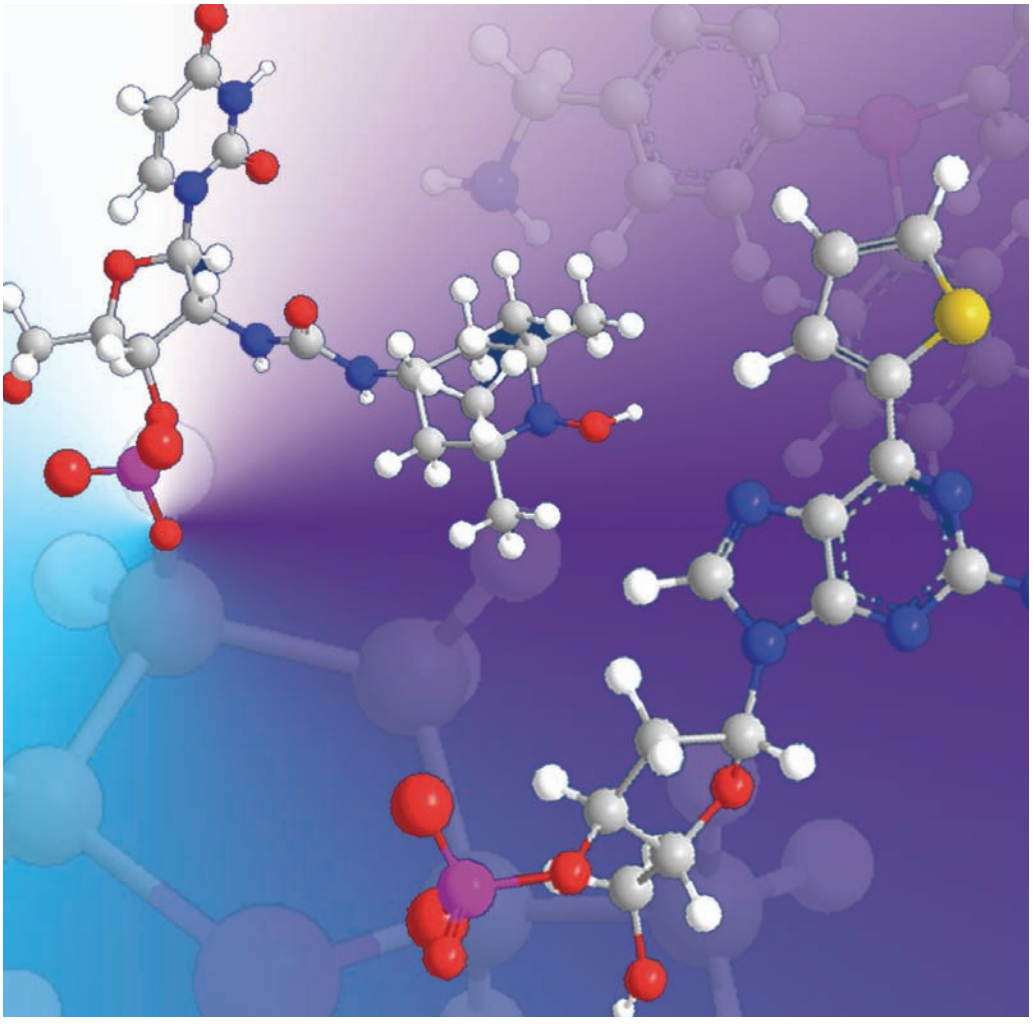
Specialist Periodical Reports

Editors D W Allen, J C Tebby and D Loakes

Organophosphorus Chemistry

Volume 39



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Organophosphorus Chemistry

Volume 39

A Specialist Periodical Report

Organophosphorus Chemistry

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A Review of the Literature Published between January 2008 and January 2009

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Preface

David Allen,[a] David Loakes[b] and John Tebby[c]
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This volume covers the literature of organophosphorus chemistry published in the period from January 2008 to January 2009, and continues our efforts in recent years to provide a more up to date survey of progress in this topic which, once again, has generated a vast amount of research. Papers from the 17th International Conference on Phosphorus Chemistry held in China in 2007 have now appeared in issues 2 and 3 of volume **183** of *Phosphorus, Sulfur, Silicon,* (2008). We welcome the return of a survey of the use of physical methods in organophosphorus chemistry, provided for the first time since 2001 by Robert Slinn. We thank the University of Liverpool for the provision of library resources to enable this chapter to be completed.

