Topics in Current Chemistry 361

Jean-Luc Montchamp *Editor*

Phosphorus Chemistry II

Synthetic Methods

Springer

361
Topics in Current Chemistry

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The series Topics in Current Chemistry presents critical reviews of the present and future trends in modern chemical research. The scope of coverage includes all areas of chemical science including the interfaces with related disciplines such as biology, medicine and materials science.

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Thus each review within the volume critically surveys one aspect of that topic and places it within the context of the volume as a whole. The most significant developments of the last 5 to 10 years should be presented. A description of the laboratory procedures involved is often useful to the reader. The coverage should not be exhaustive in data, but should rather be conceptual, concentrating on the methodological thinking that will allow the non-specialist reader to understand the information presented.

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Jean-Luc Montchamp
Editor

Phosphorus Chemistry II

Synthetic Methods

With contributions by

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Preface

The element phosphorus was discovered early in the seventeenth century, as chronicled in John Emsley's excellent and fascinating book "The 13th Element". Phosphorus chemistry is often perceived as an "old Dame" in the chemical arts. This is because many important reactions were discovered at the turn of the twentieth century, largely from the contributions of Russian chemists. Since then, phosphorus chemistry has unfortunately been considered a mature and specialized field. However, phosphorus being key to all life processes, tremendous opportunities for phosphorus research have remained ever since. So the "old Dame" is now experiencing a second (or third?) youth.

It has been my privilege to guest-edit these two volumes for Topics in Current Chemistry on phosphorus chemistry, and I am grateful to Mike Krische who gave me this opportunity. *Topics in Current Chemistry* has already produced several excellent volumes on various aspects of phosphorus chemistry. The present volumes are dedicated to various topics in organophosphorus chemistry. The first volume concerns biologically-related topics (phosphinopeptides, phosphinic acids, prodrugs) as well as P-asymmetric compounds (also called P-stereogenic, P-chiral, etc. – there is still some intense discussion about how to name this field!). The second volume deals with various synthetic methods and phosphorus functionalities (P-BH_3, phospho-aldol, H- and C-phosphonates, phosphorus tethers in synthesis, and C–H to C–P transformations). In some cases, prior reviews were available on some of the topics. However, the present chapters constitute the best, most up-to-date and in-depth resource in the field, which has been growing rapidly in the past 5–10 years. I believe these volumes will be important additions to library shelves, both institutional and personal. The writings are appropriate for experts and interested students alike.

These chapters have been written by internationally recognized leading experts in the field, both European and American researchers having contributed to the volumes. I wish to thank personally all these authors for spending countless hours to produce these outstanding chapters, which are important contributions to the chemical literature. Clearly, phosphorus chemistry is not only alive and well, but

has a promising future and offers great potential for scientific discoveries. Too often people assume that a well-researched topic no longer has anything to offer. I think these chapters prove that nothing could be further from the truth. Because phosphorus is such an important element, chemical research in organophosphorus chemistry has a very bright future indeed. The "old Dame" will remain young!

Fort Worth, TX, USA Jean-Luc Montchamp
9 November 2014

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Recent Advances in Synthesis of P-BH_3 Compounds

Carole Alayrac, Sami Lakhdar, Ibrahim Abdellah, and Annie-Claude Gaumont

Abstract This chapter is dedicated to the main achievements since 2007 regarding the synthesis of BH_3-phosphorus complexes. Among this class of compounds, phosphine-boranes are the most studied derivatives, mainly as valuable surrogates of phosphines, enabling easy handling and purification. In contrast, metal phosphido-boranes have so far only been considered as in situ intermediates in the P-functionalization of secondary phosphine-boranes. Thorough investigations of their structures as well as their chemical properties have recently been reported. Besides phosphine-boranes and their phosphides, new families of phosphorus-BH_3 complexes, have emerged as useful precursors of new structures in the asymmetric series. New routes toward optically active phosphinous-acid boranes and their esters were developed and applied to the synthesis of enantiopure *P*-stereogenic secondary and tertiary phosphine-boranes. The stereoselective synthesis of *P*-stereogenic aminophosphine-boranes, precursors of a new class of chiral ligands, has been reported. Studies dealing with the synthesis and reactivity of phosphonite-boranes were successfully applied to the development of efficient syntheses of functionalized *H*-phosphinates, compounds difficult to access by other routes.

Keywords Aminophosphine-boranes · Phosphido-borane complexes · Phosphine-boranes · Phosphinous acid-boranes · Phosphonite-boranes

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Abbreviations

Abs. Conf	Absolute configuration
AIBN	Azobisisobutyronitrile
An	Anisyl
aq.	Aqueous
B3LYP	Becke's three-parameter, Lee–Yang–Parr exchange-correlation functional
BDE	Bond dissociation energy
BiPh	Bi-phenyl
Bn	Benzyl
COD	1,5-Cyclooctadiene
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCE	Dichloroethane
DCM	Dichloromethane
de	Diastereomeric excess
DFT	Density functional theory
D-FW	Diffusion coefficient-formula weight
dia	Diastereomer
DIBAL-H	Di-isobutyl aluminium hydride
DKR	Dynamic Kinetic Resolution
DMAc	*N*,*N*-Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DOSY	Diffusion ordered spectroscopy
dppf	1,1′-Bis-(diphenylphosphino)-ferrocene
dppp	1,3-Bis-(diphenylphosphino)-propane
dr	Diastereomeric ratio

EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
Eq.	Equation
equiv.	Equivalent
ESR	Electron spin resonance
Fc	Ferrocenyl
FLP	Frustrated Lewis pairs
FT-ICR	Fourier transform ion cyclotron resonance
GA	Gas-phase acidity
HCA	Hexachloroacetone
HOBt	Hydroxybenzotriazole hydrate
HOESY	Heteronuclear Overhauser spectroscopy
HPLC	High-performance liquid chromatography
HWE	Horner–Wadsworth–Emmons
LDA	Lithium diisopropylamide
LiDMAE	Lithiated dimethylaminoethanol
LiHMDS	Lithium hexamethyldisilazide
Mes	Mesityl
mM	Millimolar
MW	Microwave
nbd	Norbornadiene
NMR	Nuclear magnetic resonance
o-An	*ortho*-Anisyl (2-methoxyphenyl)
phen	Phenanthroline
pmdeta	*N*,*N*,*N*′,*N*″,*N*″-Pentamethyldiethylenetriamine
PMHS	Polymethylhydrosiloxane
Py	Pyridine
RCM	Ring closing metathesis
rt	Room temperature
SET	Single electron transfer
S_NAr	Aromatic nucleophilic substitution
sp	Sparteine
SPOs	Secondary phosphine oxides
TBAF	Tetrabutylammonium fluoride
Tf	Triflate
THF	Tetrahydrofuran
TIBAO	Tetraisobutyldialuminoxane
TIPS	Tri-isopropylsilyl
TMCDA	*N*,*N*,*N*′,*N*′-Tetramethylcyclohexane-1,2-diamine
TMDS	Tetramethyldisiloxane
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TOF	Turnover frequency
Tol	Tolyl
Tos	Tosyl
TsCl	Tosylchloride

1 Introduction

The topic of this chapter is the main achievements since 2007 regarding BH_3-phosphorus complexes. The review is divided into two main sections. The first focuses on the most studied derivatives of this family, secondary and tertiary phosphine-boranes (Fig. 1) and their applications. Several reviews dealing with their synthesis and applications have already appeared (for a recent review about the preparation of phosphines and phosphine-boranes, see [1]; for reviews focusing on phosphine-boranes, see [2–5]). The second section is dedicated to selected phosphorus-BH_3 derivatives, which have recently received special attention regarding their structure, synthesis, reactivity and applications: phosphido-boranes, phosphinous acid-boranes, aminophosphine-boranes and, finally, phosphonite-boranes (Fig. 1). According to a literature survey, to the best of our knowledge, no review of these compounds has appeared so far except one dealing with phosphinous acid-boranes [6].

A new category of compounds named Frustrated Lewis Pairs (FLPs) [7, 8], in which the interaction between the Lewis base and the Lewis acid is precluded, mainly through steric and structural factors, has triggered huge interest as these compounds were shown to activate inert small molecules such as CO and H_2 and serve as hydrogen storage materials. However, FLPs, which usually display pentafluorophenyl substituents on the boron atom, are beyond the scope of this review.

Phosphorus-borane compounds are Lewis acid–base complexes resulting from the interaction between the lone pair of the phosphorus atom and the empty orbital of the boron atom. For scheme clarity throughout the chapter, we draw *a simple bond between P and B atoms rather than an arrow (dative bond)* (Fig. 2).

One of the main applications of phosphine-boranes is their use as protected phosphines. Indeed, most of the trivalent phosphorus compounds, being air sensitive, often require a temporary protection as oxide, sulphide or borane derivatives for their isolation, handling or storage. However, deprotection is sometimes the bottleneck of the strategy involving oxides or sulphides under harsh conditions may be required to achieve their reduction. By contrast, the deprotection of borane complexes is usually carried out under rather mild conditions, and is known to

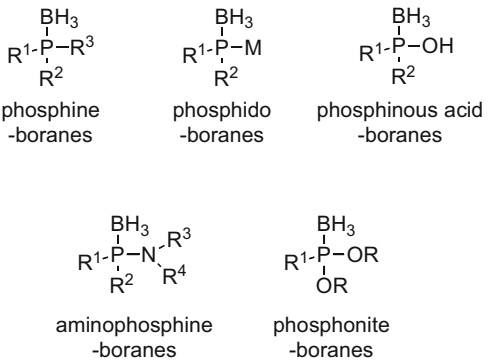


Fig. 1 Structures of surveyed phosphorus-BH_3 derivatives

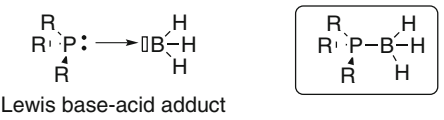
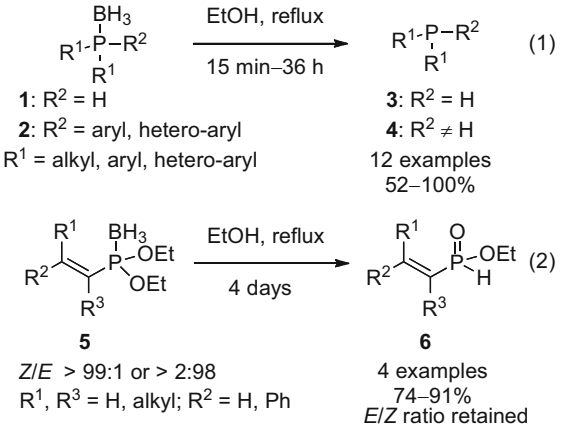


Fig. 2 Structure of phosphorus-borane complexes



Scheme 1 Deprotection of phosphine- and phosphonite-borane complexes though ethanolysis

proceed with retention of the *P*-stereochemistry. Classically, aryl-containing phosphorus compounds undergo borane decomplexation by treatment with an amine, most often DABCO [9], whereas electronically rich phosphorus derivatives such as trialkylphosphines require treatment with a strong acid, mainly HBF_4•OEt_2 [10, 11]. A method based on a simple alcoholysis under reflux was recently reported for aryl-containing secondary or tertiary phosphine-boranes **1** or **2** (Scheme 1, (1)) [12]. It relies on a revised protocol of a former reaction [13]. The attractive feature of the method is the fact that no work-up or purification is needed and the triethyl borate by-product (bp 117–118°C) and the residual solvent are eliminated under high vacuum. A drawback of the method, however, is the extended reaction time of up to several days, which can nevertheless be shortened through microwave activation.

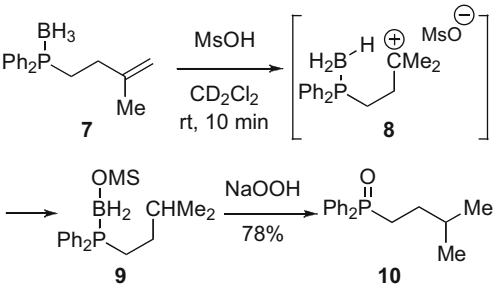
Trialkylphosphine-boranes and phosphite-boranes [$(RO)_3$P-BH_3] were found to be inert under the alcoholysis conditions, whereas the decomplexation of phosphonite-boranes was successfully achieved [14]. The method was found particularly useful in the case of (*Z*)-alkenylphosphonite-boranes **5** [15], which failed to react properly with a strong acid or amines but were readily converted into the corresponding *H*-phosphinates **6** upon refluxing in ethanol (Scheme 1, (2)). Importantly, the borane decomplexation of most (*Z*)- or (*E*)-alkenylphosphonite-boranes **5** proceeded with retention of configuration.

The role of the BH_3 group cannot, however, be restricted to a protecting group, as its presence has a strong acidity-enhancement effect on the proton directly linked to the phosphorus atom as well as on the protons on the carbon atom located at the α-position to the phosphorus atom. This acidity enhancement in the gas phase of the proton atoms of primary phosphine-boranes induced by the borane was recently

Table 1 Gas-phase acidity (GA) values in kJ mol^{-1}, experimental and calculated at the B3LYP/6-311++G (3d,2p) level (in italic) for a set of primary phosphines and their borane complexes

Phosphine	GA (RPH_2)	GA (RPH_2•BH_3)	–δGA
$PhPH_2$	1,457.3 (±0.8) *1,455.1*	1,375.0 (±2.5) *1,379.1*	82.3 *76.0*
$PhCH_2PH_2$	1,493.8 (±0.9) *1,495.3*	1,380.4 (±2.5) *1,382.8*	113.4 *115.1*
c-$C_3H_5PH_2$	1,510.0 (±3.0) *1,507.8*	1,408.9 (±2.8) *1,402.0*	101.1 *105.8*
CH_3PH_2	1,530.0 (±2.5) *1,530.7*	1,411.9 (±2.3) *1,410.2*	118.1 *120.5*

Scheme 2 Ionic hydrogenation of unsaturated phosphine-borane **7** via internal hydride transfer



quantified by means of Fourier transform ion cyclotron resonance (FT-ICR) spectroscopy and DFT calculations (Table 1) [16]. The difference in gas phase acidity between a primary phosphine and its borane complex is significant (from 80 to 110 kJ mol^{-1}). A huge acidity enhancement effect of the borane group, between 13 and 18 orders of magnitude in terms of ionization constants, was demonstrated.

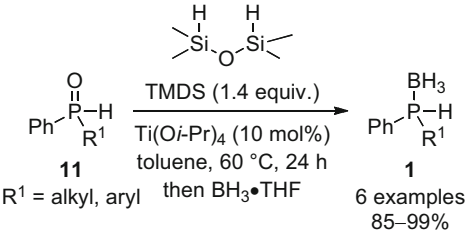
The borane group may also have an influence beyond phosphorus chemistry, as it can also actively participate in the reactivity of the phosphorus-borane complexes as a reducing agent. For example, alkenyl phosphine-borane **7** upon treatment with methanesulfonic acid was converted into a tethered carbocation **8**, which underwent an internal hydride transfer to give saturated phosphine oxide **10** after oxidative work-up (Scheme 2) [17].

As a further example, $Ph_2P(BH_3)Li$ was found to display the dual reactivity of phosphination and reducing agent toward carbonyl compounds in THF depending on the control (kinetic or thermodynamic) defined by the reaction conditions (see Sect. 3.1) [18].

2 Phosphine-Boranes

2.1 Synthesis of Secondary Phosphine-Boranes

Secondary phosphine-boranes, which are key precursors of tertiary phosphine-boranes through a broad range of methods (see Sect. 2.2), are classically obtained



Scheme 3 Reduction of secondary phosphine oxides and borane complexation

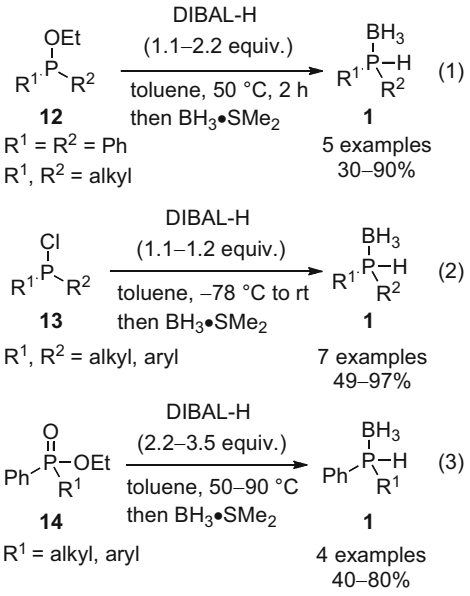
through the reduction of secondary phosphine oxides (SPOs). Recently, new procedures applicable on a large scale, and/or suitable for the industrial requirements have been developed. Moreover, the *O*-functionalization of optically active phosphinous acid-boranes followed by $NaBH_4$ reduction has emerged as a concise and efficient stereoselective route toward secondary phosphine-boranes.

Hydrosiloxane derivatives have attracted attention for a few years as safe reducing agents. Because of their low reactivity, however, an activation agent is required to afford high conversion. As an improvement of the well-established reducing system involving polymethylhydrosiloxane (PMHS) combined with a stoichiometric amount of titanium(IV)isopropoxide [19], the use of the lower molecular weight hydrosiloxane TMDS (tetramethyldisiloxane) was reported to be effective with only 10 mol% of Ti(O*i*-Pr)$_4$. Thus, secondary phosphine oxides **11** could be readily reduced in toluene at 60°C in excellent yields and afforded the corresponding secondary phosphine-boranes **1** after treatment with BH_3•THF complex (Scheme 3) [20].

Besides silanes, the organoaluminium reductant DIBAL-H is known to reduce SPOs into secondary phosphines efficiently [21]. The scope of suitable substrates was recently extended to phosphinites **12** (Scheme 4, (1)), which were generated in situ through the reaction between ethyldichlorophosphite ($EtOPCl_2$) and 2 equiv. of the corresponding Grignard reagents. The DIBAL-H reduction of compounds **12** was performed at 50°C followed by borane complexation at rt [22]. Chlorophosphines **13** were also suitable substrates and readily underwent reduction at rt (Scheme 4, (2)). In the case of unhindered chlorodiphenylphosphine, the formation of tetraphenyldiphosphine, resulting from the reaction of product with starting material, was observed. Nevertheless, this side product could be reduced by DIBAL-H provided the reduction temperature was increased to 50°C and the amount of reductant to 2.2 equiv. The versatility of DIBAL-H was further demonstrated through the reduction of a set of phosphinates **14** into secondary phosphine-boranes **1** after treatment with BH_3•SMe_2 complex (Scheme 4, (3)).

Whereas the direct reduction of phosphinous acid-boranes into secondary phosphine-boranes is known to be difficult [23], their *O*-alkylated or *O*-acylated counterparts were found to undergo reduction readily, making them interesting intermediates for the conversion of phosphinous acid-boranes into secondary phosphine-boranes. Application of this strategy to enantiopure phosphinous acid-boranes (see Sect. 3.2 for their preparation) allowed the stereoselective access to optically active secondary phosphine-boranes [24].

