wide range of biological activities. A large number of methods have been devised for the preparation of α-aminophosphonates.[48] The author and his co-workers have reported a general method for the one-pot

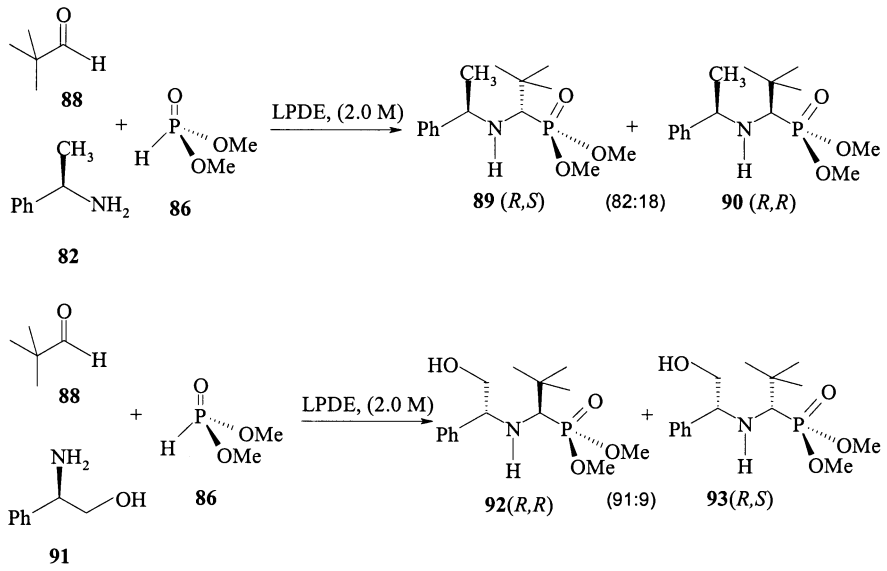


Scheme 21.

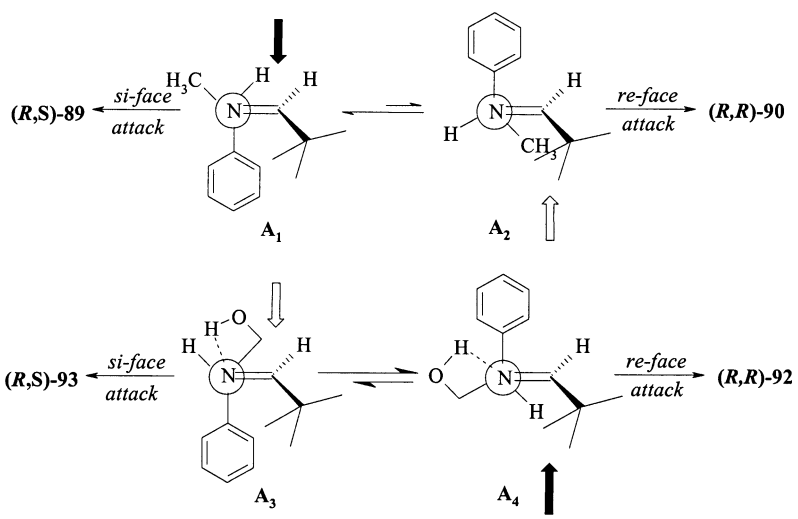
α-aminoalkylation[44] and α-aminocyanation[45] of aldehydes in a solution of LPDE (5.0 M). In order to extend this methodology, the reaction was examined using dimethyl phosphite as the nucleophile and α-aminophosphphosphonate **87** were prepared by stirring a mixture of phenylacetaldehyde **85**, diethylamine **79** and dimethyl phosphite **86** in 5.0 M LPDE (Scheme 21).[49]

Optically active α-aminophosphonates were synthesised by using (*R*)-(+)- or (*S*)-(−)-α-methylbenzylamine **82**, (*R*)-(−) or (*S*)-(+)-2-phenylglycinol **91**. α-Aminophosphonates **89** and **90** can be generated from aldehyde **88**, amine **82**, and dimethyl phosphite **86**, in an 82:18 ratio. When aminoalcohol **91** is treated with aldehyde **88** and dimethyl phosphite **86**, the main product is α-aminophosphonate **92**. (*R*)-(+)-α-methylbenzylamine affords predominantly (*S*)-α-aminophosphonates and (*R*)-(−)-2-phenylglycinol leads predominantly to (*R*)-α-aminophosphonates (Scheme 22).