The use of a wide range of tervalent phosphorus ligands in homogeneous catalysis has continued to be a major driver in the chemistry of both traditional P–C-bonded phosphines and also that of tervalent phosphorus acid derivatives. This is also reflected in the publication of a major survey of this topic (*Phosphorus Ligands in Asymmetric Catalysis: Synthesis and Applications*, edited by Armin Börner, John Wiley & Sons, 2008–2009). Strong interest has also continued in the ability of a combination of sterically-crowded arylphosphine-arylboranes to cleave molecular hydrogen to form phosphonium hydridoborate salts that have the ability to act as reducing agents. Also significant is the increasing interest in the use of phosphonium salts as ionic liquids, with many new applications being reported. New approaches to the Wittig reaction continue to be developed, including the use of water as a solvent. In phosphine chalcogenide chemistry, the synthesis of enantioenriched phosphine oxides and the use of phosphine oxides and sulfides as ligands has continued to attract attention.

One of the primary uses to which tervalent phosphorus compounds have been applied during this period is as ligands for catalysts in synthetic reactions, including a variety of mono- and bi-naphthyl phosphacycles used in rhodium- and palladium-catalysed hydrogenation and Suzuki reactions, respectively. A large number of novel phosphite reagents has been prepared for synthetic reactions with aldehydes, but perhaps the most significant area of research has been in the synthesis of tervalent phosphorus amides and phosphoramidites; such reagents have found wide application as ligands in diastereo- and enantio-selective reactions. Quinquevalent phosphorus acid compounds, on the other hand, have primarily been investigated for biological applications. Phosphate derivatives of biologically-active compounds have been prepared, as well as some biologically active phosphate

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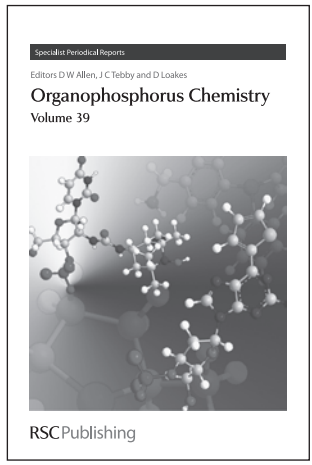
derivatives. In addition, quinquevalent phosphorus compounds have been used as ligands in a broad range of stereoselective reactions.

Nucleotides and oligonucleotides continue to be a source of much research, with the introduction of a vast range of modifications to nucleobase, sugar and phosphate backbone. In addition, a broad range of cargoes have been attached to oligonucleotides with the view of enhanced cellular delivery or for the delivery of the cargo to defined nucleic acid targets. With improvements to structural methods continuing, the complexity of nucleic acid structures solved by NMR and X-ray crystallography has been increasing, but in addition to these more conventional structural methods a range of other techniques, such as electron microscopy, have been used to obtain structural information on a more global scale. Perhaps the fastest growing area has been in the use of oligonucleotides in nanotechnology, with a wide range of nanostructures as well as nanodevices having been described. One of the main applications of nucleotides studied during this period is as therapeutic agents, and covers a broad range of products from phosphonates to base analogues, and various prodrug chemistries have been described for nucleoside analogues. A number of different internucleotide linkages have been examined, in particlular the stereospecific synthesis of phosphorothioates. The well-reported Click reaction between an azide and alkyne has featured heavily in nucleotide chemistry, used for the synthesis of fluorescent analogues as well as a means of conjugation.

Studies of hypervalent phosphorus compounds in biological phosphoryl transfer reactions include the preparation of novel anti-apicophilic pentacoordinated phosphoranes with frozen stereomutation using bulky bidentate ligands. Kinetic studies have enabled the activation enthalpy of the stereomutation of an *O*-equatorial phosphorane to its *O*-apical stereoisomer to be calculated. The involvement of hexacoordinated phosphoranes in phosphate transfer reactions has been clarified by theoretical calculations as well as *in vitro* studies. Applications of hexacoordinated compounds as catalysts have also been described.