Scheme 4 DIBAL-H as a versatile reducing agent to access secondary phosphine-boranes

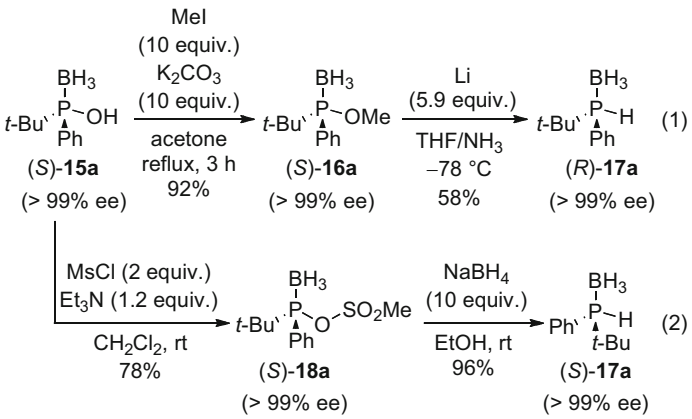


As an example, enantiopure *tert*-butylphenylphosphinous acid-borane (*S*)-**15a** was converted into its methyl ester (*S*)-**16a** in 92% yield through reaction with methyl iodide in the presence of potassium carbonate in boiling acetone. The cleavage of the ester bond was subsequently achieved by treatment with lithium in THF/NH_3 at −78°C and led to the targeted *tert*-butylphenylphosphine-borane (*R*)-**17a** in 58% yield (Scheme 5, (1)). Both steps proceeded with full retention of stereopurity. The stereocomplementary approach was achieved through the reaction of (*S*)-**15a** with mesyl chloride in the presence of triethylamine in dichloromethane, affording *tert*-butylphenylboranatophosphinous methane sulfonic anhydride (*S*)-**18a** in 78% yield. The consecutive reduction of (*S*)-**18a** by $NaBH_4$ in ethanol proceeded with clean inversion of configuration and gave *tert*-butylphenylphosphine-borane (*S*)-**17a** in 96% yield (Scheme 5, (2)).

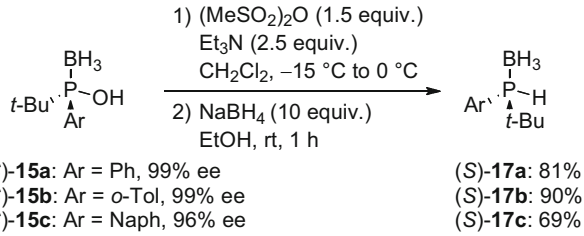
The reaction of bulkier phosphinous acid-boranes **15b, c** with mesyl chloride gave complex mixtures, probably because of the presence of nucleophilic chloride ions in the medium. A revised protocol was reported involving mesyl anhydride instead of mesyl chloride and was successfully applied to the synthesis of two additional examples of optically active secondary phosphine-boranes, (*S*)-**17b** and (*S*)-**17c** (Scheme 6) [25].

2.2 *Synthesis of Tertiary Phosphine-Boranes via C–P Bond Formation*

Original synthetic procedures involving non-catalytic C–P bond formation have recently been developed, based on aryne chemistry or on alkyne, alkene and allene



Scheme 5 Stereoselective conversion of enantiopure phosphinous acid-borane (*S*)-**15a** into both enantiomers of *tert*-butylphenylphosphine borane (**17a**)

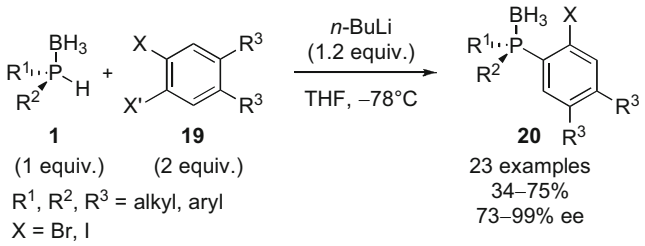


Scheme 6 Conversion of phosphinous acid-boranes (*S*)-**15** into bulky secondary phosphine-boranes (*S*)-**17**

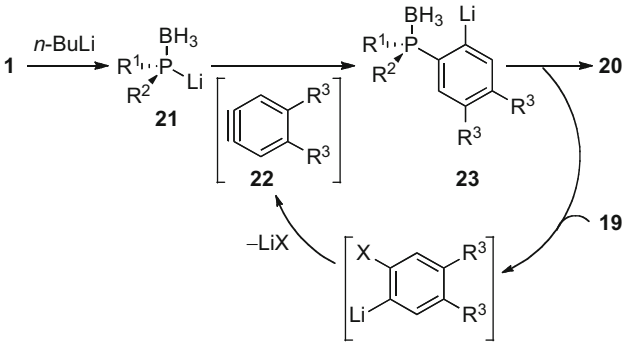
hydrophosphination using secondary phosphine-boranes as reagents. Recent advances in metal-mediated C–P bond-forming reactions mainly deal with the use of new cross-coupling partners of secondary phosphine-boranes such as 1-bromoalkynes, alkenyl tosylates or enol phosphates. A major goal of these strategies is the extension to the asymmetric series to provide an efficient access to new functionalized optically active *P*-stereogenic phosphine structures.

2.2.1 C–P Bond Formation via Aryne Chemistry

An efficient synthesis of *o*-halogenoaryl *P*-stereogenic tertiary phosphine-boranes based on aryne chemistry has been reported [26]. It consists of the reaction between secondary phosphine-boranes **1** and 1,2-dihaloarenes **19** in the presence of *n*-butyllithium in slight excess (1.2 equiv.). The reaction of chiral secondary phosphine-boranes **1** proceeded with retention of configuration at phosphorus and without racemization, yielding the corresponding enantioenriched arylphosphine-boranes **20** in moderate to good yields with *ee* up to 99% (Scheme 7).



Scheme 7 Synthesis of *o*-halogenoaryl phosphine-boranes **20** based on aryne chemistry

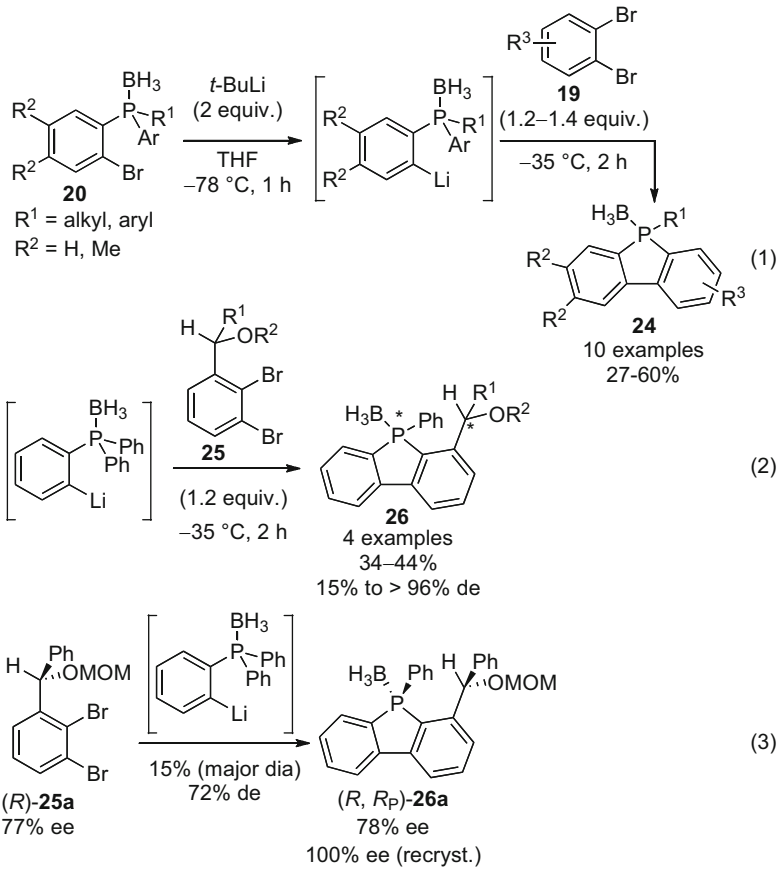


Scheme 8 Proposed mechanism for the formation of *o*-halogenophenylphosphine-boranes **20**

As outlined in Scheme 8, the proposed mechanism involves the deprotonation of the phosphine-borane **1** by *n*-BuLi to give the lithium phosphide **21**, which reacts with aryne **22**. The latter is generated in situ from the 1,2-dihaloarene **19** via metal-halogen exchange mediated by the excess of *n*-BuLi (0.2 equiv.) followed by LiX elimination. The resulting *o*-lithiated phosphine-borane **23** undergoes halogen-metal exchange with the 1,2-dihaloarene **19** producing the *o*-halophenyl-phosphine-borane **20** and promoting the aryne formation, which allows the reaction to proceed further.

The *P*-stereogenic *o*-bromophenylphosphine-boranes **20** were readily converted into *P*-stereogenic *o*-(hydroxyalkyl)phenyl phosphines, which served as new functional chiral Lewis bases [27].

The aryne coupling methodology was also successfully applied to the stereoselective synthesis of unprecedented *P*-stereogenic dibenzophosphole-boranes **24** [28], using *o*-bromoaryl tertiary phosphine-boranes **20** and 1,2-dibromoarenes **19** as starting materials and *tert*-butyllithium (2 equiv.) as base (Scheme 9, (1)). The key features are the regioselective nucleophilic addition of the *o*-lithiated phosphine-boranes at the less sterically hindered side of the transient arynes, and the chemoselective intramolecular cyclization at phosphorus, controlled by the basicity of the eliminated organolithium moiety. It should be noted that racemization was observed when an enantiopure *P*-stereogenic phosphine-borane was used as substrate. Nevertheless, the reaction could be performed

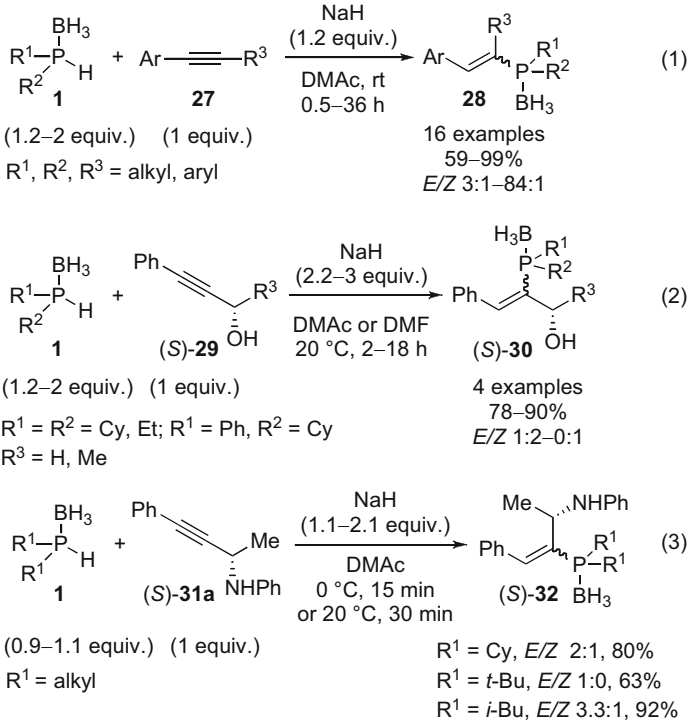


Scheme 9 Synthesis of *P*-stereogenic dibenzophosphole-boranes

diastereoselectively by introducing chiral auxiliaries in the *ortho*-position on the 1,2-dibromobenzene (Scheme 9, (2)). Importantly, the use of an enantioenriched 1,2-dibromoarene (*R*)-**25a** (77% *ee*) afforded an entry to enantiopure dibenzophosphole-borane (*R*,R_P)-**26a** after recrystallization (Scheme 9, (3)).

2.2.2 C–P Bond Formation via Hydrophosphination with Phosphine-Boranes

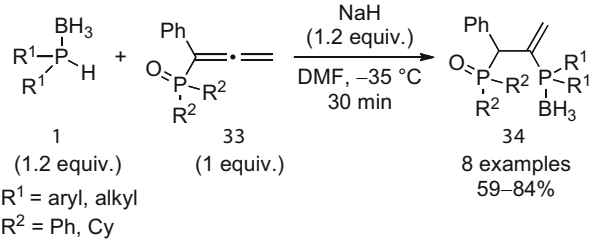
Hydrophosphination (addition of a P–H bond to an unsaturated C–C bond) is a highly valuable reaction, as it fulfils the atom-economy principle. Secondary phosphine-boranes have been found particularly effective alkyne, allene and alkene hydrophosphinating agents under metal-free basic or neutral conditions offering an access to a broad range of alkenyl and alkyl phosphine-boranes under mild reaction conditions.



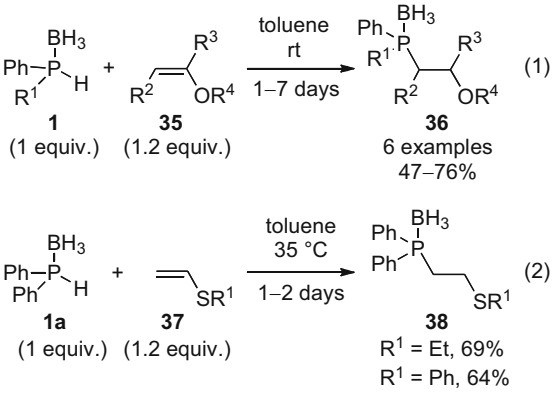
Scheme 10 Alkyne hydrophosphination with phosphine-boranes under basic conditions

The hydrophosphination of unactivated internal alkynes **27** with phosphine-boranes **1** was reported to proceed at rt under basic conditions [29]. The reaction was performed with NaH (1.2 equiv.) in *N*,*N*-dimethylacetamide (DMAc) at rt, with a broad scope of phosphine-boranes displaying various steric and electronic properties as well as alkyl-aryl- and diaryl alkynes. The reaction is highly regioselective, the addition of the phosphorus atom preferentially occurring at the β-position to the most electron-withdrawing alkyne substituent. Moreover, a high stereoselectivity in favour of the (*E*)-isomer was observed (Scheme 10, (1)). By contrast, the hydrophosphination of propargylic alcohols **29** under similar conditions predominantly led to the formation of the (*Z*)-isomer, probably as a result of the coordination of the sodium alkoxide fragment with the alkenyl anion intermediate (Scheme 10, (2)) [30]. The reaction between a racemic *P*-stereogenic phosphine-borane and an enantiopure propargyl alcohol furnished the two diastereomeric alkenyl phosphine-borane products, which could be separated by fractional crystallization. The hydrophosphination of propargylamines **31** readily proceeded at 0°C, delivering the corresponding amino-substituted alkenyl phosphine-boranes **32** with high (*E*)-selectivity in this case (Scheme 10, (3)). Borane transfer from the phosphorus to the nitrogen atom was not observed with the dialkyl phosphine-boranes used.

Scheme 11 Allene hydrophosphination with phosphine-boranes under basic conditions



Scheme 12 Hydrophosphination of vinyl (thio)ethers

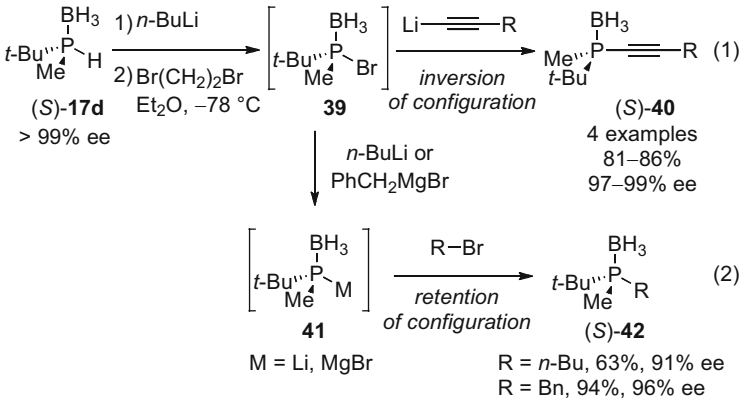


The hydrophosphination of allenyl phosphine oxides **33** was also studied under basic conditions. The addition of secondary phosphine-boranes **1** was completed within 30 min at −35°C in DMF as solvent (Scheme 11) [29].

The presence of a base is not always required as in the case of the hydrophosphination of alkenyl ethers **35** with diphenyl- and alkylphenylphosphine-boranes **1**. The reaction proceeds at rt under neutral conditions in the presence of a slight excess of alkene (Scheme 12, (1)) [31]. The reaction regioselectively afforded the *anti*-Markovnikov products with terminal substrates. The absence of borane decomplexation under these mild conditions and the fact that no work-up is required are additional attractive features of this procedure. The reaction conditions were successfully extended to the hydrophosphination of vinyl thioethers **37** with diphenylphosphine-borane (**1a**), but a slightly higher temperature of 35°C was required (Scheme 12, (2)). With the bulky and electron-rich dicyclohexylphosphine-borane, a radical activation (Et_3B) was employed to favour the addition.

2.2.3 Stereospecific Nucleophilic Substitution at the P-Atom

Previously reported methods dealing with the synthesis of *P*-stereogenic enantiopure phosphines were limited to substrates bearing at least one aryl group. An efficient access to the borane complexes of some enantioenriched



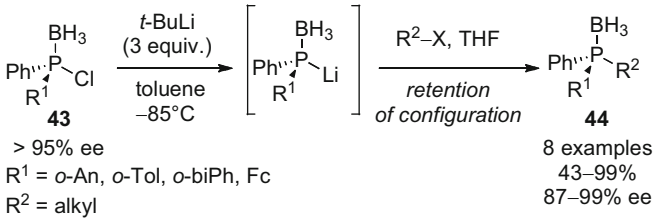
Scheme 13 Synthesis of enantioenriched alkynylphosphine-boranes and trialkylphosphine-boranes

alkynyldialkylphosphines and trialkylphosphines derived from *tert*-butylmethylphosphine-borane (**17d**) was recently developed [32]. The procedure relies on the in situ generation of a *P*-stereogenic bromophosphine-borane from an enantiopure secondary dialkylphosphine-borane via deprotonation by *n*-butyllithium in diethyl ether at −78°C and subsequent halogenation of the resulting lithium phosphido-borane by treatment with 1,2-dibromoethane. Enantiopure *tert*-butylmethylbromophosphine-borane (**39**) was not isolated because of its tendency to racemize at rt, but was directly reacted with a set of alkynyl lithium reagents. The nucleophilic substitution reaction was found to occur stereospecifically with clean inversion of configuration at the phosphorus atom, delivering the alkynylphosphine-boranes **40** in high yields and excellent enantioselectivity (Scheme 13, (1)). By contrast, the trialkylphosphine-boranes **42**, resulting from the reaction of *n*-butyllithium or benzylmagnesium bromide, were obtained with retention of configuration (Scheme 13, (2)). This stereochemical outcome was explained by a halogen-metal exchange.