The diastereoselectivity achieved by this method can be explained on the basis of the aza analogue of the Anh–Eisenstein hypothesis.[47] According to this hypothesis, nucleophilic attack on the imine should take place antiperiplanar to the α-phenyl group. Other work on



Scheme 22.



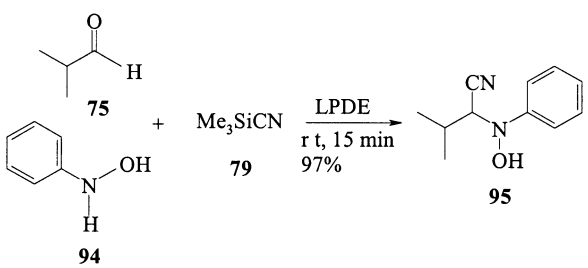
Scheme 23.

the attack of nucleophiles on imines with an adjacent stereogenic centre, has been explained in the same way (Scheme 23).[50]

Of the possible transition states $\mathbf{A_1}/\mathbf{A_2}$ and $\mathbf{A_3}/\mathbf{A_4}$ where the phenyl group is perpendicular to the imine π-plane, conformers $\mathbf{A_1}/\mathbf{A_4}$, in which the attack takes place from the *si*-face or *re*-face of the imine, give rise to the major (*R*,*S*)-**89** and (*R*,*R*)-**92** diastereomers. The transition state $\mathbf{A_4}$ is more favourable not only for steric reasons, the hydroxymethyl group being located away from the imine moiety and the incoming nucleophile, but also for extra stabilisation intramolecular five-membered ring H-bonding.[51] This explains the enhanced diastereoselectivity observed with α-phenylglycinols in comparison with α-methylbenzylamines as the chiral auxiliary where stabilisation due to intramolecular H-bonding is not possible.

4.4. Cyanohydroxylamination of aldehydes

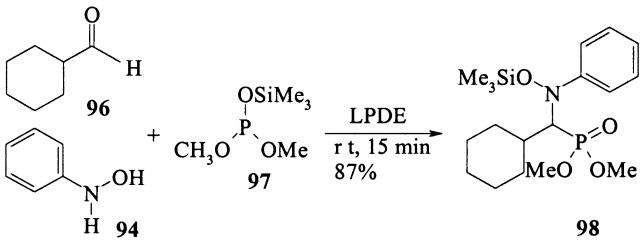
Nitrones are a particularly interesting class of compounds by virtue of their utility in organic synthesis. They are reactive starting materials in a large number of 1,3-dipolar cycloadditions and can act as electrophiles with a variety of both carbon and heteronucleophiles. Lewis acids are known to promote these reactions. Some nitrones, however, especially α-aliphatic nitrones, are unstable under these conditions and low yields are sometimes observed.[52] It is desirable from a synthetic point of view that the nitrones, which are prepared in situ from aldehydes and hydroxylamines, react immediately with the nucleophiles. Although a solution of the aldehyde **75**, phenylhydroxylamine **94** and trimethylsilyl cyanide **80** in diethyl ether remains unchanged after 4 h at room temperature, the reaction in 5.0 M LPDE solution, followed by hydrolysis, leads to the formation of the α-cyanohydroxylamine **95** within 15 min, in high yields. α-Cyanohydroxylamines are an important class of compounds, their hydrolysis producing *N*-hydroxylamino acids, which undergo catalytic hydrogenation to give amino acids. It is of interest to note that α-cyanohydroxylamines can be converted into the corresponding nitrones upon treatment with bases, with elimination of hydrogen cyanide.[53] It should be also noted that most Lewis acids cannot be used in this reaction since they are decomposed or deactivated by the amines and water which exist at the stage of nitrone formation.[52] Not only aromatic, but also aliphatic and heterocyclic, aldehydes reacted smoothly under these conditions (Scheme 24).