Use of sulfonated phosphazenes as conductive membranes has been reviewed and there has been keen interest in fluorinated phosphazenes as coatings for medical implants and as lubricants in critical applications such as computer hard disk drives. Also highly conjugated pendant groups have produced significant optical and photonic properties. Phosphazenes containing strained rings and robust dendrimeric structures have been described. Expansion of nanotechnology based on polyphosphazenes with controlled thermolysis gave carbon nanostructures.

This volume marks the return of the Physical Methods chapter last presented in 2001. Most notable is a very marked increase in theoretical and computational studies facilitated by the availability of increasingly more sophisticated and powerful personal computer software programs. These studies combined with experimental observations invariably give valuable evidence towards the understanding of the chemistry. There have been three excellent reviews on newer methods in combinatorial synthesis, asymmetric synthesis and 'green' electrosynthesis that include a range of physical methods.



Cover

A selection of organophosphorus molecules. Image reproduced by permission of Dr David Loakes.

Abbreviations

BAD	Benzamide adenine dinucleotide
cDPG	Cyclodiphospho D-glycerate
CE	Capillary electrophoresis
CK	Creatine kinase
CPE	Controlled potential electrolysis
Cpmp	1-(2-chlorophenyl)-4-methoxylpiperidin-2-yl
CV	Cyclic voltammetry
DETPA	Di(2-ethylhexyl)thiophosphoric acid
DMAD	Dimethylacetylene dicarboxylate
DMF	Dimethylformamide
DMPC	Dimyristoylphosphatidylcholine
DRAMA	Dipolar restoration at the magic angle
DSC	Differential scanning calorimetry
DTA	Differential thermal analysis
ERMS	Energy resolved mass spectrometry
ESI-MS	Electrospray ionization mass spectrometry
EXAFS	Extended X-ray absorption fine structure
FAB	Fast atom bombardment
Fpmp	1-(2-fluorophenyl)-4-methoxylpiperidin-2-yl
HPLC	High-performance liquid chromatography
LA-FTICR	Laser ablation Fourier Transform ion cyclotron resonance
MALDI	Matrix assisted laser desorption ionization
MCE	Micellar electrokinetic chromatography
MIKE	Mass-analysed ion kinetic energy
PAH	Polycyclic aromatic hydrocarbons
QDA	Hydroquinone-O,O′-diacetic acid
PMEA	9-[2-(phosphonomethoxy)ethyl] adenine
SATE	S-acyl-2-thioethyl
SIMS	Secondary ion mass spectrometry
SSAT	Spermidine/spermine-N1-acetyltransferase
SSIMS	Static secondary ion mass spectrometry
TAD	Thiazole-4-carboxamide adenine dinucleotide
tBDMS	tert-Butyldimethylsilyl
TFA	Trifluoroacetic acid
TGA	Thermogravimetric analysis
TLC	Thin-layer chromatography
TOF	Time of flight
XANES	X-Ray absorption near edge spectroscopy

Phosphines and Related P–C-bonded Compounds

D. W. Allen[a]

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1. Introduction

This chapter covers the literature published during 2008 relating to the above area, apart from a few papers from 2007 in less accessible journals which came to light in *Chemical Abstracts* in 2008. As in recent years, it has been necessary to be somewhat selective in the choice of publications cited but, nevertheless, it is hoped that most significant developments have been noted. The use of a wide range of tervalent phosphorus ligands in homogeneous catalysis has again been a major driver in the chemistry of traditional P–C-bonded phosphines (and also that of tervalent phosphorus acid derivatives, covered in detail elsewhere in this volume). Noteworthy in this context is a major review of the catalytic asymmetric synthesis of chiral phosphines.[1]