A related transformation was described with several bulky chloroarylphenylphosphine-boranes **43** as substrates (Scheme 14) [33]. They are classically stereospecifically converted into tertiary phosphine-boranes via nucleophile attack with inversion of configuration at phosphorus [34]. However, they underwent metal–halogen exchange upon treatment with *tert*-BuLi in toluene at −85°C and delivered *P*-stereogenic tertiary phosphine-boranes **44** with retention of configuration and *ee* up to 99% after addition of an excess of alkyl halide.

2.2.4 Metal-Mediated C–P Cross-Coupling Reactions

The use of a phosphine-borane as phosphine surrogate in metal-mediated cross-coupling reactions has the major advantage of limiting the possible poisoning of the metal catalyst. Moreover, such an activated phosphine allows the cross-couplings to



Scheme 14 Synthesis of enantioenriched *P*-stereogenic phosphine-boranes from chlorophosphine-boranes

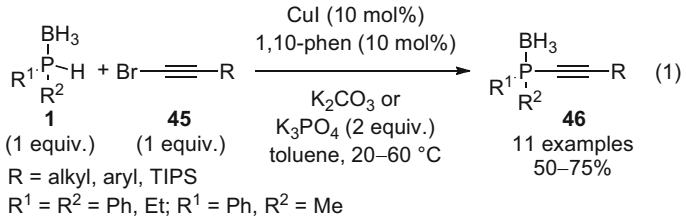
proceed under milder conditions, broadening the substituent scope and the structure complexity.

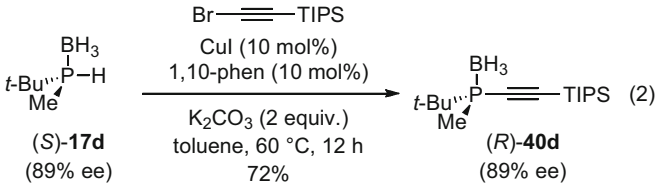
Recent achievements in this field deal with the synthesis of alkynyl- and alkenylphosphine-boranes using copper and palladium complexes, notably in the asymmetric series.

Alkyne Series

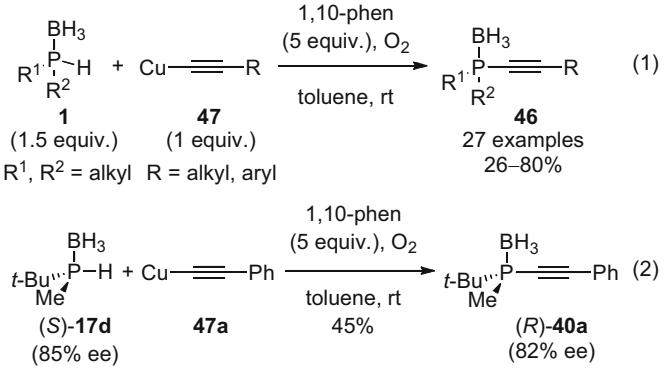
The classical method for the synthesis of alkynylphosphines relies on the reaction between a chlorophosphine as the electrophile and a metal acetylide as the nucleophile partner [35]. (For recent catalytic protocols based on the use of terminal alkynes and nickel or copper complexes, see [36, 37].) The use of a stoichiometric amount of organometallic bases precludes the access to alkynylphosphines bearing sensitive functional groups, and the scope of the phosphorus substituents is most often limited to the few commercially available chlorophosphines. The first example of the synthesis of alkynylphosphines involving nucleophilic phosphorus reagents was reported in 2011. The methodology is based on the copper-catalyzed cross-coupling of secondary phosphine boranes **1** with alkyl, aryl or silyl 1-bromoalkynes **45** using the CuI/1,10-phenanthroline couple as catalyst (Scheme 15, (1)) [38]. The reaction proceeds in toluene under mild conditions (20–60°C, weak base). The steric hindrance of the phosphorus substituents has a strong influence on the reaction. Indeed, *tert*-butylmethylphosphine-borane (**17d**) could be successfully cross-coupled, while *tert*-butylphenylphosphine-borane (**17a**) failed to react under the reported conditions. Importantly, the reaction was shown to proceed with full retention of configuration and stereopurity when applied to stereoenriched secondary *tert*-butylmethylphosphine-borane (*S*)-**17d** (89% *ee*) (Scheme 15, (2)) [39].

More recently, the synthesis of alkynylphosphine-boranes was achieved through oxidative P-alkynylation of secondary dialkylphosphine-boranes **1** with copper acetylides **47** in the presence of the 1,10-phenanthroline ligand (Scheme 16, (1)) [40]. The reaction was carried out in toluene at rt under an oxygen atmosphere. Remarkably, the choice of a phosphine-borane as a coupling partner allowed the oxidative transfer of the alkynyl group from copper to phosphorus to prevail over





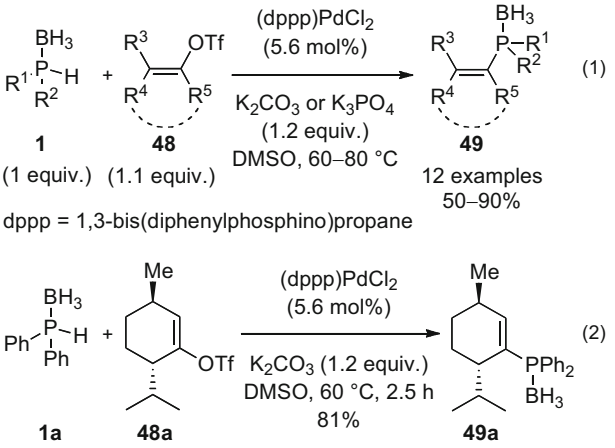
Scheme 15 Copper(I)-catalyzed reaction of secondary phosphine-boranes with 1-bromoalkynes toward alkynylphosphine-boranes



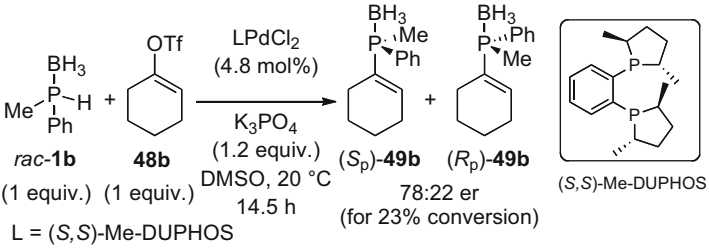
Scheme 16 Oxidative alkynylation of secondary dialkylphosphine-boranes with alkynylcopper reagents

the obvious side-reactions, which are the oxidation of the phosphorus reagent and the dimerisation of the alkynylcopper derivative.

This oxidative procedure nicely complements the catalytic method relying on the P-alkynylation with 1-bromo-alkynes reported above, as it allows the reacting of very bulky phosphine-boranes. Indeed, even di-*tert*-butylphosphine-borane, which is known as a poor cross-coupling partner, was able to undergo the alkynylation reaction with octynylcopper (26% yield). When applied to enantioenriched *tert*-butylmethylphosphine-borane (*S*)-**17d**, (85% *ee*), retention of configuration at phosphorus was observed with only a slight erosion of optical purity (82% *ee*) (Scheme 16, (2)). The only limitation is that the reaction is not applicable to arylphosphine derivatives.



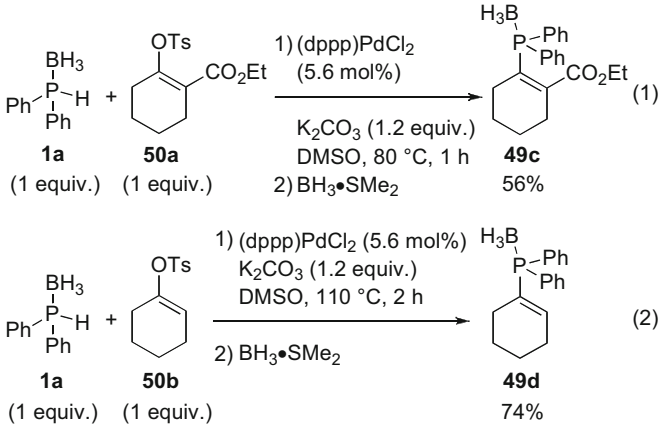
Scheme 17 Palladium-catalyzed C–P coupling reaction of alkenyltriflates and secondary phosphine-boranes



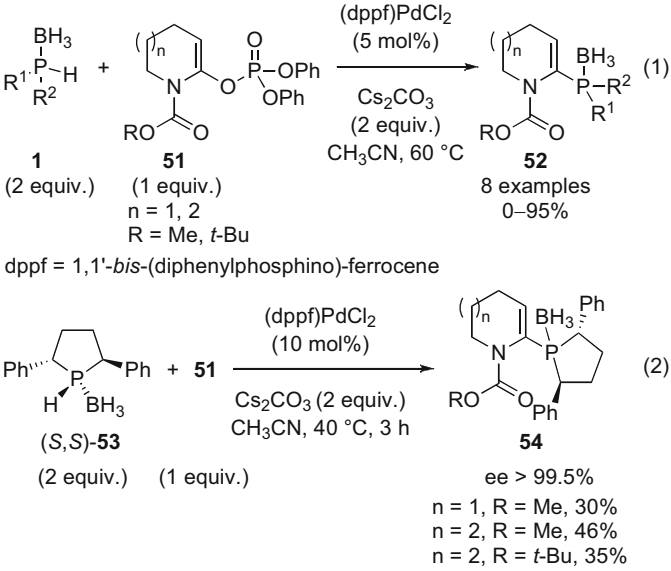
Scheme 18 Asymmetric cross-coupling between cyclohexenyl triflate and methylphenyl-phosphine-borane

Alkene Series

As an alternative to alkenyl halides, it was recently reported that enol derivatives such as alkenyl triflates **48**, alkenyl tosylates **50**, or enol phosphates **51**, easily available from carbonyl derivatives, could be valuable partners in C–P cross coupling reactions under palladium catalysis yielding alkenyl phosphine-boranes **49**, **52** and **54** (Schemes 17, 18, 19 and 20). The first example involving diphenylphosphine-borane (**1a**) and an activated alkenyl triflate was reported in 1999 [41], but the versatility of the procedure was demonstrated in 2007 [42]. The coupling is performed under rather mild conditions (60–80°C) and completed in a very short time (2.5–6 h) in the presence of a weak and inexpensive base (potassium carbonate or potassium phosphate) and a catalytic amount of a palladium catalyst (dppp)$PdCl_2$ (Scheme 17, (1)). The reaction is applicable to a broad range of phosphines with various electronic and steric properties (diaryl-, dialkyl- and alkyl-aryl-phosphines) and to cyclic or acyclic triflate precursors **48**. Microwave



Scheme 19 Pd-catalyzed C-P cross-coupling with alkenyl tosylates



Scheme 20 Pd-catalyzed P–C cross-coupling from enol phosphates

activation can be used to ensure even shorter reaction time (20–55 min). Enantiopure phosphines were readily obtained by using chiral triflates, easily available from the chiral pool, with camphor and menthol triflates as examples (Scheme 17, (2)).

A study aimed at developing an enantioselective version of this coupling reaction was carried out with cyclohexenyltriflate (**48b**) and racemic methylphenylphosphine-borane (**1b**). The best results were obtained with ((*S*,*S*)-Me-Duphos)$PdCl_2$ as chiral precatalyst, which afforded enantiomeric ratios up to 78:22 (Scheme 18) [43].

Alkenyl tosylates **50**, which are known to be poorly reactive in cross-coupling reactions, could also be efficiently coupled with diphenylphosphine-borane (**1a**) using a simple and inexpensive precatalyst such as (dppp)$PdCl_2$ [44]. The optimized conditions involve a weak base (K_2CO_3), a polar solvent (DMSO) and thermal activation (80–110°C). Alkenyl tosylates bearing an electron-withdrawing group can be coupled under conditions quite similar to alkenyl triflates (Scheme 19, (1)). Less reactive alkenyl tosylates required a higher temperature (110°C) (Scheme 19, (2)). It should be noted that borane decomplexation occurred during the reaction but that the conversion was lower when diphenylphosphine was used as reagent, demonstrating the positive effect of the borane in the coupling process.

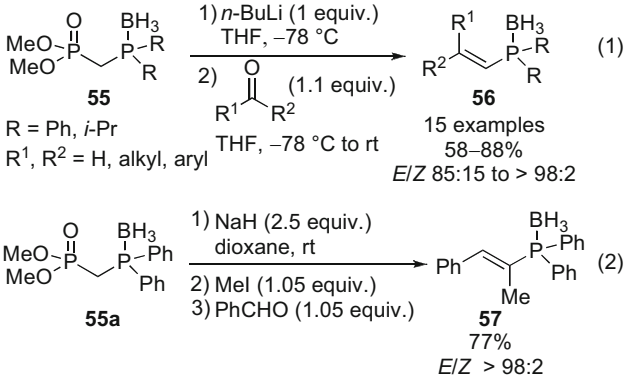
Enol phosphates can also serve as valuable reagents. The palladium-catalyzed P–C cross-coupling reaction between diarylphosphine-boranes and α-amido enol phosphates was reported to proceed under mild conditions affording alkenyl phosphine-boranes bearing an amido group in the α-position to the P-center (Scheme 20, (1)) [45]. The best-defined conditions involved using (dppf)$PdCl_2$ as catalyst, Cs_2CO_3 as base and acetonitrile as solvent at a temperature of 60°C. It should be noted that the *N*-Boc 6-membered enol phosphate failed to react and that racemization at phosphorus was observed when the reaction was performed with enantiopure (*S*)-(*o*-anisyl)phenylphosphine-borane. Nevertheless, the use of enantiopure (*S*,*S*)-2,5-diphenylphospholane-borane (**53**) as cross-coupling partner afforded the corresponding enantiopure α-enamido phosphine derivatives **54** (>99.5% *ee*) (Scheme 20, (2)).

2.3 Synthesis of Tertiary Phosphine-Boranes via Modification of the Carbon Part

Structural modification of the carbon moiety of alkyl, alkenyl, alkynyl or aryl phosphine is a valuable tool to prepare new useful building blocks. Alkenyl phosphines and triazolyl phosphines are some of the achievements of this strategy. The most striking one is probably the development of concise and efficient routes to acyclic and cyclic optically active *P*-stereogenic phosphine-boranes based on the Evans' *n*-BuLi/(−)-sparteine desymmetrisation methodology of prochiral dimethylphosphine-boranes [46].

2.3.1 Synthesis of Stereodefined Alkenyl Phosphine-Boranes via Modification of the Carbon Moiety

A straightforward and stereoselective access to alkenyl phosphine-boranes based on the Horner–Wadsworth–Emmons (HWE) olefination reaction applied to mixed 1,1-bisphosphorus compounds **55** bearing a phosphonate and a phosphine-borane

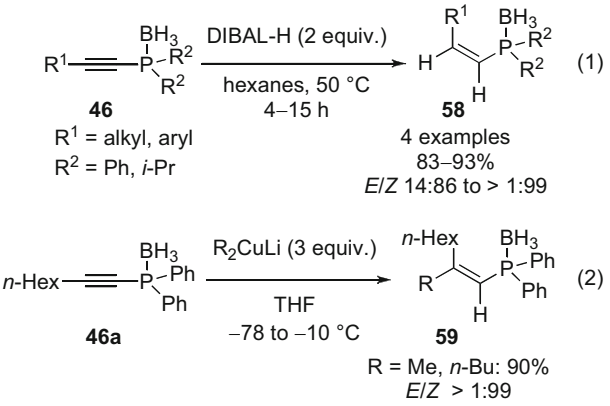


Scheme 21 Synthesis of (*E*)-alkenylphosphine-boranes from 1,1-mixed bisphosphorus compounds

moiety was recently developed [14]. The reaction readily proceeds with both aldehydes and ketones leading to the corresponding di- and tri-substituted alkenyl phosphine-boranes **56**, respectively, with high (*E*)-stereoselectivity (Scheme 21, (1)). This procedure is particularly useful for the synthesis of vinyl derivatives, such as vinyldiphenylphosphine-borane, which is obtained in low yield via classical nucleophilic substitution of vinylmagnesium bromide at the P-atom of chlorodiphenylphosphine [47].

1,2-Trisubstituted alkenyl phosphine-boranes are also accessible and with excellent (*E*)-stereoselectivity, as illustrated by the synthesis of alkenyl phosphine-borane **57** via a one-pot process involving the alkylation of 1,1-phosphonate-diphenylphosphine-borane (**55a**) followed by HWE-olefination with benzaldehyde (Scheme 21, (2)) [14].

A stereocomplementary approach to the HWE-olefination of 1,1-mixed bisphosphorus compounds leading exclusively to (*Z*)-alkenyl phosphine-boranes was also proposed [15]. The procedure is based on the hydroalumination or carbocupration of alkynylphosphine-boranes. The reduction of alkynylphosphine-boranes **46** with diisobutylaluminium hydride (DIBAL-H) proceeded with high stereoselectivity in favour of the (*Z*)-isomer with the exception of the styrene derivative (R^1=Ph), which was obtained with a *Z*/*E* ratio of 86:14 (Scheme 22, (1)). Deuterium experiments with D_2O revealed that the reaction proceeded through conjugate addition of the hydride. Attempts to perform the alkylation of the alkenyl aluminium intermediates instead of the hydrolysis were unsuccessful. However, the preparation of (*Z*)-trisubstituted alkenyl phosphine-boranes **59** was achieved through carbocupration of alkynyl phosphine-borane **46a** with R_2CuLi reagents (Scheme 22, (2)).