Scheme 24.

4.5. One-pot synthesis of *N*-trimethylsilyloxy-α-aminophosphonates

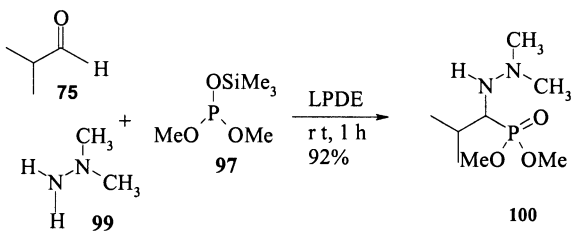
Although the chemistry of α-hydroxyphosphonates and α-aminophosphonates has been extensively studied, the author was surprised to note that, to the best of his knowledge, only a few syntheses of chiral *N*-hydroxy-α-aminophosphonic acids have been reported in the literature. These included addition of phosphite anions and tris(trimethylsilyl) phosphite to chiral *N*-glycosyl-*C*-aryl-nitrones in the presence of Lewis acids,[54] and a Mitsunobu S_N2-type displacement reaction of the corresponding α-hydroxyphosphonates with *N*-(phenoxycarbonyl)-*O*-*tert*-butyloxycarbonyl hydroxylamine.[55] In 2001, the author's group reported that *N*-trimethylsilyloxy-α-aminophosphonates **98** can be prepared in good yields by a novel three-component synthesis in with a nitrone (generated in situ from the aldehyde **96** and phenylhydroxylamine **94**) is reacted with dimethyl trimethylsilyl phosphite **97** as a nucleophile in LPDE solution (5.0 M) at room temperature, within 15 min (Scheme 25).[56]



Scheme 25.

4.6. One-pot synthesis of α-hydrazinophosphonates

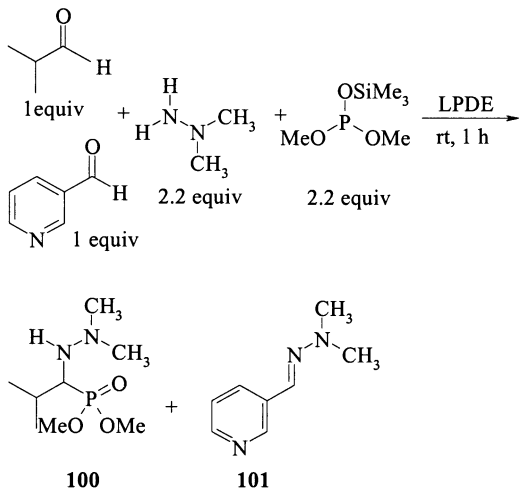
As analogues of α-aminoalkylphosphonic acids, α-hydrazinoalkylphosphonic acids and their derivatives are of potential biological importance. These compounds, for example, show a good safening effect against the phytotoxic action of chloroacetanilide herbicides.[57] To the best of the author's knowledge, relatively few examples of the synthesis of α-hydrazinophosphonic acids have been reported, namely base-catalysed condensation of diethyl phosphite with aliphatic aldazines followed by subsequent acid hydrolysis[58] (this method was, however, not suitable for aryl aldazines), selective reduction of the α-hydrazonophosphonic acids with $NaBH_3CN$ or BH_3·THF,[59] nucleophilic substitution of 1-sulfonyloxyalkylphosphonates by



Scheme 26.