2. Phosphines

2.1 Preparation

2.1.1 From halogenophosphines and organometallic reagents. This route has continued to be applied widely, with most work again involving the use of organolithium reagents. Nevertheless, a few papers describing Grignard routes continue to appear, these having been found to be advantageous for the synthesis of the 1,2-bisphosphinobenzene (**1**),[2] and the crowded, arene-functional, *t*-alkylphosphine (**2**).[3] A procedure for the preparation of polyfunctional arylmagnesium reagents, involving direct magnesium insertion into aryl- and heteroaryl-halides in the presence of lithium chloride, has also been reported, having considerable potential for use in phosphine synthesis.[4] A very similar approach using aryllithium reagents has also been developed and used subsequently to prepare a range of C-functionalised phosphinobiaryls, e.g., (**3**).[5] Traditional halogen-metal exchange procedures involving butyllithium reagents with halo-arenes or -alkenes, followed by treatment with chlorophosphines, have formed the basis of routes to a range of new phosphines. Among new monophosphines prepared in this way are a range of sterically crowded *o*-alkyl-substituted aryl(alkyl)phosphines,[6] 2-, 3- and 4-quinolyl(diphenyl)phosphines,[7] the crowded biarylphosphine (**4**),[8] the phosphino-allene (**5**),[9] and the phosphinoferrocene (**6**).[10] Stereochemical assignments relating to phosphines of the Taniaphos series (**7**), also prepared by the above route, have been corrected, following comments from other workers.[11] Other new phosphines also prepared in this way include a series of mono- and diphosphino-anthracenes (**8**),[12] the unsymmetrical 2,2′-bis(phosphino)diphenylamine (**9**),[13] the *p*-phenylenediphosphines (**10**),[14] the diphosphine (**11**), (capable of quaternisation at nitrogen to give water-soluble

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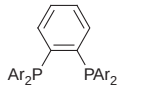
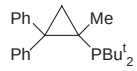


(**1**) Ar = 2-EtC$_6$H$_4$



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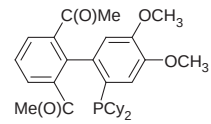

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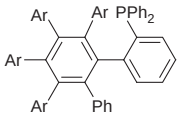

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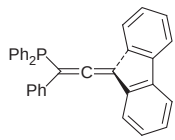

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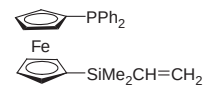

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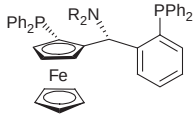

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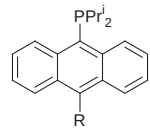
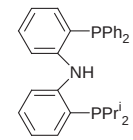
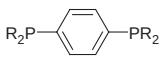


(**8**) R = H, Br or PPr$^i_2$

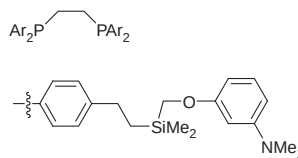


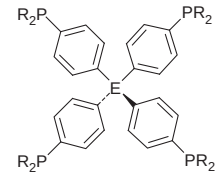
(**9**)



(**10**) R = Cy or Pr^i

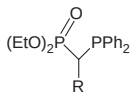
(**11**) Ar =



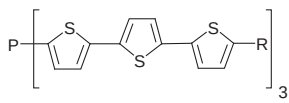


(**12**) E = C, Si or Sn
R = e.g., Ph, Et, Cy or Bu^t

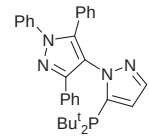
complexes),[15] and the tetraphosphines (**12**) that act as rigid scaffolds which prevent interactions of metal complexes with oxide supports.[16] A novel approach to 1,1′-bisphosphorus compounds is provided by treatment of diethyl chloromethylphosphonate (a carbene precursor) with butyl lithium, followed by a trialkylborane, which results in transfer of an alkyl group from boron to the carbenoid α-carbon. Subsequent metallation at the α-carbon with butyllithium, followed by treatment with a chlorophosphine, gives the phosphinomethylphosphonates (**13**).[17] The phosphonatophosphine (**13**, R = SiMe$_3$) was prepared in a similar way by sequential treatment of diethyl methylphosphonate with LDA (2 mol), followed by chlorotrimethylsilane (1 mol) and chlorodiphenylphosphine (1 mol).[18] Direct lithiation of acidic carbon precursors has also been used in the synthesis of various heteroarylphosphines, including oligothienylphosphines, e.g., (**14**),[19] tris-2-(3-methylindolyl)phosphine, (which demonstrates an ability to bind anions through the indole NH sites and coordinate to metals *via* phosphorus),[20] and the phosphinobipyrazole (**15**).[21] Depending on relative quantities of butyllithium and chlorodiphenylphosphine, 1-(1-naphthyl)-1*H*-benzimidazole undergoes monophosphination at either the 2-naphthyl or 2-benzimidazole positions, or at both, to give a diphosphine. The latter undergoes selective