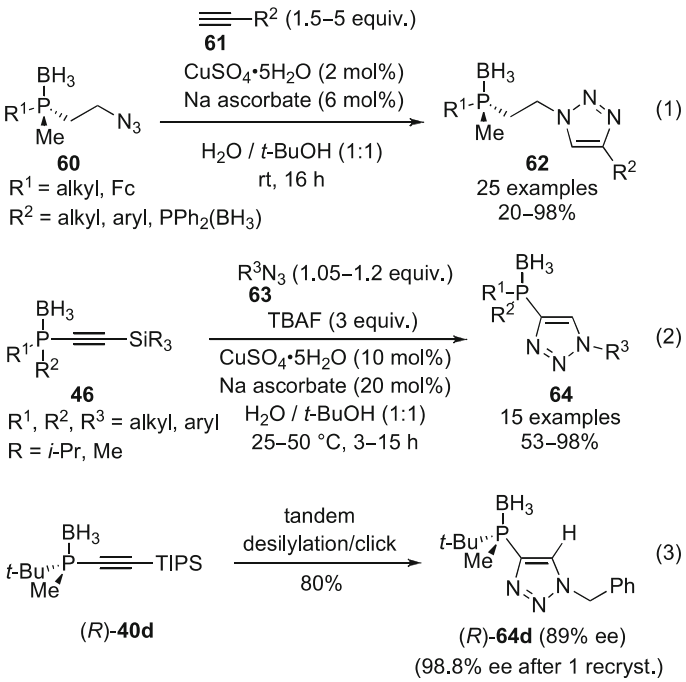


Scheme 22 Synthesis of (*Z*)-alkenyl phosphine-boranes through hydroalumination or carbocupration of alkynyl phosphine-boranes

2.3.2 Synthesis of Triazole-Functionalized Phosphine-Boranes Through Click Chemistry

The copper-catalyzed [3+2] dipolar cycloaddition between azides and alkynes (Click reaction) [48, 49] was used to access phosphine ligands functionalized by a triazolyl moiety. The borane complexation was crucial to avoid the occurrence of the competitive Staudinger reaction [50, 51]. The introduction of the phosphorus moiety was achieved either via the azide (strategy 1) [52] or via the alkyne reagent (strategy 2) [39]. In both cases, the classical Click reaction conditions were used [48]. They involve copper(II) sulphate pentahydrate as catalyst in the presence of sodium ascorbate solubilized in the biphasic solvent system *tert*-butanol/water (1:1). Sodium ascorbate is used for the in situ reduction of the metal complex into a copper(I) complex, which is the active species in this reaction. In the first strategy, optically active functionalized azides **60** were readily prepared in four steps from tertiary prochiral dimethyl phosphine-boranes bearing a bulky substituent (*tert*-butyl, adamantyl, ferrocenyl (Fc), etc.) (see Sect. 2.3.4), and reacted with a broad range of terminal alkynes **61** to deliver a library of *P*-stereogenic phosphines **62** (Scheme 23, (1)). Some of these ligands were tested as catalysts on a typical palladium-catalyzed asymmetric allylic alkylation and afforded high conversion but low stereoselectivity (<12%).

The second strategy deals with the use of readily available silyl-protected alkynylphosphine-boranes **46** (see Sect. 2.2.4, Scheme 15 for their preparation), which were submitted to a one-pot two-step procedure involving desilylation with TBAF followed by copper-catalyzed azide-alkyne-cycloaddition to furnish 1,2,3-triazolyl-4-phosphine-boranes **64** (Scheme 23, (2)). The efficiency of the procedure relies on the fact that the isolation of sensitive terminal alkynylphosphine-boranes is skipped. It should be noted that the first example of an enantioenriched *P*-stereogenic 1,2,3-triazolyl-4-phosphine (*R*)-**64d** (98.8% *ee*) was readily available

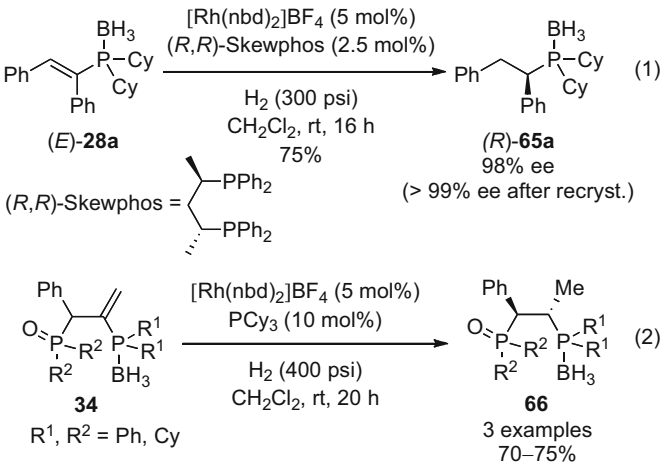


Scheme 23 Synthesis of triazolyl-functionalized phosphine-boranes through Click chemistry

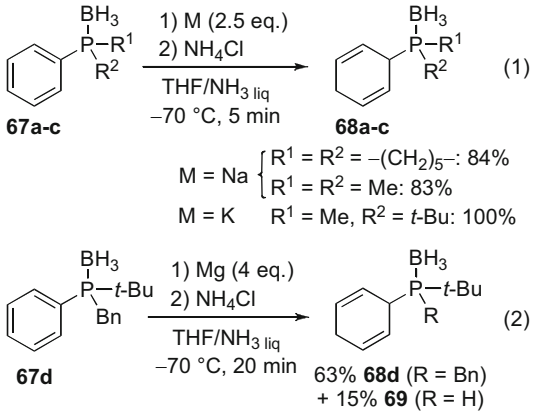
according to this procedure (Scheme 23, (3)). Preliminary studies on the catalytic activity of this phosphine family with the 4-(di-*tert*-butyl)phosphino-triazolyl derivative (R^1=R^2 = *t*-Bu; R^3=Bn) demonstrated that it was a highly active catalyst in Suzuki–Miyaura cross-coupling reactions of poorly reactive aryl chlorides [39].

2.3.3 Synthesis of Tertiary Phosphine-Boranes Through Reduction of the Carbon Moiety

Structural modification through reduction of the carbon moiety is mainly associated with the transformation of the alkynyl moiety through hydroalumination (see Sect. 2.3.1, Scheme 22) [15] or the conversion of an alkenyl moiety into an alkyl one. A recent example of the latter deals with the catalytic asymmetric hydrogenation of the alkenyldicyclohexylphosphine-borane **28a** using bis(norbornadiene) rhodium(I)tetrafluoro-borate as precatalyst combined with the (*R*,*R*)-Skewphos ligand, affording the chiral trialkylphosphine-borane **65a** with full control of the stereochemistry (Scheme 24, (1)) [29]. It should be noted that the reaction readily proceeds without affecting the phosphine-borane moiety. Under similar reaction conditions, but using tricyclohexylphosphine as ligand, the bisphosphines **34** resulting from the hydrophosphination of allenylphosphine oxides with secondary



Scheme 24 Catalytic hydrogenation of alkenyl phosphine-boranes



Scheme 25 Synthesis of 1,4-cyclohexadienyl-dialkyl phosphine-boranes through Birch reduction of aryl-dialkyl phosphine-boranes

phosphine-boranes (see Sect. 2.2.2, Scheme 11), were converted diastereoselectively into the bis-phosphorus derivatives **66** (Scheme 24, (2)).

By contrast, the examples of structural modification of an aryl moiety are still limited. The challenging conversion of aryl-dialkyl phosphine-boranes **67** into 1,4-cyclohexadienyl-dialkyl phosphine-boranes **68** through the Birch-type reduction was demonstrated to be possible, although alkali metals are well-known reagents for carrying out Ph–P bond cleavage (Scheme 25, (1)) [53]. The choice of the metal was found to be crucial, a screening of alkali metals revealing that the order of selectivity toward the Birch product (Li<K<Na) was reversely correlated to the redox potential of the metals. In the case of benzyl-substituted phosphine-

borane **67d**, the Ph–P bond cleavage could only be prevented with magnesium as reducing agent and the Birch product **68d** was formed along with a side-product **69** (15%) resulting from partial P–Bn bond cleavage (Scheme 25, (2)).

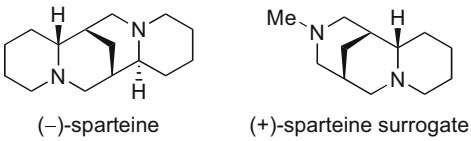
The one-pot Birch reduction/in situ alkylation of the intermediate cyclohexadienyl carbanions with primary alkyl halides afforded access to α-functionalized (cyclohexa-1,4-dien-3-yl)phosphine derivatives [54].

2.3.4 Synthesis of Acyclic *P*-Stereogenic Phosphine-Boranes from Dimethyl Phosphine-Boranes

The asymmetric deprotonation of prochiral dimethyl phosphine-boranes with *sec*-BuLi/(−)-sparteine, originally described by Evans in 1995 [46], is a powerful tool to access enantioenriched *P*-stereogenic phosphine-boranes, as well as their enantiomers, by simply switching from (−)-sparteine to O'Brien's (+)-sparteine surrogate (Fig. 3) [55, 56]. Recent progress in this field deals with the development of catalytic versions using sub-stoichiometric amount of the chiral diamines and the synthesis of new functionalized *P*-stereogenic phosphine-boranes based on this desymmetrisation methodology.

Since their first report demonstrating that high enantioselectivities could be obtained in the lithiation-oxygenation of *tert*-butyldimethylphosphine-borane (**70a**) with 0.5 equiv. instead of 1.2 equiv. of chiral diamines [57], the O'Brien group has put a lot of efforts in developing enantioselective catalytic procedures involving even smaller amount of chiral diamines [58]. For this purpose, a so-called two-ligand procedure was developed, which involves the use of only 0.2 equiv. of (−)-sparteine combined with an additional achiral ligand in stoichiometric amount [59]. The best results were obtained with lithiated dimethylaminoethanol (LiDMAE) or bispidine as achiral ligands for the lithiation/silylation of **70a** with *sec*-BuLi (Table 2, entry 2 vs 3, 4). Importantly, with *n*-BuLi at −78°C, (−)-sparteine was not turned over as it could not be displaced from the lithiated intermediate by *n*-BuLi (Table 2, entry 6) and only the two-ligand procedure with LiDMAE gave satisfactory results (Table 2, entry 7).

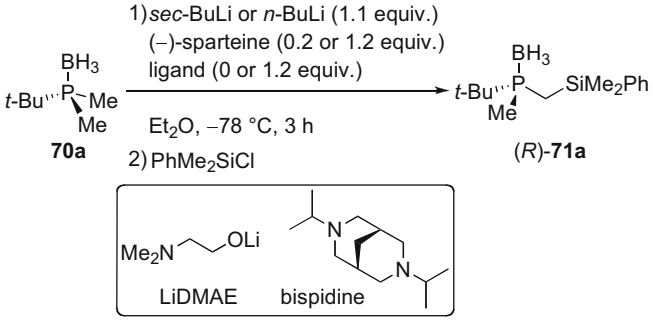
A revised catalytic protocol has been reported recently, which has the advantage of not requiring an additional achiral ligand and relies on three sequential additions of *sec*-BuLi with an optimized amount of 0.4 equiv. of (−)-sparteine or 0.3 equiv. of its (+)-surrogate (Scheme 26) [60]. This new catalytic protocol was applied to the asymmetric synthesis of both enantiomers of the borane complexes of trichikenfootphos and MiniPHOS bisphosphine ligands.



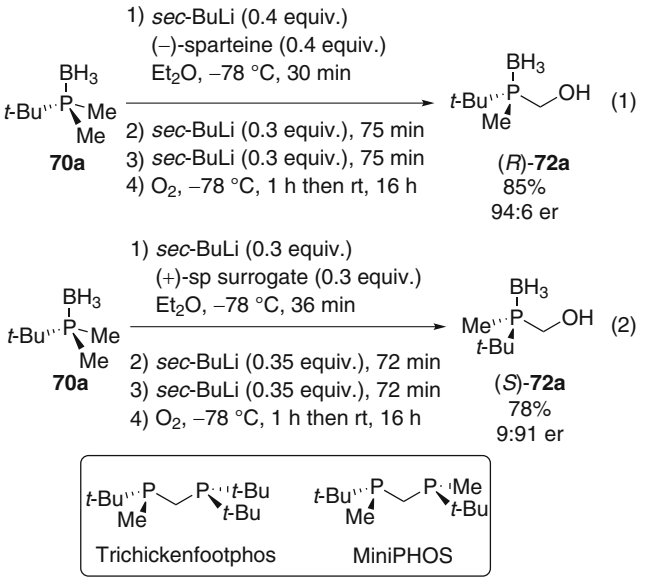
(−)-sparteine (+)-sparteine surrogate

Fig. 3 Structures of (−)-sparteine and (+)-sparteine surrogate

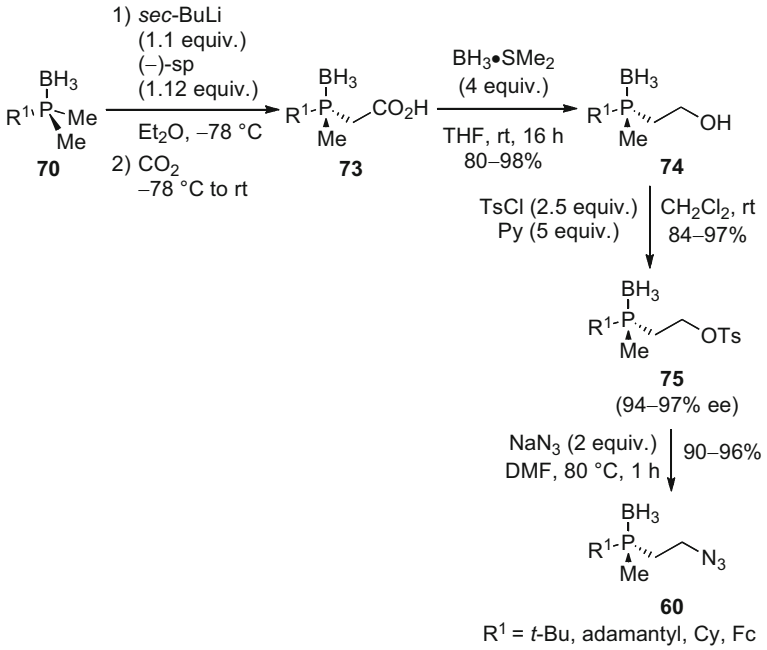
Table 2 Comparison of one-ligand and two-ligand catalytic asymmetric deprotonation of *tert*-butyldimethylphosphine-borane (**70a**)



Entry	Li-Base	(−)-spart. (equiv.)	Achiral ligand	Yield (%)	er (*R*:*S*)
1	*sec*-BuLi	1.2	0	74	92:8
2	*sec*-BuLi	0.2	0	76	74:26
3	*sec*-BuLi	0.2	LiDMAE	59	81:19
4	*sec*-BuLi	0.2	Bispidine	78	79:21
5	*n*-BuLi	1.2	0	76	89:11
6	*n*-BuLi	0.2	0	21	84:16
7	*n*-BuLi	0.2	LiDMAE	48	82:18
8	*n*-BuLi	0.2	Bispidine	52	59:41



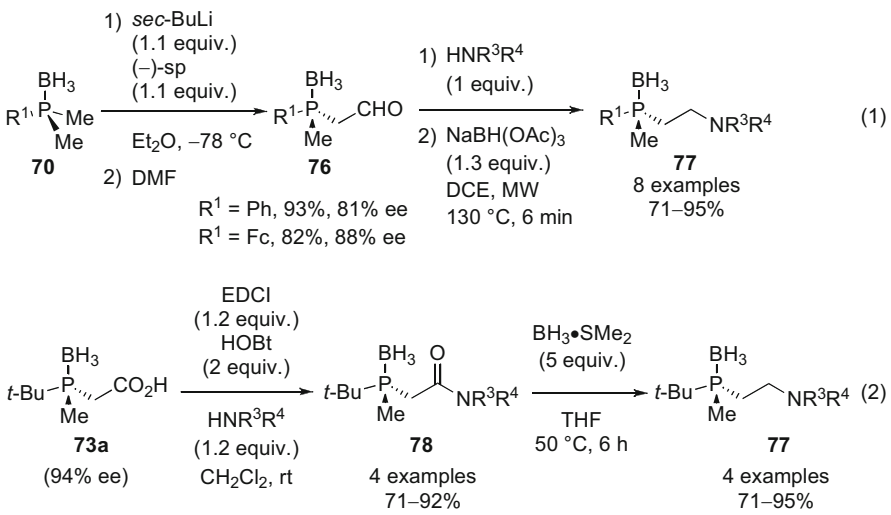
Scheme 26 One-ligand catalytic asymmetric deprotonation of *tert*-butyldimethylphosphine-borane (**70a**) through sequential additions of *sec*-BuLi and trapping with oxygen



Scheme 27 Synthesis of azido-substituted *P*-stereogenic phosphine-boranes **60**

Concise routes toward functionalized chiral phosphine-boranes have been designed according to the *sec*-BuLi/(−)-sparteine desymmetrisation strategy of prochiral dimethylphosphine-boranes. *P*-Stereogenic phosphine-boranes **60** bearing an azido moiety, which serve as precursors of triazole-functionalized phosphine ligands (see Sect. 2.3.2, Scheme 23), were synthesized within four steps from tertiary prochiral dimethylphosphine-boranes **70** bearing a bulky substituent (*tert*-butyl, adamantyl, Fc, etc.) (Scheme 27) [52]. Asymmetric deprotonation of **70** with the chiral couple *sec*-BuLi/(−)-sparteine or *sec*-BuLi/(+)-sparteine surrogate followed by reaction with CO_2 delivered α-carboxyphosphines **73**, which were reduced to the corresponding alcohols **74** by treatment with BH_3•SMe_2 complex. The resulting hydroxyl group was converted into a tosylate moiety by treatment with tosyl chloride in the presence of pyridine, and then substituted by an azido group through reaction with sodium azide in DMF at 80°C.

P-Stereogenic β-aminophosphine-boranes **77** (Scheme 28) were also readily prepared according to a two-step-sequence [61]. Using DMF as an electrophile in the desymmetrisation of prochiral phosphine-boranes **70** gave access to α-formyl derivatives **76** which underwent subsequent reductive amination by treatment with triacetoxyborohydride and different amines under microwave irradiation (Scheme 28, (1)). It should be noted that this route is not suitable for the synthesis of the *tert*-butyl derivatives. The alternative route involves α-carboxyphosphine **73a** as intermediate, which was converted into amides **78** in the presence of



Scheme 28 Synthesis of *P*-stereogenic β-aminophosphine-boranes **77**

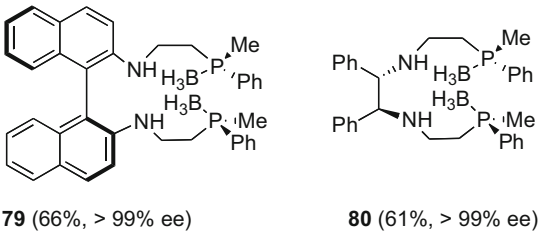
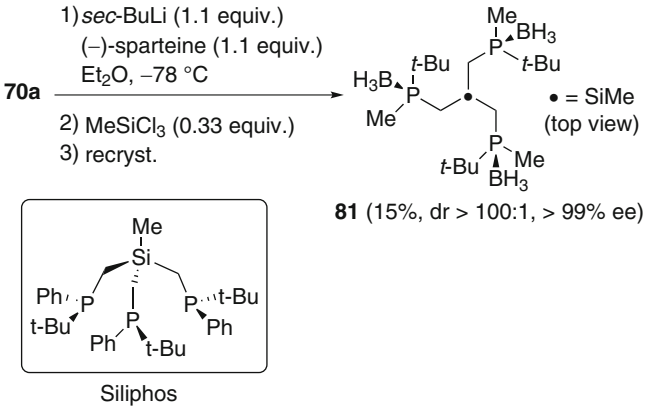


Fig. 4 Structures of optically pure C_2-symmetric *P*,*N*,*N*,*P*-ligands **79** and **80**

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole hydrate (HOBt) (Scheme 28, (2)). Borane mediated reduction delivered the β-aminophosphine-boranes **77**.