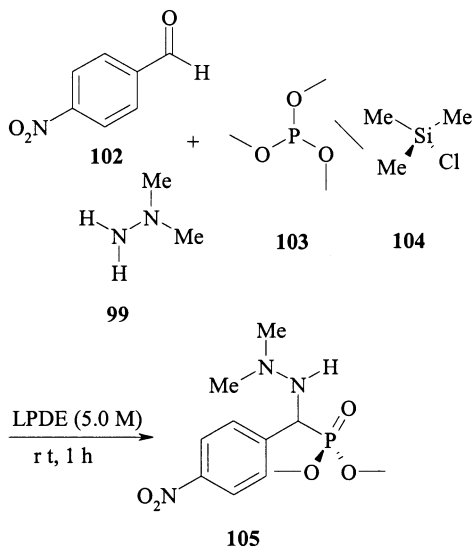
hydrazine,[60] and nucleophilic substitution of 3-methoxy-1,2,3,6-tetrahydropyridazine derivatives by dimethyl phosphite in the presence of a Lewis acid.[61] It has been reported that α-hydrazonophosphonate **100** can be prepared in good yields by a new multicomponent synthesis in which a hydrazone (generated in situ from the aldehyde **75** and *N*,*N*-dimethylhydrazine **99**) is reacted with dimethyl trimethylsilyl phosphite **97** as a nucleophile, in LPDE solution (5.0 M) at room temperature, within 1 h (Scheme 26).[62]

This method seems to be a general synthetic route to α-hydrazinophosphonates. Benzaldehyde *p*-methoxybenzaldehyde, 3-pyridinecarbaldehyde and cinnamaldehyde are, however, inert to nucleophilic addition of dimethyl trimethylsilyl phosphite in a one-pot three-component reaction.[63] Additionally, the author has found that hydrazonophosphonation of an aliphatic aldehyde rather than an aromatic was performed in more than 99% selectivity. The reaction of isobutyraldehyde, 3-pyridine carbaldehyde with *N*,*N*-dimethylhydrazine and dimethyl trimethylsilyl phosphite in 5.0 M LPDE solutions give α-hydrazinophosphonate **100** and 3-pyridinehydrazone **101**, respectively (Scheme 27).



Scheme 27.

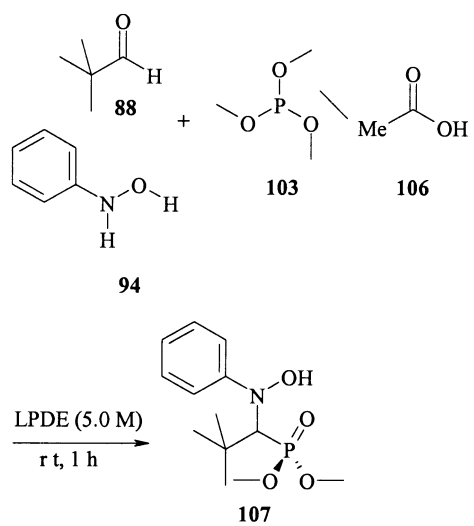
Unfortunately, the scope of application of this method is limited to α-hydrazinoalkylphosphonic esters. The author has found his successful trials on the synthesis of α-hydrazino alkyl (aryl, heterocyclic) phosphonic acids via three-component reaction of aldehyde **102**, *N*,*N*-dimethylhydrazine **99** and trimethylphosphite **103**/trimethylsilyl chloride **104** in LPDE solution (5.0 M) within 1 h in high yields.[64] Without LPDE solution, no reaction was observed after 4 h. These results clearly indicate that the present strategy becomes a general phosphonilation protocol for a variety of alkyl, aryl and α,β-unsaturated hydrazone derived from different aldehydes. In conclusion, the author has shown the first example of the successful dimethyl trimethylsilyl phosphite (the formation of dimethyl trimethylsilyl phosphite has been postulated without real investigation)[65] addition to a wide range of hydrazones which would provide a novel and general method for preparing not only α-hydrazinoalkylphosphonates but also α-hydrazinoaryl (heterocyclic)phosphonates via the four-component coupling reactions (Scheme 28).



Scheme 28.