(**13**) R = alkyl



(**14**) R = n-hexyl or H



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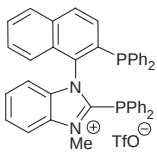

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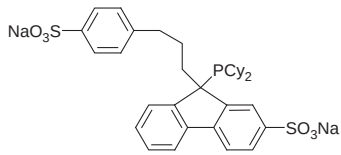

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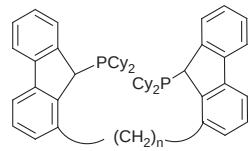
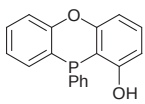


(**18**) n = 1-5



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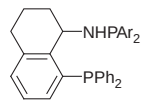
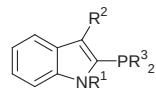
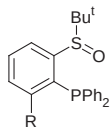


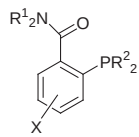
(**20**) Ar = Ph, 3,5-$F_2C_6H_3$, *p*-$CF_3C_6H_4$ or 3,5-$(CF_3)_2C_6H_3$



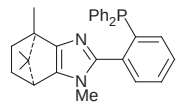
(**21**) R^1 = $CONPr^i_2$, CO_2Bu^t, or SO_2Ph
R^2 = H or Me
R^3 = Ph, Cy or Bu^t



(**22**) R = H, OMe or OCH_2OCH_3



(**23**) R^1, R^2 = alkyl; X = Cl, Bu or Ph



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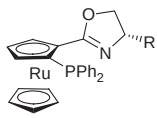

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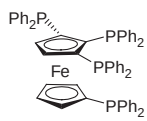
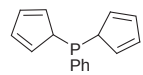


(**26**)

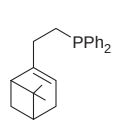


(**27**)

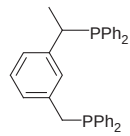
alkylation at nitrogen on treatment with methyl triflate to give the amidiniodiphosphine ligand (**16**).[22] Plenio *et al*. have continued to develop the chemistry and applications of 9-alkylfluorenylphosphine ligands, accessible by direct lithiation and phosphination of 9-alkylfluorenes. An efficient large scale route to these compounds has now been described,[23] and among new examples reported are the sulfonated ligand (**17**)[24] and the diphosphines (**18**).[25] Directed lithiation at a site near to an appropriate donor atom has also been widely utilised in the synthesis of new phosphines. Among new systems prepared in this way are the P-chirogenic phenoxaphosphine (**19**),[26] various 2,6-bis(phosphino)thiophenol derivatives[27] and 1,4-bis(phosphino)-2,5-difluoro-3,6-dihydroxybenzenes,[28] a series of modular phosphine-aminophosphine ligands (**20**) based on a chiral 1,2,3,4-tetrahydro-1-naphthylamine backbone,[29] families of tunable indolylphosphine- (**21**),[30] *t*-butylsulfinylphosphine- (**22**),[31] and *o*-phosphinoarylamide- (**23**)[32]

ligands and the chiral phosphinoaryl imidazole (**24**).[33] Donor group-directed metallation has also been used to prepare planar chiral ruthenocene-based phosphino-oxazoline ligands (**25**)[34] and in a four-step synthesis of the chiral tetraphosphinoferrocene (**26**).[35] An improved route to dicyclopentadienyl(phenyl)phosphine (**27**) has been developed, involving use of a cyclopentadienylthallium reagent.[36]

2.1.2 From metallated phosphines. This route has continued to find wide application, although the volume of published work seems to have decreased again in the past year. Lithiophosphide reagents remain the most commonly used, sometimes as borane-protected systems, the borane group also providing protection against oxidation of the new phosphine during purification steps. Lithium arylphosphide reagents have been employed in traditional procedures involving nucleophilic displacement reactions of mesylate esters and alkyl halides in the synthesis of the terpene-derived phosphine (**28**),[37] the diphosphine (**29**),[38] and the phosphirane (**30**, $R = SiMe_3$).[39] Attempts to prepare polymeric alkylphosphines by treating (**30**, R = Me or Ph) with lithiophosphide reagents by inducing nucleophilic ring-opening at carbon failed, the preferred route being attack at phosphorus to form a diphosphide anion, e.g., (**31**), and an alkene.[40] On the other hand, the established nucleophilic ring opening of epoxides by attack