The reaction sequence (Scheme 28, (1)) was successfully applied to the synthesis of two optically pure C_2-symmetric *P*,*N*,*N*,*P*-ligands **79** and **80** (Fig. 4) starting from chiral diamines, 2,2′-diaminobinaphthalene and 1,2-diphenylethylenediamine.

The asymmetric synthesis of a C_3-symmetric *P*-stereogenic triphosphine was also reported based on the *sec*-BuLi/(−)-sparteine desymmetrisation strategy (Scheme 29) [62]. Indeed, asymmetric deprotonation of *tert*-butyldimethylphosphine-borane (**70a**) and subsequent treatment with trichloromethylsilane (0.33 equiv.) delivered a 2.6:1 mixture of diastereomeric C_3- and C_1-symmetric triphosphine-boranes **81**. The C_3-diastereomer could be separated by recrystallization in 15% isolated yield. Triphosphine-borane **81** is the first enantiopure methyl-analogue of the Siliphos ligand [63]. In view of its shortness and scalability,



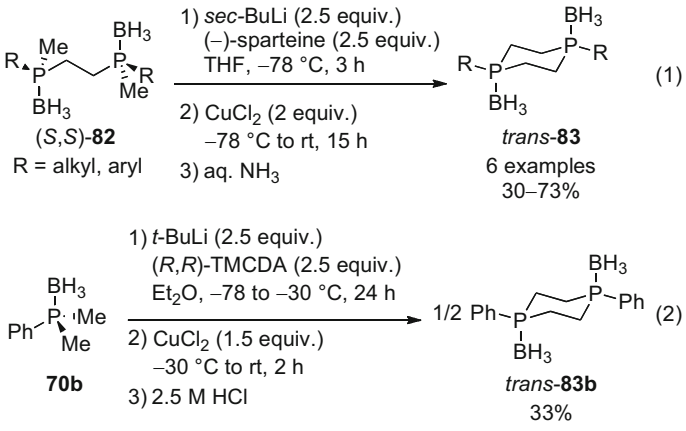
Scheme 29 Asymmetric synthesis of the C_3-symmetric *P*-stereogenic triphosphine **81**

the method is quite attractive for the synthesis of this kind of ligand, which has been little-explored so far because of the lack of practical synthetic routes.

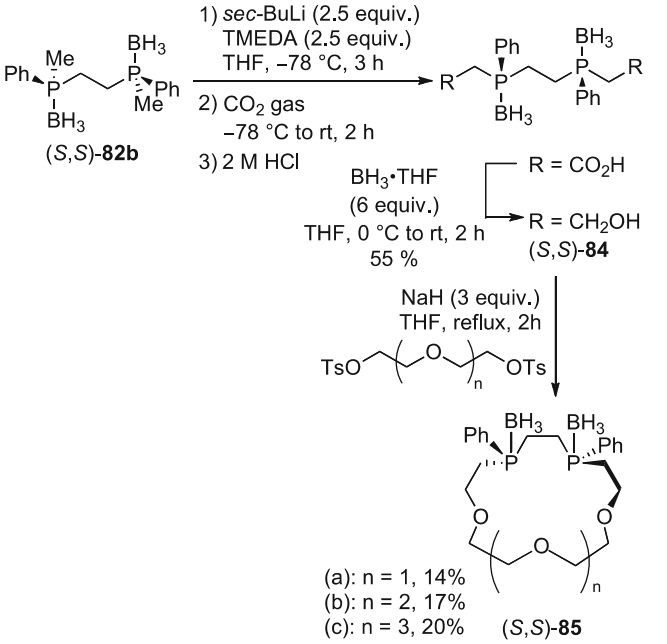
2.3.5 Synthesis of Phosphorus-Containing Ring Systems

Straightforward syntheses of diphosphacycloalkanes and diphosphacrowns as well as original routes to *P*-stereogenic five- and six-membered benzophosphacycles and phospholene-boranes were developed by taking advantage of the activating effect of borane, which facilitates the α-lithiation of methylphosphine-boranes and by using the well-established asymmetric deprotonation of dimethylphosphine-boranes with the *sec*-BuLi/(−)-sparteine couple (see Sect. 2.3.4).

The *trans*-1,4-diphosphacyclohexane-diboranes **83** were stereospecifically synthesized from optically active (*S*,*S*)-BisP*-borane complexes **82**, through lithiation with *sec*-BuLi in the presence of (−)-sparteine, followed by oxidative intramolecular coupling through transmetallation from Li to Cu using copper (II) chloride and treatment with aqueous NH_3 (Scheme 30, (1)) [64, 65]. Although a chiral amine is not necessary in this reaction, (−)-sparteine offered better results than other amines such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). It should be noted that the cyclization prevails over oligomer formation and that the *trans*-isomers are solely formed from (*S*,*S*) or (*R*,*R*)-BisP*-borane complexes. On the other hand, the procedure led to an equimolar mixture of separable *cis*- and *trans*-1,4-diphosphacyclohexane-diboranes when applied to a mixture of racemic and *meso*-bisphosphines. The stereospecific synthesis of *trans*-1,4-diphenyl-1,4-diphosphacyclohexane-diborane (**83b**) was also achieved directly from dimethylphenylphosphine-borane (**70b**) through the deprotonation of both methyl groups using *tert*-BuLi combined with (*R*,*R*)-TMCDA (*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-diamine) and subsequent treatment with copper(II) chloride (Scheme 30, (2)) [66].



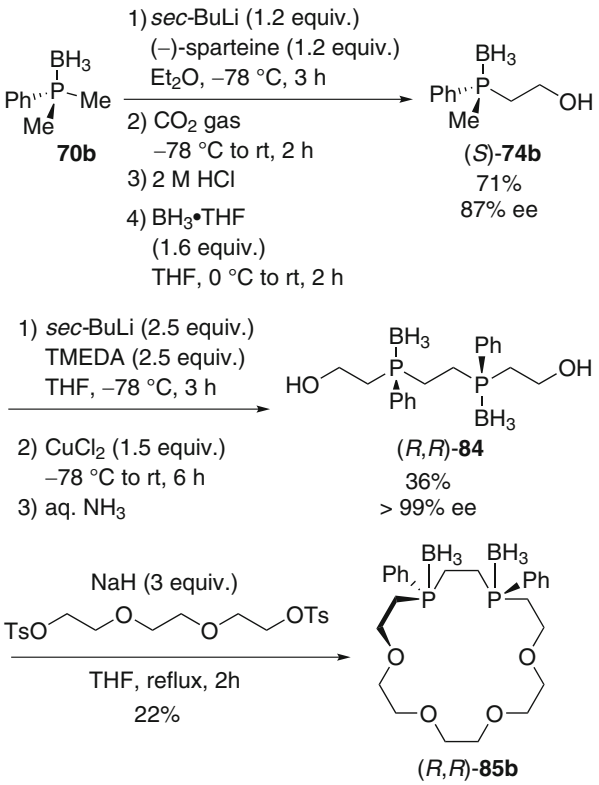
Scheme 30 Synthesis of *trans*-1,4-diphosphacyclohexanes through intramolecular oxidative coupling



Scheme 31 Synthesis of (*S*,*S*)-diphosphacrowns **85**

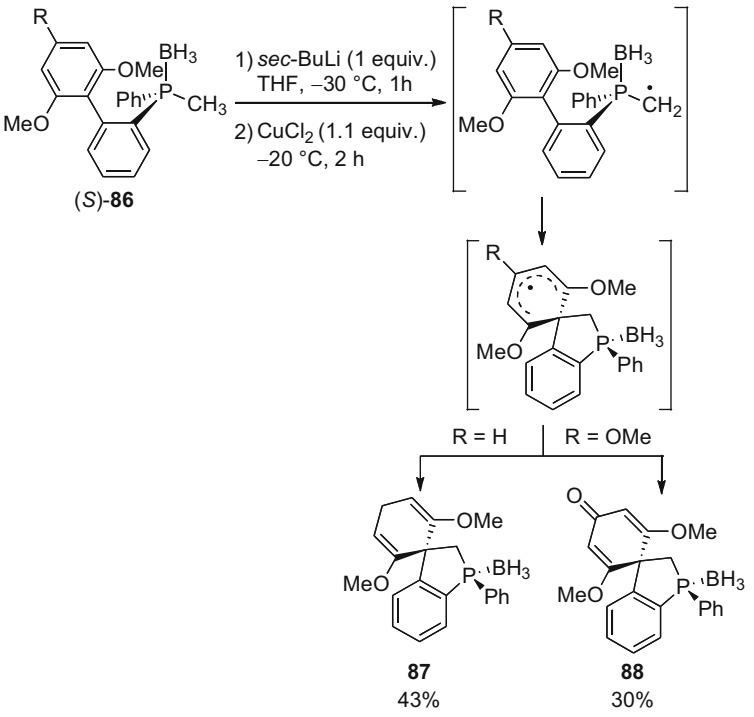
The optically active (*S*,*S*)-BisP*-borane complexes **82** could also serve as key-building blocks for the first practical synthesis of enantiopure *P*-stereogenic diphosphacrowns [67, 68], the only former example of an optically active diphosphacrown being obtained through optical resolution according to Pasteur's

Scheme 32 Synthesis of (*R*,*R*)-18-diphosphacrown-6 **85b**



method [69]. The bisphosphine (*S*,*S*)-**82b** (R=Ph) readily available from dimethylphenylphosphine-borane (**70b**) by lithiation with *sec*-BuLi/(−)-sparteine followed by oxidative coupling with copper(II) chloride (>99% *ee*) [64] was converted into optically active diphosphacrowns of various size according to the reaction sequence outlined on Scheme 31. The lithiation of both methyl groups of **82b** with *sec*-BuLi/TMEDA was followed by CO_2 bubbling and the resulting dicarboxylic acid was directly reduced by BH_3•THF complex into diol (*S*,*S*)-**84** in 55% overall yield from **82b**. As a final step, a Williamson ether synthesis with the appropriate ethyleneglycol *bis*(*p*-toluenesulfonate) under diluted conditions in THF (20 mM) delivered the targeted (*S*,*S*)-diphosphacrowns **85** in yields up to 20%.

The access to (*R*,*R*)-18-diphosphacrown-6 **85b** was not a straightforward application of the previously described sequence and the use of a (+)-sparteine surrogate[56] was not examined by the authors. As outlined in Scheme 32, dimethylphosphine-borane (**70b**) was first converted into the alcohol (*S*)-**74b** (87% *ee* after recrystallization) through enantioselective lithiation with *sec*-BuLi/(−)-sparteine, and subsequent CO_2 bubbling followed by the reduction of the resulting carboxylic acid by BH_3•THF. After dimerisation of **74b** by oxidative coupling, the enantiopure (*R*,*R*)-diol **84** (>99% *ee*) was isolated through repeated



Scheme 33 Synthesis of benzophospholane-P-boranes through radical-initiated dearomatizing spirocyclization

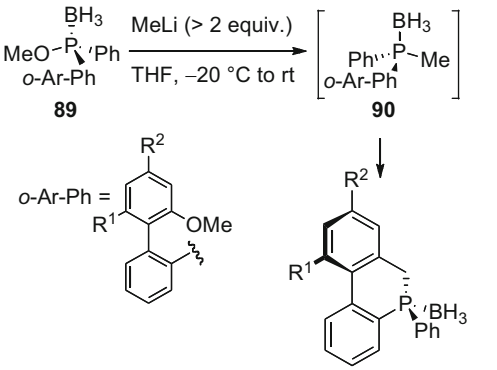
recrystallization from hot toluene in 36% yield, and converted into the targeted (*R*,*R*)-18-diphosphacrown-6 **85b** in 22% yield through Williamson ether synthesis [67].

The ability of *P*-stereogenic diphosphacrowns to serve as chiral ligands was demonstrated in the palladium-catalyzed asymmetric 1,4-addition of aryl boronic acids to cyclopentenone, which proceeded in high yields and with good enantioselectivities up to 92%.

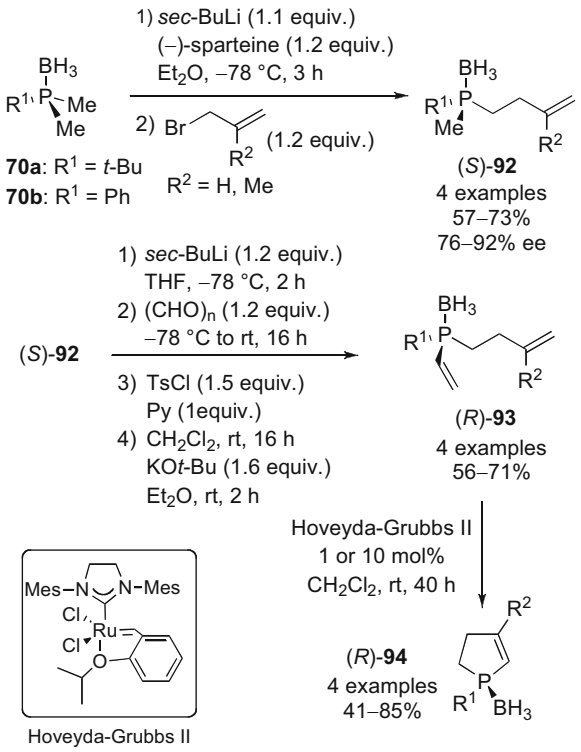
The broadly used copper-mediated dimerization of methylphosphine-boranes was found ineffective with (*o*-biaryl)(methyl)phenylphosphine-boranes because of the formation of complex mixtures [70]. With substrates bearing methoxy substituents on the top ring of the biaryl moiety, unusual cyclic structures could be selectively obtained through either a radical or an anionic process (Schemes 33 and 34). Derivatives bearing a 2,6-dimethoxyphenyl moiety underwent dearomatizing spirocyclization upon treatment with *sec*-BuLi and $CuCl_2$ through trapping of the generated P-α-radical and were converted in non-classical spiro benzophospholane *P*-borane structures (Scheme 33). When an additional methoxy group was located at position 4 (R=OMe) in the top ring, the dienone structure **88** was formed, resulting from the loss of a methyl radical.

The asymmetric synthesis of *P*-stereogenic phosphorinane-boranes **91** was achieved directly from enantiomerically pure methyl phosphinite-boranes **89** bearing a methoxy *ortho*-substituent on the top ring of the biaryl moiety, upon treatment

Scheme 34 Synthesis of *P*-stereogenic phosphorinane-boranes **91** through anionic benzannulation



Scheme 35 Synthesis of *P*-stereogenic phospholene-boranes (*R*)-**94** via asymmetric deprotonation and RCM



with an excess of methyllithium (Scheme 34). This one-pot transformation relies on the in situ formation of the corresponding methylphosphine-boranes **90**, their subsequent *P*-α-deprotonation, and then benzannulation (S_NAr) through displacement of the aryl methoxy group by the generated *P*-α-lithio carbanion.

The unprecedented asymmetric synthesis of *P*-stereogenic phospholene-boranes **94** was recently reported as relying on the ring closing metathesis (RCM) of dienyl phosphine-boranes **93** as a key-step (Scheme 35) [71]. Dimethylphosphine-boranes **70** were first submitted to classical asymmetric lithiation with *sec*-BuLi/(−)-sparteine followed by allylation with allyl or methallyl bromide affording enantioenriched allylphosphine-boranes (*S*)-**92** with enantiomeric excess up to 92%. The methyl group of compounds **92** was next converted into a vinyl moiety according to a four-step sequence, which was achieved without intermediate purification, and involved P-α-deprotonation with *sec*-BuLi and subsequent reaction with formaldehyde, tosylation of the resulting hydroxy group and its elimination by treatment with potassium *tert*-butoxide. The final RCM step was performed with the Hoveyda–Grubbs second generation catalyst in dichloromethane at rt and afforded the targeted enantioenriched phospholene-boranes (*R*)-**94** in up to 85% yield.

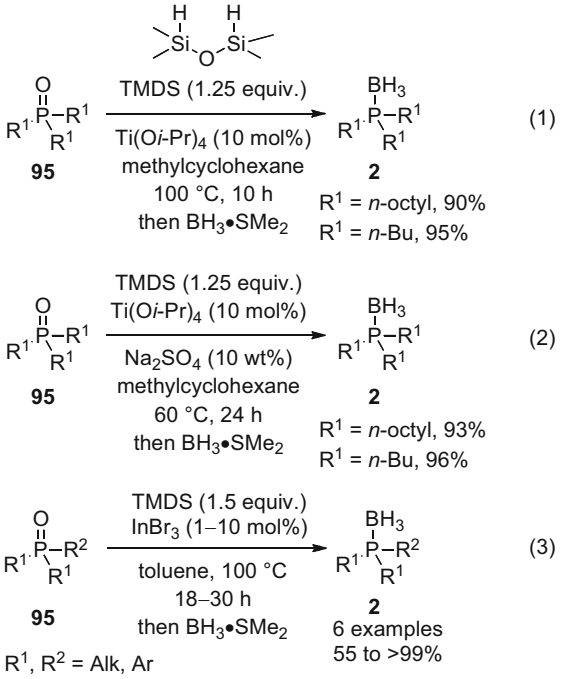
2.4 Synthesis of Tertiary Phosphine-Boranes via Reduction of Tertiary Phosphine Oxides

The reduction of phosphine oxides and subsequent borane complexation to avoid reoxidation during work-up is one of the classical routes for the synthesis of tertiary phosphine-boranes. Although many reducing agents are already known [72], the search for new ones continues to receive attention with a special focus on the safety of the reducing agent. A relevant contribution consists of the one-pot stereoselective synthesis of enantioenriched *P*-stereogenic phosphine-boranes from racemic tertiary phosphine oxides.

The well-established reduction method of tertiary phosphine oxides using polymethylhydrosiloxane (PMHS) and a stoichiometric amount of Ti(O*i*-Pr)$_4$ [19] could be turned catalytic by switching to the lower molecular weight hydrosiloxane TMDS (tetramethyldisiloxane) [73]. Thus triaryl and trialkyl phosphine oxides **95** were efficiently reduced by treatment with TMDS (1.25 equiv.) in the presence of 10 mol% of Ti(O*i*-Pr)$_4$ in methylcyclohexane at 100°C. Air sensitive trialkylphosphines were isolated as their borane complexes **2** (Scheme 36, (1)). To avoid the partial hydrolysis of any titanium species in the medium by water produced as by-product, the addition of the drying agent sodium sulphate was evaluated and found to improve the procedure significantly, as the reaction temperature could be decreased from 100 to 60°C (Scheme 36, (2)) [74]. A single electron transfer (SET) mechanism was suggested according to the recorded ESR spectra of the reaction, which showed the formation of a Ti(III) species.