On the basis of the good results obtained with different hydrazones, it seemed logical to investigate the possibility of extending this methodology to simple alkyl, aryl and α,β-unsaturated nitrones, which gave *N*-hydroxy-α-amino phosphonates. Unfortunately, there were no observable three-component reactions of aldehyde **88**, phenylhydroxylamine **94** and trimethylphosphite **103**/trimethylsilyl chloride **104** at ambient temperature in 5.0 M LPDE. In order to improve the reaction, the author's group have examined several reaction conditions and finally found that the desired product was obtained in high yield when acetic acid **106** as co-catalyst was added, and in all cases, the desired products **107** were obtained in high yields (Scheme 29).[64]

Encouraged by this result, the author replaced trimethylsilylchloride with acetic acid in one-pot three-component hydrazinophosphonilation reaction. No reaction was

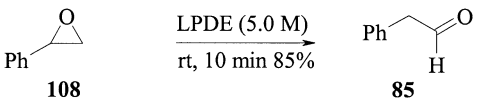


Scheme 29.

observed with this reagent, even after 4 h at room temperature.

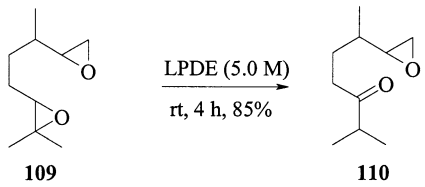
5. Chemo- and regioselective isomerisation of epoxides to carbonyl compounds

Epoxides are one of the more useful classes of substrates available to the synthetic organic chemist. Conversion of an epoxide to a carbonyl compound is a synthetically useful reaction. The acid-catalysed rearrangement of epoxides to carbonyl compounds is a well-known synthetic transformation and a number of reagents have been elaborated for this purpose. The lack of chemo-, regio- and stereoselectivity in the epoxide ring-opening/rearrangement steps can, however, lead to the formation of multiple products and can limit the use of this reaction in synthetic sequences.[66] It is therefore desirable to have a mild reagent that is capable of effecting this transformation under neutral conditions. Recently, the chemo- and regioselective isomerisation of epoxides to carbonyl compounds by 5.0 M LPDE solution has been reported.[67] The following examples illustrate the high chemo- and regioselectivity observed in LPDE. Only those oxiranes with either a benzylic or a tertiary centre undergo rearrangement in LPDE. Rearrangement of styrene oxide **108** in 5.0 M LPDE gave phenylacetaldehye **85** in 85% yield. The epoxides of terminal olefins are much less reactive than internal olefin epoxides, thus enabling the chemoselectivity. The bis-epoxide **109** rearranged to epoxy ketone **110** as the only product in which the terminal epoxide intact under reaction conditions (Schemes 30 and 31).



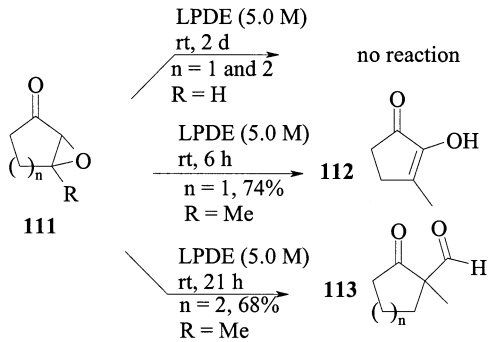
108 **85**

Scheme 30.



109 **110**

Scheme 31.



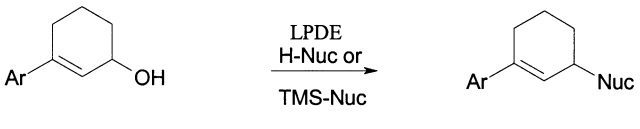
111

Scheme 32.

In a similar manner, the epoxides from α,β-unsaturated carbonyl compounds **111** rearranged with high chemo- and regioselectivities leading to the formation of 1,3-dicarbonyl compounds **112** and **113** (Scheme 32).

6. Substitution reactions of allylic acetates and allylic alcohols

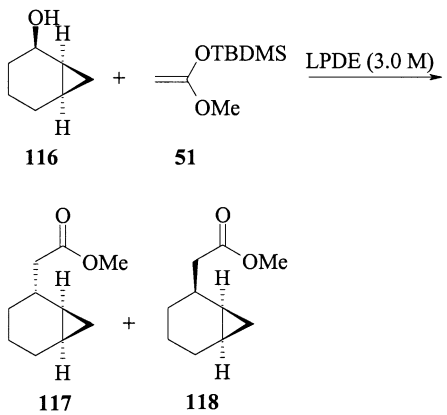
It has been shown that allylic alcohols and allylic acetates undergo facile substitution by a variety of nucleophiles (with electron-rich π-bonds such as those in ketene acetals, allyl- or propargyltrimethylsilane, enol ethers, and π-excessive heterocycles) in concentrated solutions of LPDE (3.0 M).[68] Experiments show that exposure of allylic alcohol **114** to various carbon nucleophiles let to substitution product **115** in good yield (Scheme 33).