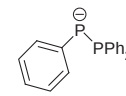


(**28**)

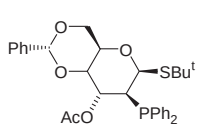


(**29**)

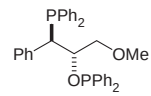
(**30**)



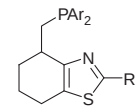
(**31**)



(**32**)



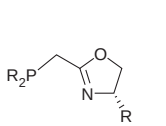
(**33**)



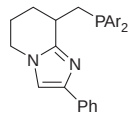
(**34**) Ar = Ph, *o*-Tol or 3,5-$Me_2C_6H_3$
R = Ph, Mes or 3,5-$Me_2C_6H_3$

of phosphide anions at carbon has received further application in the synthesis of new sulfur-containing phosphine ligands, e.g., (**32**), from sugars[41] and a series of modular P-O-P ligands (phosphine-phosphites and phosphine-phosphinites), e.g., (**33**).[42] Borane-protected lithiophosphide reagents have also been used routinely in the synthesis of the heterocycle-functionalised chiral phosphines (**34**),[43] (**35**),[44] (**36**),[45] and (**37**).[46] The latter paper also reports the synthesis, by other methods, of bis(2,5-diphenylphospholane systems having maleic anhydride or ferrocene sp^2 carbon-linking groups. In a more complex mechanistic scenario, treatment of a chromium tricarbonyl complex of *ortho*-difluorobenzene with a chiral, borane-protected, lithiophosphide reagent resulted in the formation of the related *para*-diphosphinoarene complex (**38**), *via* a *tele*-S_NAr substitution mechanism.[47] More exotic applications of lithiophosphide reagents include the synthesis

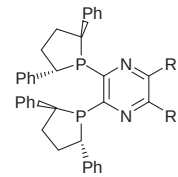
of Ge(II)-phosphides,[48] monomeric aluminium- and gallium-phosphides of the type $Bu^t_2E–PBu^t_2$ (E = Al or Ga),[49] tetraradicaloid systems, e.g., (**39**)[50] and (**40**),[51] the formation of the triphospholide (**41**)[52] and the 6π-diphosphastannylene (**42**)[53] anions, and in the alkylation of bulky primary phosphines coordinated to platinum.[54]



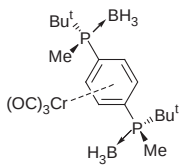
(**35**)



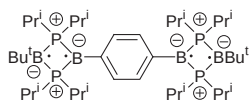
(**36**) Ar = Ph, *o*-Tol or 3,5-$Me_2C_6H_3$



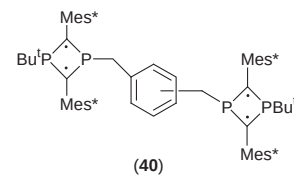
(**37**) R = H or R,R; R,R = CH=CH-CH=CH



(**38**)

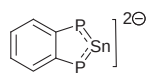


(**39**)

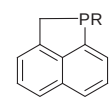


(**40**)

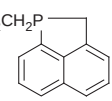
(**41**)

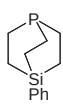


(**42**)

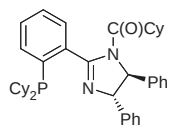


(**43**) R = Ph, Cy, CH_2Fc or CH_2CH_2P

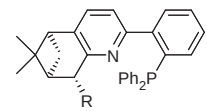




(**44**)



(**45**)



(**46**) R = H, Me or Pr^i

Sodium- and potassium-organophosphide reagents have also continued to find new applications in synthesis. Trisodium heptaphosphide has been shown to react with alkyl tosylates to give dialkylheptaphosphide anions or trialkylheptaphosphines, depending on the stoichiometric ratios of the starting reagents,[55] and also with nickel-cyclopropenyl complexes to give sodium 1,2-diphosphacyclopentadienide.[56] A platinum-catalysed enantioselective tandem alkylation of mono- and bis-primary phosphines with 1-bromo-8-chloromethylnaphthalene, in the presence of sodium trimethylsiloxide, has provided a route for the asymmetric synthesis of mono- and bis-P-stereogenic 1-phosphaacenaphthenes, e.g., (**43**).[57] Related platinum-catalysed alkylation reactions of bis(secondary) phosphines have