The reduction of tertiary alkyl and aryl phosphine oxides could also be efficiently achieved using a catalytic amount of $InBr_3$ (1–10 mol%) in combination with TMDS (Scheme 36, (3)) [75]. However, under these reaction conditions, the reduction of the double bond of alkenyl substrates such as allyldiphenylphosphine oxide could not be prevented. By contrast, the highly chemoselective phosphoryl

Scheme 36 Reduction of tertiary phosphine oxides with TMDS followed by borane complexation

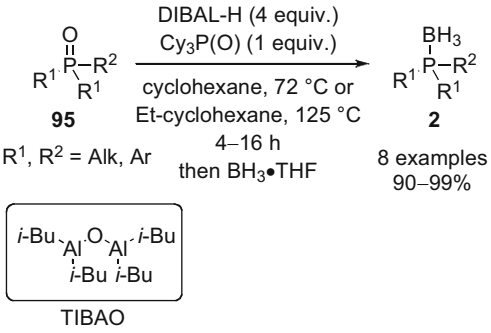


reduction of 1,3-butadienyldiphenylphosphine oxides was reported using a 3:1 mixture of phenylsilane and trichlorophenylsilane in THF at 60°C as a reducing system [76].

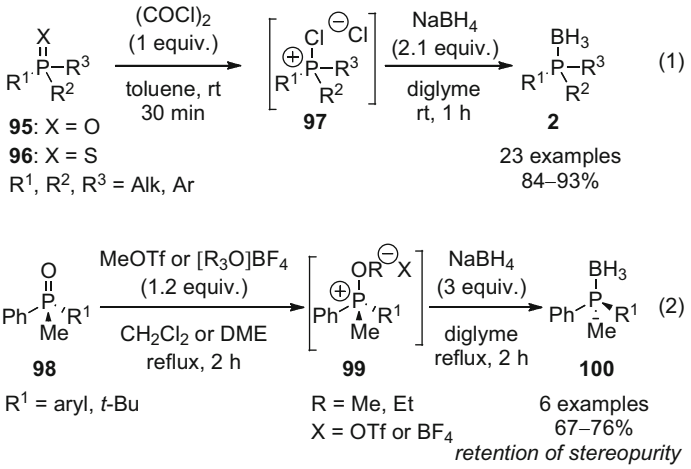
In contrast to the reduction of secondary phosphine oxides (see Sect. 2.1), the reduction of tertiary phosphine oxides scarcely involves neutral organoaluminiums as reducing agents. The use of diisobutylaluminium hydride (DIBAL-H) was, however, reported to proceed efficiently in the presence of an equimolar amount of tricyclohexylphosphine oxide to ensure a full conversion (Scheme 37) [77]. Indeed, tetraisobutyldialuminoxane (TIBAO) generated in situ was identified as the source of inhibition of the reaction, and its displacement from the starting material was necessary. Importantly, racemization was observed when the procedure was applied to an optically active diarylmethylphosphine oxide.

Tertiary phosphine oxides **95** or sulfides **96** could be converted into tertiary phosphine-boranes in one-pot via the corresponding chlorophosphonium salts **97** by treatment with oxalyl chloride and sodium borohydride sequentially, the latter playing a dual role of reducing agent and borane source (Scheme 38, (1)) [78].

Full racemization was observed with optically active substrates **98**, probably because of the nucleophilicity of the chloride counterion of **97**. Indeed, switching from chlorophosphonium to alkoxyphosphonium salts **99** as intermediates by using methyl triflate or Meerwein's type salts as alkylating agents allowed the reaction to proceed stereospecifically with inversion of configuration (Scheme 38, (2)). Unlike $LiAlH_4$, which is the reducing agent used in combination with methyl triflate in the



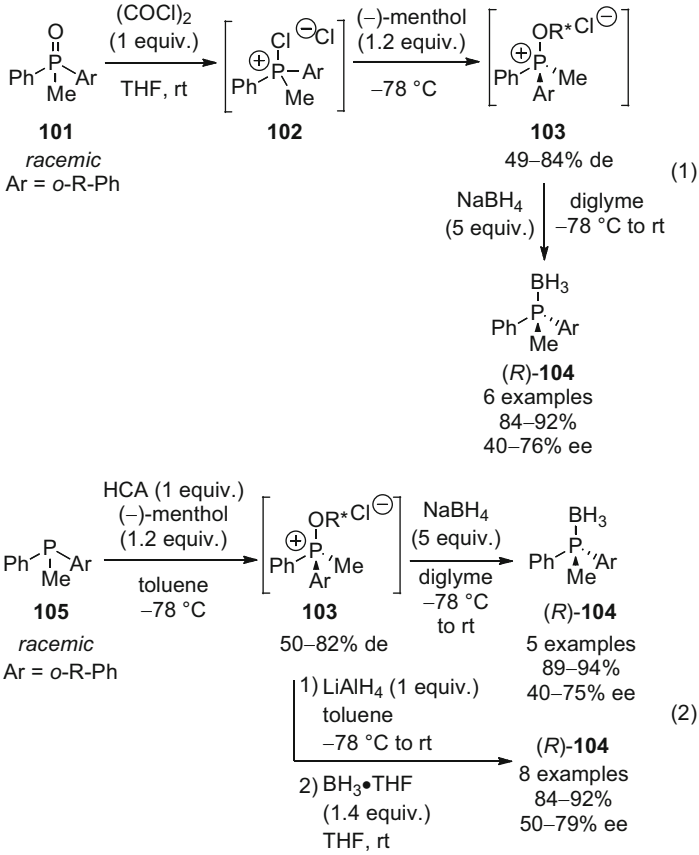
Scheme 37 Reduction of tertiary phosphine oxides with DIBAL-H followed by borane complexation



Scheme 38 One-pot conversion of phosphine oxides or sulphides into phosphine-boranes using $NaBH_4$ and an alkylating reagent

related well-known Imamoto's procedure [79], $NaBH_4$ is unable to reduce phosphine oxides directly, and this inert character may also account for the clean retention of stereopurity.

As an extension of this chemistry to the asymmetric series, the stereoselective synthesis of enantioenriched *P*-stereogenic tertiary phosphine-boranes was developed from racemic tertiary phosphines oxides. It relies on the dynamic resolution of diastereomeric alkoxyphosphonium salts followed by their reduction with $NaBH_4$. Thus, treatment of racemic phosphine oxides **101**, which display an *ortho*-substituted aryl group with oxalyl chloride, delivered racemic chlorophosphonium salts **102**, which were reacted with chiral alcohols such as (−)-menthol at −78°C, giving unequal amounts of diastereomeric alkoxyphosphonium salts **103** (Scheme 39, (1)) [80]. The reduction of the alkoxyphosphonium salts with

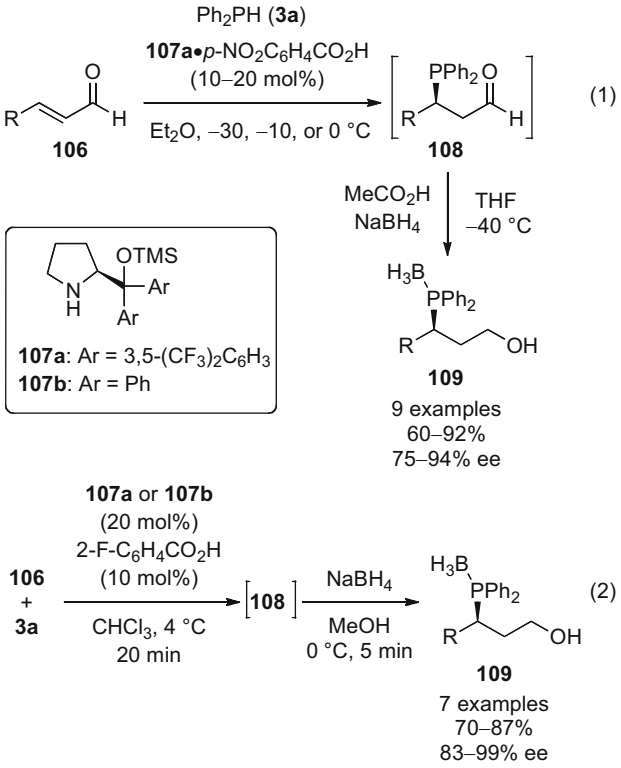


Scheme 39 Stereoselective synthesis of enantioenriched *P*-stereogenic phosphine-boranes from racemic tertiary phosphines or their oxides

$NaBH_4$, gave the enantioenriched tertiary phosphine-boranes **104**. As an alternative, the diastereomerically enriched alkoxyphosphonium salts **103** were available with similar stereoselectivities from racemic tertiary phosphines **105** through their treatment with hexachloroacetone (HCA) and (−)-menthol in toluene at −78°C [81]. Reduction of **103** by $NaBH_4$ or $LiAlH_4$ and subsequent borane complexation delivered the targeted tertiary phosphine-boranes **104** (Scheme 39, (2)).

2.5 *Applications of Phosphine-Boranes*

During the last few years, phosphine-boranes have found various applications mainly in the fields of organic synthesis and catalysis. They have shown their



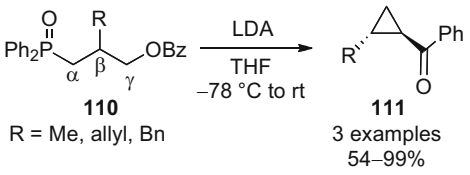
Scheme 40 Enantioselective synthesis of phosphine-boranes **109** by the groups of Melchiorre (1) and Córdova (2)

complementarity and even their superiority to phosphine oxides or free phosphines in various reactions.

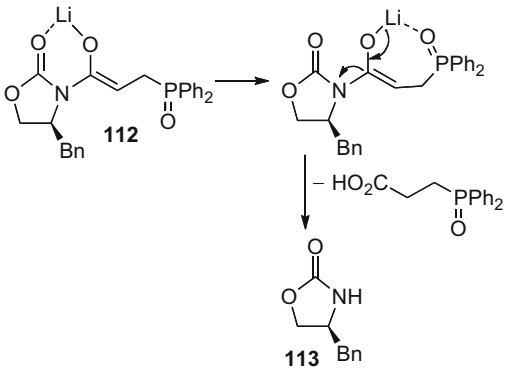
2.5.1 Phosphine-Boranes as Protected Phosphines

The in situ transformation of air-sensitive phosphines into their borane complexes as the last step of a reaction sequence is often used to evaluate the efficiency and eventually the stereoselectivity of new synthetic methodologies. For example, the groups of Melchiorre [82] and Córdova [83] independently reported the first examples of asymmetric organocatalytic hydrophosphination of α,β-unsaturated aldehydes **106** (Scheme 40). The resulting formyl phosphines **108** were transformed in situ into air-stable phosphine-boranes **109** in order to facilitate the purification step and to evaluate the enantioselectivity of the process.

The organocatalytic asymmetric hydrophosphination of nitroalkenes based on the use of a bifunctional *Cinchona* alkaloid catalyst was also reported by Melchiorre et al. as a new route toward optically active β-nitrophosphine-boranes [84].



Scheme 41 Phosphine oxide mediated cyclopropanation cascade reaction



Scheme 42 Plausible mechanism for the loss of the free auxiliary **113**

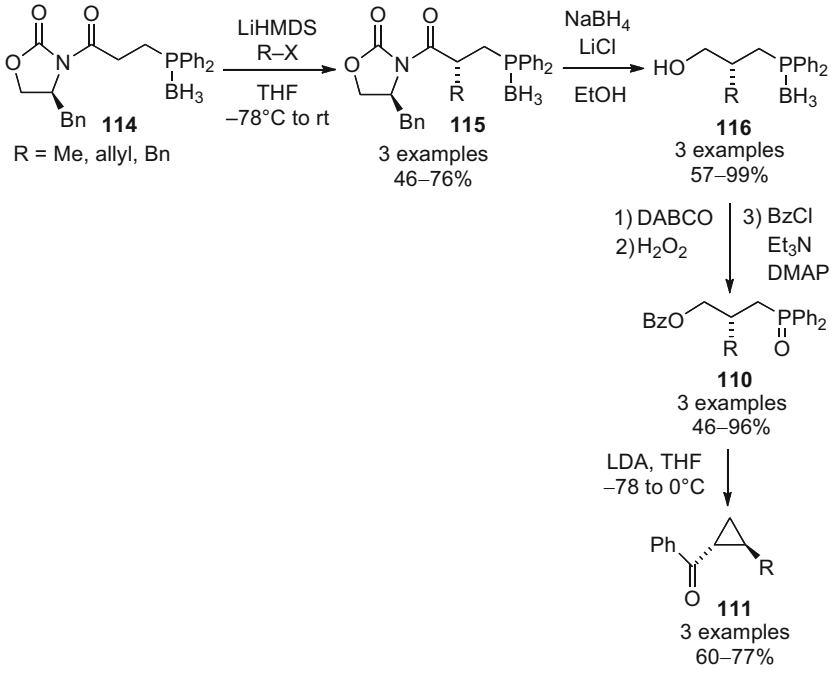
2.5.2 Phosphine-Boranes as Reagents for Organic Synthesis

Fox, Warren et al. have recently shown that β-substituted phosphine oxides could undergo the phosphine oxide mediated cyclopropanation cascade reaction to afford the *trans*-disubstituted cyclopropyl ketones **111** (Scheme 41) [85].

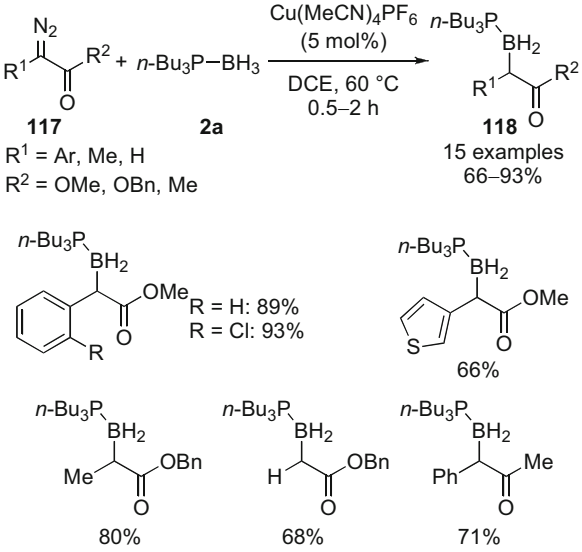
However, the asymmetric version using the Evans oxazolidinone auxiliary **113** was unsuccessful. Indeed, the direct β-alkylation on the phosphine oxide **112** mainly led to the leaving of the auxiliary group. This could be attributed to the high Lewis basicity of phosphine oxides, which compete with the carbonyl group of the Evans oxazolidinone to complex lithium (Scheme 42).

This side reaction could be avoided by using phosphine-borane derivatives as protected "phosphine oxides" in the alkylation step. After decomplexation and reoxidation, the enantioenriched phosphine oxides were reacted under the conditions previously described to afford the expected enantioenriched cyclopropanes in good yields (Scheme 43).

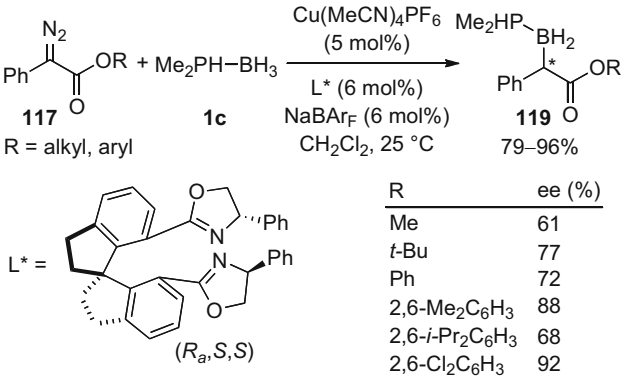
Transition-metal-catalyzed insertion of Fisher type carbenes into heteroatom–hydrogen bonds is an efficient strategy for the formation of heteroatom–carbon bonds. Zhu, Zhou et al. [86] recently reported an original access to chiral organoboron derivatives involving the copper-catalyzed B–H bond insertion starting from diazo esters and phosphine-borane adducts as the B–H source. The high reactivity of the B–H bond in these systems was explained by its activation induced by the complexation of the borane with the Lewis base, i.e. the phosphine. With these borane complexes, the copper-catalyzed C–B bond formation occurred under mild conditions. Three complexes were tested, $Bu_3P{\bullet}BH_3$, $Ph_3P{\bullet}BH_3$ and



Scheme 43 Asymmetric version of the phosphine oxide mediated cyclopropanation cascade



Scheme 44 Substrate scope of copper-catalyzed B–H bond insertion reactions



Scheme 45 Enantioselective version of copper-catalyzed B–H bond insertion reactions

$(MeO)_3P{\bullet}BH_3$. The electron-rich and poorly-hindered $Bu_3P{\bullet}BH_3$ (**2a**) was the best substrate both in terms of reaction rate and yields. Optimal conditions are the use of 5 mol% of $Cu(MeCN)_4PF_6$ in 1,2-dichloroethane (DCE) at 60°C. Under these conditions, the scope was broad (Scheme 44).

The asymmetric version was studied by using a chiral spirobisoxazoline ligand. A screening of various phosphine-borane complexes ($Bu_3P{\bullet}BH_3$, $Bu_2PH{\bullet}BH_3$, i-$Pr_2PH{\bullet}BH_3$, $Me_2PH{\bullet}BH_3$, n-$BuPH_2{\bullet}BH_3$) was performed. The best results were obtained with the use of a secondary phosphine borane complex, $Me_2PH{\bullet}BH_3$ (**1c**). Although this phosphine-borane also has a reactive P–H bond, no P–H insertion was observed during the process. It should be noted that the steric and electronic properties of the ester moiety of the diazoester deeply affected the enantioselectivity of the reaction (Scheme 45).

2.5.3 Phosphine-Boranes as Precursors of Chiral Phosphine Ligands

Phosphine-boranes have been used frequently as precursors of new families of chiral phosphine ligands. The initial work in this field was reported by Imamoto [79, 87, 88]. Since then, various groups have applied this strategy.

In 2011, Muller [89] reported the synthesis of various enantiomerically pure *P*-stereogenic monophosphines (Fig. 5), which were prepared according to Evans' [46] or Jugé's [90] procedures using a phosphine-borane as the starting material. These phosphines contain pendant groups bearing functionalities capable of having secondary interactions with the transition metal. The ligands were obtained after borane deprotection with morpholine.