114 **115**

Scheme 33.

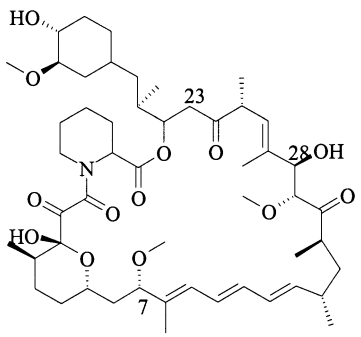
In addition to carbon–carbon bond formation, these nucleophiles led to the introduction of carbonyl, alkene, allene and cyano functional groups, as well as heterocyclic rings. The formation of the allylic azide illustrates the possibility of carbon–heteroatom bond formation. In principle, the chemistry depicted in Scheme 33 should be applicable to cyclopropyl carbinols. Indeed, the cyclopropyl carbinol **116** upon exposure (15 min) to 2.0 equiv. of the ketene acetal **51** in 3.0 M LPDE undergoes smooth transformation into a 4:1 mixture of **117** and **118** in 75% yield (Scheme 34).



116 **51** **117** **118**

Scheme 34.

Wustrow and co-workers[69] have used triethylsilane in LPDE solution for the selective deoxygenation of allylic alcohols and acetates. A series of cyclic secondary allylic alcohols and acetates was deoxygenated. Under these conditions, the allylic oxygen functionality was selectively removed in the presence of esters, isolated olefins, ketals and *tertiary* alcohols. Primary alcohols were not deoxygenated under these conditions.



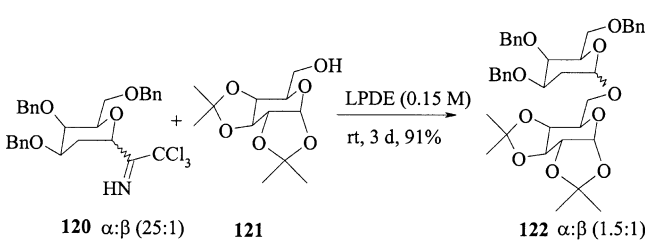
119

In 1995, Luengo[70] reported that anhydrous 5.0 M LPDE promotes the smooth ionisation of the allylic C7 methoxy group in rapamycin **119** (a highly functionalised molecule which displays a number of different reaction sites under Lewis acid catalysis) to provide either substitution or elimination products.

7. Glycosidation reactions

Glycoside synthesis is a very common reaction in nature, providing a wide range of compounds, such as oligosaccharides, glycolipids, glycoproteins and many other naturally occurring substances. The development of a stereoselective glycosidation reaction is an important topic in organic chemistry and a variety of glycosidation methods have been developed since the first use of the classical Koenigs–Knorr[71] reaction. Of these methods, glycosyl halides (fluorides, chlorides and bromides) in combination with silver or mercury salts belong to the well-established and reliable techniques of carbohydrate chemistry. As an alternative to the classical Koenigs–Knorr process, the use of glycosyl trichloroacetimidates, thioglycosides, glycosyl phosphites and glycosyl phosphates has been developed.

Waldmann et al. have used lithium perchloride in various organic solvents to activate glycosyl donors in the absence of any other harsh and strong Lewis acids and heavy metal salts, and have reported a number of glycosidation reactions under essentially neutral conditions.[72] If the glycosyl trichloroacetimidate **120** is treated with protected glucose derivative **113** in 0.15 M solution of LPDE, the disaccharide **122** are formed under neutral condition in 91% yield with the α-anomer predominating (Scheme 35).

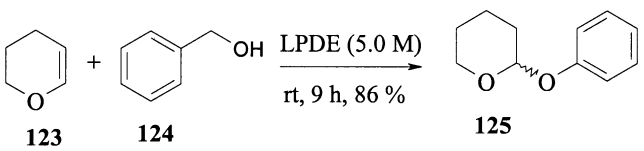


120 α:β (25:1) **121** **122** α:β (1.5:1)

Scheme 35.

8. Protection of alcohols as tetrahydropyranyl ether

Treatment of 3,4-dihydro-2*H*-pyran with a variety of alcohols (benzylic, primary, secondary, tertiary, allylic or propargylic) in 5.0 M LPDE at ambient temperature afford the corresponding tetrahydropyranyl ether.[73] treatment of pyran **123** with benzyl alcohol **124** afforded 2-benzyl tetrahydropyranyl ether **125** in 86% yield (Scheme 36).

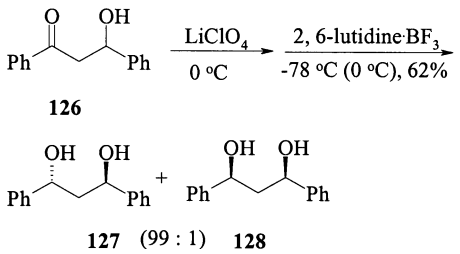


123 **124** **125**

Scheme 36.

9. Diastereoselective reduction of β-hydroxyketones

The *syn* and *anti* 1,3-diols are found in a variety of natural products. In 1997, Kabalka[74] found that the reduction of β-hydroxyketone **126** with amineboranes in the presence of lithium perchlorate produces the corresponding *anti* 1,3-diol **127** as the major products. Among the amineboranes that were utilised, *N*,*N*-diethylanilineborane and 2,6-lutidineborane gave the highest diastereoselectivity (Scheme 37).



126

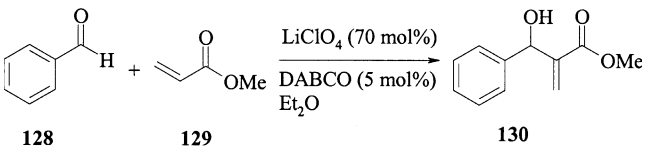
127 (99 : 1) **128**

Scheme 37.

The *anti*-selectivity suggests that the borane complexes can bind to the hydroxyl group, an intramolecular transfer of hydride results and the *anti* 1,3-diol is the major product. The reactions are apparently not proceeding via a cyclic, lithium-chelated intermediate since the *syn* product would have expected. The lithium ion presumably increases the diastereoselectivity by coordinating with the carbonyl group.

10. Baylis–Hillman reaction

The coupling of α,β-unsaturated carbonyl compounds with aldehydes, the Baylis–Hillman reaction, is one of the most important carbon–carbon bond-forming processes in organic synthesis. Kobayashi[75] has reported that the Baylis–Hillman reaction was accelerated in the presence of catalytic amounts of 1,4-diazabicyclo[2,2,2]octane (DABCO) and lithium perchlorate in diethyl ether. A kinetic study of the reaction of benzaldehyde with methyl acrylate revealed that the relative rate of the reaction using 5 mol% DABCO and 70 mol% of $LiClO_4$ in ether was 8.0×10^2 times faster than that of the reaction using 5 mol% of DABCO (without $LiClO_4$). It is noted that methyl acrylate **129** reacted with benzaldehyde **128** to produce the



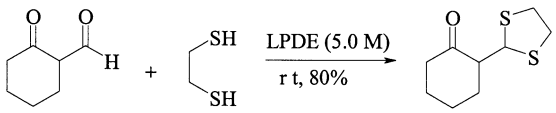
128 129 130

Scheme 38.

desired Baylis–Hillman adduct **130** in 72% yield. α,β-Unsaturated ketones as well as aldehydes, and nitriles reacted smoothly under these conditions (Scheme 38).