Reaction of these phosphines with the Pd dimer $[Pd(\eta^3\text{-2-Me-allyl})(\mu\text{-Cl})]_2$ gave neutral allylic complexes $[PdCl(\eta^3\text{-2-Me-}C_3H_4)P^*]$ ($P^* =$ **120**, **121**, **122**) which, after abstraction of the chloride ligand by $AgBF_4$, afforded cationic complexes which were used as catalyst precursors in the hydrovinylation of styrene. These

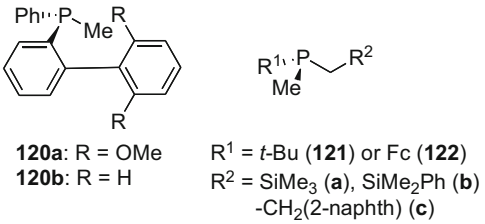
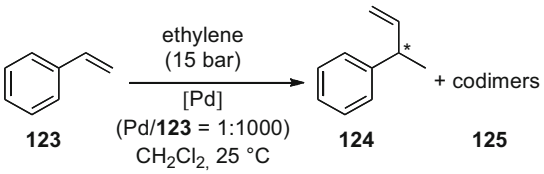


Fig. 5 Structure of phosphine ligands produced through Jugé's methodology (*left*) and Evans' methodology (*right*)

Table 3 Hydrovinylation of styrene catalyzed by [PdL(η-2-Me-C_3H_4)P^*]BF_4 complexes



[Pd] = [PdL(η^3-2-Me-C_3H_4)P*]BF_4
(L = styrene, solvent)

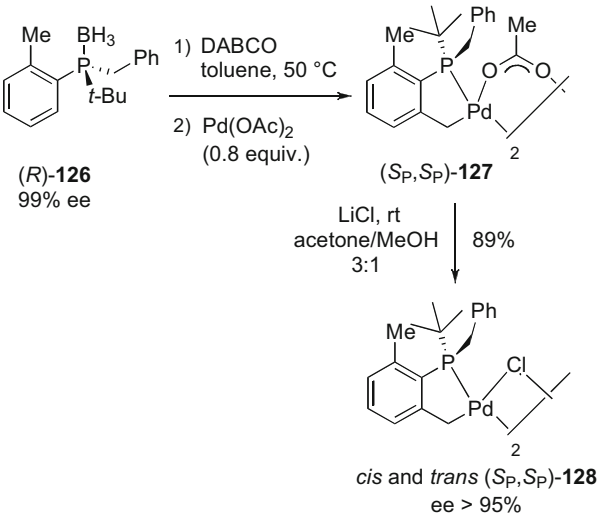
Entry	P^*	T (h)	Conv. (%)[a]	**124/125** (%)	TOF[b] (h^{-1})	*ee* (%)
1	**120a**	3	10.7	96.3	35	<5(−)
2	**120b**	1	10.5	97.2	100	23 (*S*)
3	**121a**	3	96	83	322	<5 (−)
4	**121c**	1	100	67	1015	35 (*R*)
5[c]	**122a**	3	85	74	283	20 (*R*)
6	**122b**	3	72	84	241	35 (*R*)
7	**122c**	3	50	92	145	17 (*R*)

[a]Conversion of starting styrene (**123**)
[b]TOF calculated as the total amount of phenylbutenes (**124** + **125**)
[c]**122a** had 80% *ee*

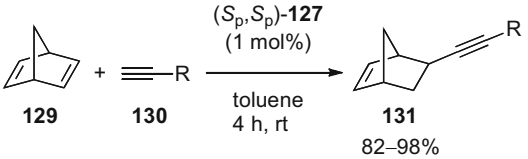
catalysts gave good TOFs up to 1,015 h^{-1}, but moderate regio- and enantioselectivities (<45% *ee*) (Table 3). The structure of the ligand proved to be crucial both for activity and selectivity, the best ligand for activity being the *t*-Bu methylphosphine compound **121c** having a CH_2(2-naphthyl) substituent as R^2.

Gatineau, Giordano and Buono reported the preparation of optically active phosphapalladacycles **127** and **128** from bulky *ortho*-tolyl *P*-stereogenic tertiary phosphine-borane (*R*)-**126** (Scheme 46) [25]. The dimeric phosphapalladacycle (S_P,S_P)-**127** was obtained upon borane decomplexation of (*R*)-**126** with DABCO followed by addition of $Pd(OAc)_2$. An acetato to chloro ligand exchange afforded a mixture of *cis*- and *trans*-chloropalladacycle (S_p,S_p)-**128**. The pure complex *trans*-(S_p,S_p)-**128** could be crystallized and analyzed by X-ray diffraction analysis. It showed a square-planar geometry and retention of configuration at the phosphorus atom.

Scheme 46 Synthesis of optically active phosphapalladacycles (S_P, S_P)-**127** and (S_P,S_P)-**128**



Scheme 47 Asymmetric addition of alkynes **130** to norbornadiene **129** catalyzed by palladacycle (S_P,S_P)-**127**

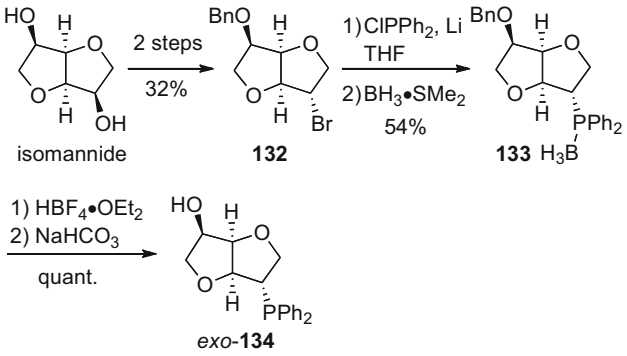


R	ee (%)
Ph	27
p-$MeOC_6H_4$	29
1-cyclohexen-1-yl	24
CH_2OAc	36

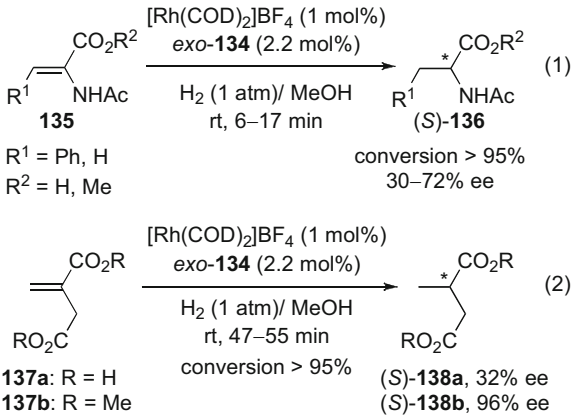
The reactivity of palladacycle (S_P,S_P)-**127** was briefly investigated in the asymmetric version of the addition of alkynes to norbornadiene, a reaction for which the Hermann-Beller phosphapalladacycle is known to be a key intermediate. Buono's phosphapalladacycle was found to be effective in this reaction, leading to the formation of the desired alkynes **131** in excellent yields (Scheme 47). Although the enantioselectivities in this reaction are rather low, they are quite promising for non-optimized conditions.

The group of Vo-Thanh [91] reported the synthesis of a new class of monophosphine ligands prepared from a natural chiral renewable resource, 1,4:3,6-dianhydrohexitol compounds. For example, chiral monophosphine exo-**134** was prepared via the phosphine-borane complex **133** in six steps, starting from isomannide (Scheme 48).

Complexes formed in situ from $[Rh(COD)_2]BF_4$ and *exo*-**134** ligand were examined as catalysts for the enantioselective hydrogenation of activated olefins (Scheme 49, (1)). Good conversions and enantioselectivities up to 95% and 72%,



Scheme 48 Synthesis of monophosphine *exo*-**134** obtained from isomannide



Scheme 49 Rhodium-catalyzed hydrogenation of activated olefins with chiral ligand *exo*-**134**

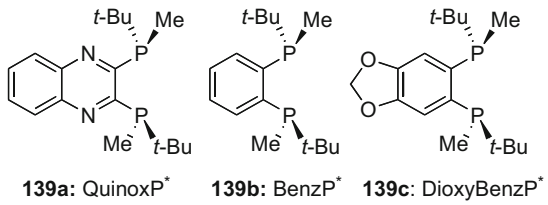
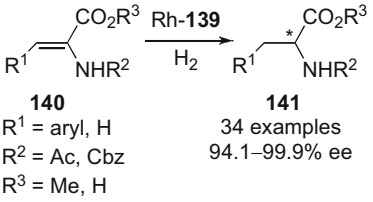


Fig. 6 Structure of bidentate ligands: QuinoxP*, BenzP* and DioxyBenzP*

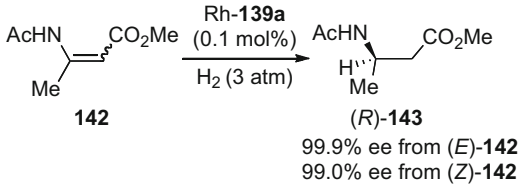
respectively, were obtained. With dimethyl itaconic ester, a high conversion of 95% was achieved with *ee* as high as 96% (Scheme 49, (2)). Compared to literature values, these results are quite modest but are the highest value ever obtained with monophosphine ligands.

Imamoto and Gridnev [92] reported the synthesis of both enantiomers of three new bidentate ligands **139a–c**, QuinoxP*, BenzP* and DioxyBenzP* (Fig. 6), from enantiopure (*S*)- and (*R*)-*tert*-butylmethylphosphine-boranes (**17d**) as key

Scheme 50 Asymmetric hydrogenation of α-dehydroamino acid derivatives



Scheme 51 Asymmetric hydrogenation of β-dehydroamino acid derivatives



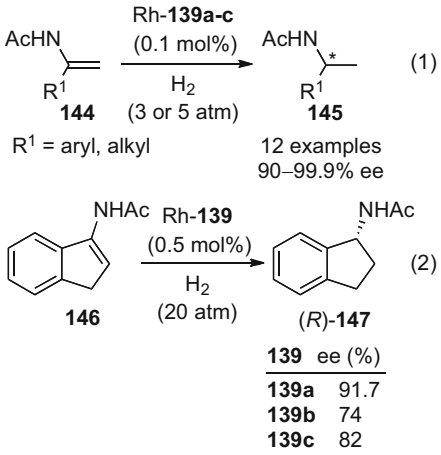
intermediates. A common feature of these three ligands is that two stereochemically equivalent *tert*-butylmethylphosphino groups are attached to the 1,2-positions of the aryl group. This should lead to the formation of rigid C_2-symmetric five-membered chelates, which are important for enantioselectivity. From an electronic point of view, the quinoxaline derivative displays electron-attracting properties while DioxyBenzP* should display electron-donating ones compared to BenzP*, taken as a reference.

The rhodium complex of each new ligand was prepared. All exhibited excellent enantioselectivities and high catalytic activities in the asymmetric hydrogenation of functionalized alkenes, such as dehydroamino acid derivatives and enamides. The hydrogenation with a substrate/catalyst ratio of 1,000 under 3 atm H_2 pressure at rt was completed within 0.3–0.5 h using any ligand affording the corresponding product with 99.9% *ee* (Scheme 50). Interestingly, both enantiomer catalysts afforded the same *ee*. Several chiral pharmaceutical building blocks having an amino acid or a secondary amine component were prepared to show the efficiency of the process. At higher substrate/catalyst ratio (S/C = 10,000) under 5 atm H_2 pressure, BenzP*-Rh catalyst (Rh-**139b**) afforded the product with the highest *ee* (99.8%).

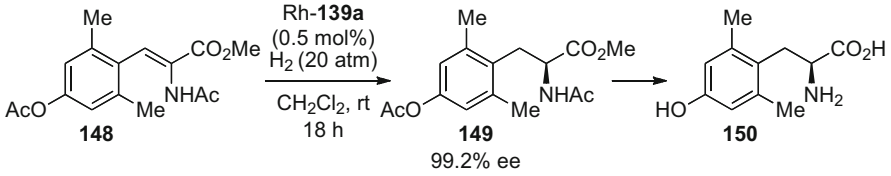
These rhodium catalysts were also tested in the hydrogenation of several β-substituted β-(acetylamino)acrylates (37 examples). As an example, the hydrogenation of methyl (*E*)-3-acetamido-2-butenoate (**142**) with (*R*,*R*)-QuinoxP*-Rh catalyst under 3 atm of H_2 afforded the expected product with 99.9% *ee* (Scheme 51). It should be noted that the hydrogenation of the more demanding (*Z*)-isomer also afforded the product with a high *ee* (99.0%).

Lastly, the Rh-ligand complexes were tested in the asymmetric hydrogenation of α-substituted enamides **144**, a major route to chiral amines. The hydrogenation was performed in methanol at rt in the presence of 0.1 mol% of rhodium complex under 3 or 5 atm H_2 pressure (Scheme 52, (1)). The asymmetric hydrogenation of cyclic enamides **146** was also performed (Scheme 52, (2)).

In order to demonstrate further the utility of these new catalysts (Rh-QuinoxP*, Rh-BenzP* and Rh-DioxyBenzP*), they were used for the preparation of chiral



Scheme 52 Asymmetric hydrogenation of α-substituted enamides

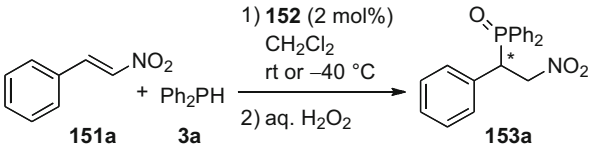


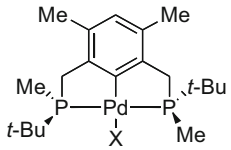
Scheme 53 Asymmetric hydrogenation toward *(S)*-2′,6′-dimethyltyrosine **150**, a non-natural amino acid

building blocks present in several important pharmaceuticals. As an example, (*S*)-2′,6′-dimethyltyrosine **150**, an unnatural amino acid used as a component of the δ-opioid antagonist Dmt-Tic pharmacophore, was prepared in excellent yield and *ee* (99.2%) using Rh-Quinox complex (Scheme 53).

Optically pure *tert*-butylmethylphosphine-borane (**17d**) was also used by the group of Imamoto to produce novel palladium-*P*-stereogenic P–C–P pincers, which were successfully applied in the asymmetric addition of diarylphosphines to nitroalkenes [93]. Although this reaction offers easy access to valuable precursors of pharmaceutically important compounds and potentially useful chiral *P*,*N* ligands or organocatalysts, it has only been poorly studied until now. The prepared *P*-stereogenic pincer-Pd complexes **152** were tested in a model reaction using *trans*-β-nitrostyrene **151a** and diphenylphosphine **3a** as precursors. Dichloromethane proved to be the best solvent to produce the expected adduct in good yield (96%). However, the *ee* did not exceed 43% at rt. Better *ee*s were obtained upon decreasing the temperature, and at −40°C a reasonable *ee* of 76% was obtained with **152a** (X=OAc) as catalyst (Scheme 54).

Studying the scope of the reaction showed that both electron-donating and electron-withdrawing aromatic *para*-substituted nitroalkenes **151** are suitable substrates with diphenylphosphine (**3a**) to provide the desired products in high yields and with high enantioselectivities (92–96% yield, 72–83% *ee*). However, when the

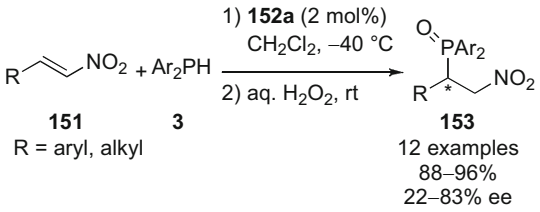




X = OAc (**a**), Cl (**b**), I (**c**), OTf (**d**)

X	Temp. (°C)	Time (min)	Yield (%)	ee (%)
OAc	25	15	96	43
Cl	25	20	95	2
I	25	10	95	0
OTf	25	10	93	0
OAc	–40	50	96	76

Scheme 54 Pd-catalyzed asymmetric addition of diphenylphosphine to *trans*-β-nitrostyrene



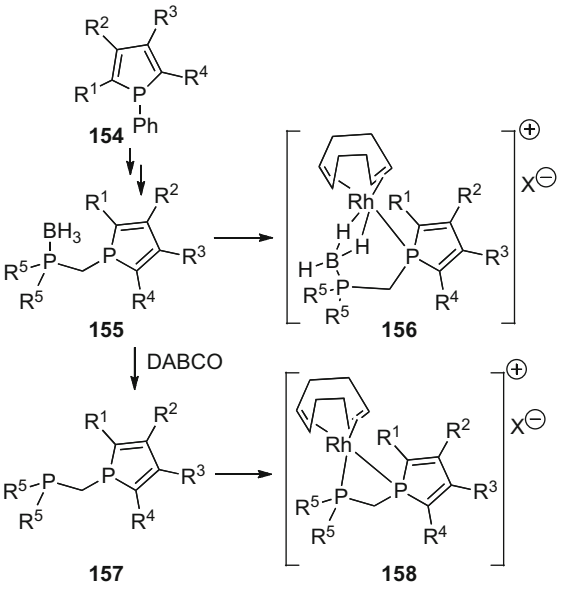
Scheme 55 Pd-catalyzed asymmetric addition of diarylphosphines to *trans*-β-nitroalkenes

substitution was in *ortho* or *meta* position, reduced enantioselectivities were obtained (Scheme 55).

2.5.4 Phosphine-Boranes as Ligands

In the same way as tertiary amine-boranes, tertiary phosphine-boranes are able to form stable borane σ-complexes such as $[M(CO)_5(\eta^1\text{-}BH_3{\bullet}PR_3)]$ (M = Cr, W) and $[CpMn(CO)_2(\eta^1\text{-}BH_3{\bullet}PR_3)]$. The groups of Kawano and Shimoi demonstrated that the strength of the borane–metal interaction resulted mainly from the electron-donation from the BH σ-orbital to the metal rather than the back-donation into the BH σ*-orbitals [94]. The complex stability was found to increase when an electron-releasing substituent was introduced on the boron atom in the following order: $BH_2Ph{\bullet}PMe_3 < BH_3{\bullet}PMe_3 < BH_2Me{\bullet}PMe_3$. A stabilization effect was also observed while increasing the strength of the Lewis base: for example, a better stabilization of the M–H–B bond was observed with BH_3-NMe_3 in comparison to BH_3-PMe_3. Thus, phosphine-boranes contrast with classical σ-ligands such as H_2 or silanes for which the coordination to metal involves a strong back-donation to the σ* orbital. According to this study, the formation of complexes with electrophilic metal centers should be favoured with phosphine-boranes.

Scheme 56 Synthesis of phospholyl phosphine-(borane) ligands

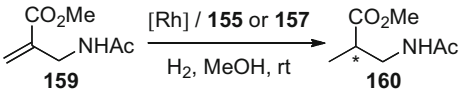


Metal complexes involving a chelating P-(η^2-BH_3)-ligand reported so far were all based on bis(diphenylphosphino)methane-BH_3 ligand. The groups of Jugé and Gouygou [95, 96] reported the synthesis of air and moisture stable hybrid phospholyl phosphine-borane ligands starting from 1-phenylphospholes through P–C bond coupling on the methane bridge (Scheme 56). Rhodium(I) cationic complexes (X=BF_4, TfO, BPh_4) were next prepared with these ligands following classical organometallic processes.