11. Protection of aldehydes as dithioacetals

Dithioacetals often serve as protecting groups as well as masked acyl anions in organic synthesis. Although a number of methods using protic and Lewis acids have been developed for the protection of aldehydes and ketones as dithioacetals, chemoselective thioacetalisation methods capable of discerning aldehydes from ketones have been rare. In 1994, Sankararaman et al.[76] has reported that aldehydes and acetals were very efficiently converted to dithioacetals in a 5.0 M LPDE medium at ambient temperature in high yields. Under the same conditions, ketones and their acetals also reacted, albeit very slowly compared to aldehydes and acetals, to yield dithioacetals. The difference in their reacting was successfully employed in the chemoselective dithioacetalisation of aldehydes in the presence of ketones. The bis-carbonyl **131** reacted with dithiol **132** to yield dithioacetal **133** as the only product in which the ketone intact under reaction conditions (Scheme 39).



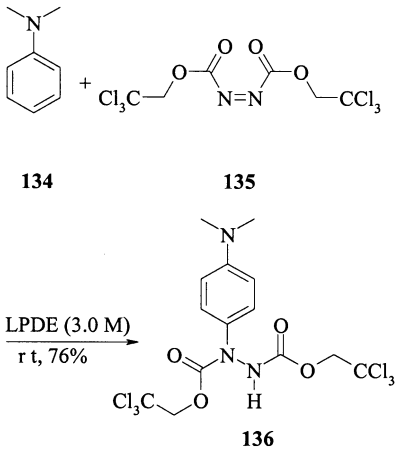
131 132 133

Scheme 39.

By using lithium perchlorate as the Lewis acid and propane-1,3-dithiol, even highly acid-labile α- and β-hydroxyaldehydes could be transformed into the corresponding thioacetals, without the formation of the corresponding alkenes.[77]

12. Synthesis of aromatic amines

Aromatic amines are key intermediates in the synthesis of a variety of important aromatic compounds via diazotisation and nucleophilic substitution reactions. Conventional methods for the synthesis of aromatic amines involve an electrophilic aromatic substitution usually via a nitration followed by reduction. It has been demonstrated that azodicarboxylates are an effective source of positive nitrogen. As an example, the thermal and acid-catalysed electrophilic reactions of azodicarboxylates with alkylbenzenes and some substituted phenols have been reported. High temperatures or strongly acidic conditions were, however required to allow the amination reaction.[78] In



134 135

136

Scheme 40.

1993, it was observed that electron-rich arene **134** react with bis(2,2,2-trichloroethyl)azodicarboxylate **135** to give the desired aryl hydrazide **136** under neutral conditions in 3.0 M LPDE solution in high yield. The corresponding aromatic amines are readily obtained by reducing the hydrazides with zinc in acetic acid (Scheme 40).[79]

13. Conclusions

This article provides the first general review of organic reactions in LPDE solution. The review has shown the diversity and potential usefulness of carrying out organic reactions in LPDE media. A rapid development of this field can therefore be envisioned.

Acknowledgments

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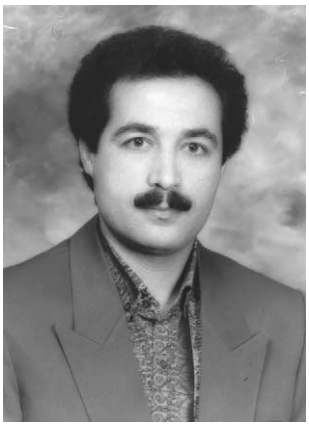
Biographical sketch



Akbar Heydari was born, raised and educated in ShahreRey, Iran. He received his BS degree from the Tarbiat Moallem University in 1987 and his MS in chemistry in 1989 from the Tehran University. He then completed his PhD at Justus liebig Universitaet Giessen, Germany in 1994 under the supervision of Professor J. Ipaktschi with a thesis on $LiClO_4$/-Diethylether als Reaktionsmedium in der organiche Chemie. In 1994, he joined the Chemistry Department at the Tarbiat Modarres University as an Associate Professor. Dr Heydari is recipient of the Research Award of the *Volkswagen Stiftung*, *DAAD Stiftung* and *Alexander von Humboldt Stiftung*. His major research interest is focused on various topics related to selective synthesis.