These original rhodium complexes were investigated in the catalytic hydrogenation of methyl 2-(acetamidomethyl)acrylate and in the hydroboration of styrene with catecholborane. In both reactions, the catalytic systems prepared either from the phospholyl-(phosphinoborane)methane ligands **155** or the corresponding free ligands **157**, obtained through removal of the BH_3 moiety using DABCO, gave good to excellent conversions. A complete conversion was achieved for a substrate-to-[Rh] ratio of 50. For a ratio of 100, the conversion stopped after 85%, even under a higher pressure of H_2 (40 bar). The rhodium catalyst bearing the 2,5-diphenylphospholyl substituent (**158b**) was found to be the most active one (Table 4).

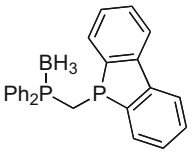
The hydroboration reaction was performed using either isolated complexes formed by reaction between the ligand or directly with species prepared in situ (1 mol%) in THF by mixing the precursor [Rh(η^4-COD)$_2$][BF_4] and ligand **155** or **157**. The reactions were carried out at rt for 22 h, followed by a classical oxidation to afford the expected alcohols. The results are reported in Table 5. The conversions are good to excellent (50–92%), affording a mixture of linear/branched alcohols in ratios ranging from 43:57 to 55:45, depending on the ligands used. Surprisingly, the selectivity was somehow better when a BH_3-protected ligand was used to generate the catalyst. No explanation was given.

Table 4 Hydrogenation of methyl 2-(acetamidomethyl) acrylate

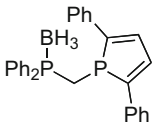


159 **160**

[Rh] = [Rh(η⁴-COD)₂][CF₃SO₃]



155a: 157a•BH_3

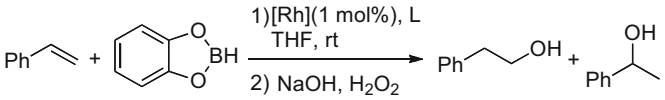


155b: 157b•BH_3

Entry	Ligand[a]	**159**/Rh	P_{H2} (bar)	Yield (%)
1	**157a**	100	20	100
2	**157b**	100	20	100
3	**157b**	200	20	100
4	**157b**	400	20	91
5	**157b**	100	10	100
6	**155a**	100	40	17
7	**155b**	50	40	100
8	**155b**	100	40	85

[a]Formation of the precatalyst ([P]/[Rh] = 2) during 3 h in the absence of H_2

Table 5 Hydroboration of styrene with catechol borane



161 **162** **163** **164**

[Rh] = [Rh(η⁴-COD)₂][BF_4]

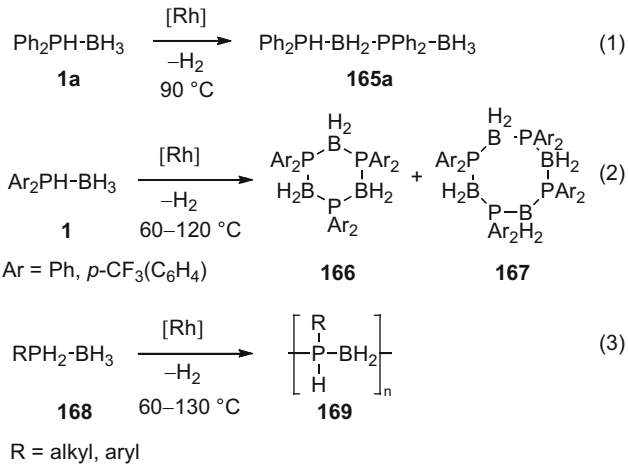
Entry	Cat. [Rh]L	Rh/L	Conv. (%)	**163/164**
1	No cat.		16	100/0
2	**156a**	1/1	84	51/49
3	**156b**	1/1	87	43/57
4	[Rh]/**157a**	1/1	92	46/54
5	[Rh]/**157b**	1/1	90	46/54
6	[Rh]/**155a**	1/2	50	55/45
7	[Rh]/**155b**	1/2	63	53/47

2.5.5 P–B Bond Formation Through Catalytic Dehydrocoupling of Phosphine-Boranes

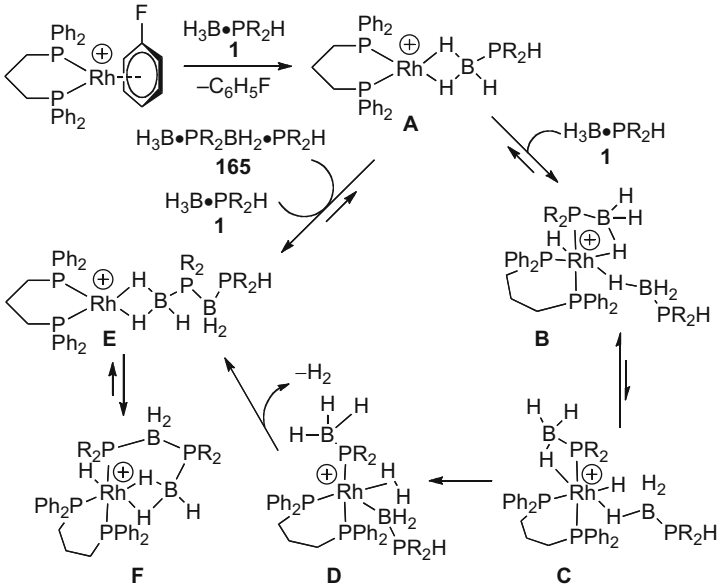
The formation of P–B bonds through catalytic dehydrocoupling of phosphine-boranes is well-known as a useful tool for the synthesis of linear dimers or cyclic oligomers from secondary phosphine-boranes (Scheme 57, (1, 2)) and high molecular weight polymers from primary phosphine-boranes (Scheme 57, (3)) [97]. The P–B polymers are valence isoelectronic with polyolefins and may find interesting applications in material chemistry.

The ability of metal complexes other than the classically employed rhodium catalysts to catalyze the dehydrocoupling has been recently reported, for example iron complexes $[CpFe(CO)_2(PPh_2{\bullet}BH_3)]$ and $[Fe_2(CO)_9]$ [98]. However, the original rhodium-catalyzed process described in 1999 by Manners'group, which relies on the use of $[Rh(COD)_2][OTf]$ as precursor in neat phosphine-borane under melt conditions (90–140°C), is still the best procedure to perform phosphine-borane dehydrocoupling [99].

By contrast to amine-borane dehydrocoupling, the rhodium-catalyzed phosphine-borane dehydrocoupling is supposed to be a homogeneous process. The mechanistic fundamentals had been poorly documented, probably because phosphine-borane dehydrocoupling proceeds at high temperature in melted state reaction conditions, making the identification of intermediates difficult. By selecting $[Rh(L)(\eta^6\text{-}FC_6H_5)][(BAr^F{}_4)]$ as precatalyst and performing the reaction in fluorobenzene, Weller's group was able to propose a catalytic cycle (Scheme 58) for the rhodium-catalyzed dehydrocoupling of secondary phosphine-boranes based on the isolation of intermediates (R=Ph, *t*-Bu), and kinetic/isotopic labelling experiments (R=Ph) [100, 101]. The main features of the catalytic cycle is the formation of the σ-borane complex **A**, which undergoes P–H oxidative addition followed by the reaction with another equivalent of phosphine-borane to give **B**, which is in equilibrium between



Scheme 57 Catalytic dehydrocoupling of secondary and primary phosphine-boranes



Scheme 58 Proposed catalytic cycle for the dehydrocoupling of secondary phosphine-boranes **1** to linear dimers **165**. $[BAr^F{}_4]^-$ anions are not shown for clarity

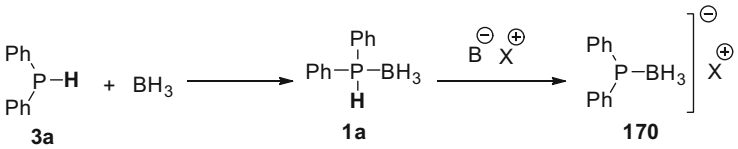
A and **C**. Subsequent B–H activation (**C**) leads to a short-lived intermediate **D**, which undergoes reductive P–B bond formation giving **E** with loss of H_2. For R=Ph, the rate-determining step(s) is(are) located within the transformation of **B** into **D** and the limiting-step for the turn-over of the catalytic process is the displacement of the linear dimer from the metal (transformation **F** to **A**), but this may be different under melted conditions. For R=*t*-Bu, no chelate product **F** is formed for steric reason and the limiting step is believed to be the P–H activation/dehydrocoupling steps.

The influence of the phosphine steric and electronic properties on the rhodium-catalyzed phosphine-borane dehydrocoupling was studied [102]. The dehydrocoupling was shown to be faster with a diarylphosphine-borane bearing an electron-withdrawing substituent (CF_3) than with diphenylphosphine-borane but P–B bond cleavage also occurred as a side-reaction. With bulky electron-rich bis-adamantylphosphine-borane, products resulting from P–B bond cleavage were mainly obtained.

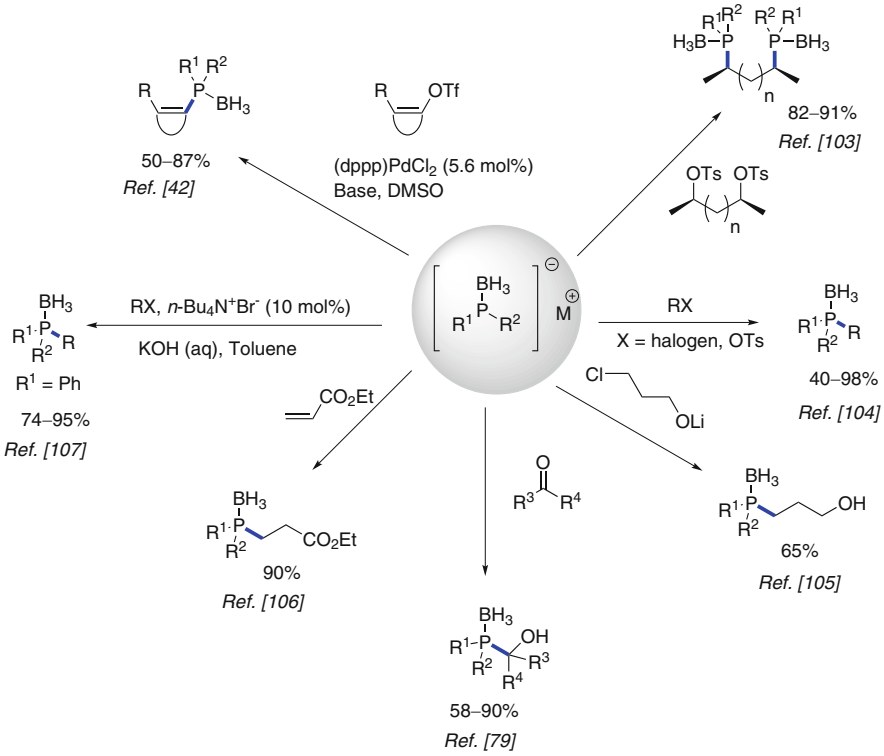
3 Borane Complexes of Other Phosphorus Compounds

3.1 Phosphido-Boranes

As pointed out in the introduction of this review, the association of primary or secondary phosphines with borane results in the formation of stable phosphine-borane



Scheme 59 Formation of diphenylphosphido-boranes **170** by deprotonation of diphenylphosphine-borane (**1a**) with a base



Scheme 60 Reactivity of phosphido-boranes [42, 79, 103–107]

complexes. Because of the electron-withdrawing character of BH_3, phosphine-borane complexes are known to have relatively low P–H bond dissociation energies (BDE) and also low pK_a values compared to that of free phosphines [16]. These properties allow their deprotonation with relatively weak bases to give rise to the so-called phosphido-borane anions (Scheme 59).

As exemplified in Scheme 60, phosphido-boranes have been employed as nucleophiles in various organic transformations including transition metal catalysis and organocatalysis.

Because the reactivity of phosphido-boranes depends on the electronic nature of the phosphorus substituents, solvent and counterion, the elucidation of their

structures in solid state as well as in solution is highly important for a deep understanding of their reactivities.

3.1.1 Solid State Structures of Alkali Metal Phosphido-Boranes

Wagner et al. have studied the structures of phosphido-boranes **170b** and **170c** derived from the addition of potassium hydride (KH) to secondary phosphine-boranes **1a** and **1d**. These anions were crystallized in the presence of 18-crown-6 to yield compounds $[Ph_2P(BH_3)K(18\text{-crown-6})]$ (**170b**) and $[t\text{-}Bu_2P(BH_3)K(18\text{-crown-6})]$ (**170c**), respectively. The X-ray structure of **170b** demonstrated the η^2-coordination of the P–B fragment to potassium (d(K–P) = 3.20(2) Å, d(K–B) = 3.162 Å] (Fig. 7) [108].

In contrast, the X-ray structure of the more sterically demanding compound **170c** shows that the potassium ion is coordinated to the boron atom. This might be explained by the steric hindrance of the *tert*-butyl groups, which prevents the P–K coordination from occurring.

In a subsequent paper, Wagner et al. have synthesized the bis(phosphido-borane) **171**, which was characterized by X-ray diffraction analysis. As shown in Fig. 8, each borane group coordinates with a potassium ion, which is bound to a boron group of a second molecule of **171**, and to two molecules of THF to form a linear polymeric supramolecular assembly [109].

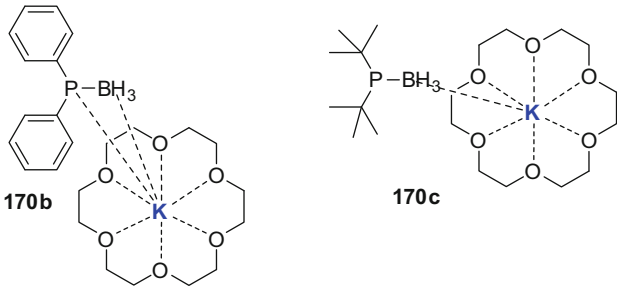


Fig. 7 Structures of phosphido-boranes **170b** and **170c**

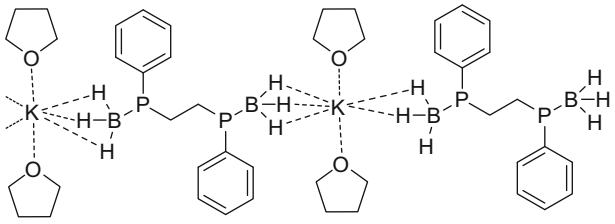


Fig. 8 Structure of phosphido-borane **171** in the solid state

In 2011, Izod et al. investigated the structures of phosphido-borane complexes bearing peripheral donor functionalization through the incorporation of either a benzyl ether or thioether group in the ligand. Interestingly, the single-crystal X-ray structure of the various compounds shows the presence of M–O or M–S interactions and the subsequent formation of chelate rings in the complexes (Fig. 9) [110, 111].

The same group has recently studied the synthesis and structural characterization of a new phosphido-borane and has carefully investigated the counterion effect on the structure of the complex. The reaction of $\{(Me_3Si)_2CH\}(Ph)PH$ (**173**) with 1 equiv. of $BH_3{\bullet}SMe_2$ led to the formation of the phosphine-borane complex **174**, which was subsequently deprotonated with 1 equiv. of *n*-BuLi to give rise to the lithium complex $[[\{(Me_3Si)_2CH\}(Ph)P(BH_3)]Li(THF)_2]_\infty$ (**175**). Single-crystal X-ray structure of the lithium phosphido-borane complex shows that it crystallizes as infinite chains of alternating lithium cations and phosphido-borane anions. Each lithium cation was found to be coordinated to the phosphorus atom of each phosphido-borane, and also to the two boron hydrides (η^2-manner). The coordination sphere of each lithium cation is completed by two molecules of THF [112].

Similarly, the deprotonation of phosphine-borane **174** with 1 equiv. of either $PhCH_2Na$ or $PhCH_2K$ in THF gives the corresponding heavier alkali metal phosphido-borane complexes, which were obtained as separated ion pairs $[\{(Me_3Si)_2CH\}(Ph)P(BH_3)]Na(12\text{-crown-}4)_2]$ **176** and dimer $[[\{(Me_3Si)_2CH\}(Ph)P(BH_3)]K(pmdeta)]_2$ **177** in good yields after crystallization in the presence of a co-ligand [pmdeta=*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine] (Scheme 61).

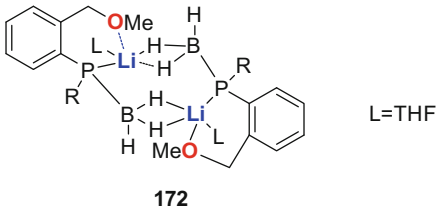


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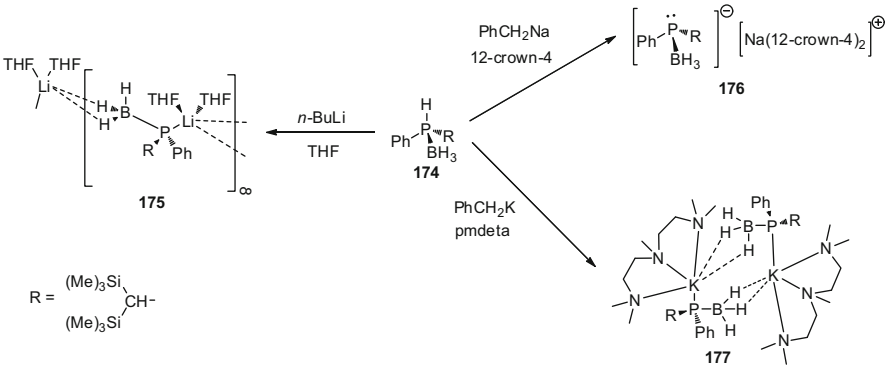
Fig. 9 Structure of phosphido-borane **172** in the solid state



Scheme 61 Reactions of phosphine-borane **174** with different bases

The sodium complex **176** is the first example of a phosphido-borane characterized as a solvent-separated ion pair. However, no significant differences have been found between this type of complex and the one isolated as a contact ion pair (lithium). It should be noted that the coordination sphere of each potassium ion in the dimer structure of **177** is completed by the three nitrogen atoms of the ligand, an η^2-BH_3 interaction from the second phosphido-borane in the dimer, and two short K···Me contacts with two methyl groups of the pmdeta co-ligand.

3.1.2 Structures of Alkali Metal Phosphido-Borane Complexes in Solution

As discussed earlier, phosphido-borane complexes can adopt different structures in the solid state depending on the nature of the counterion. They can exist as monomers, dimers or even as polymeric chains. Furthermore, it is well known that the structures of phosphido-boranes in the solid state might be different from that determined in solution. It is therefore crucial to elucidate the structure of phosphido-boranes in solution in order to gain insights into reaction mechanisms in which these anions are involved.

Gaumont, Gérard and Maddaluno have recently investigated the structure of lithium diphenylphosphido-borane (**170a**) in solution (THF) by performing an extensive multinuclear NMR study. It was shown that the deprotonation of diphenylphosphine-borane by one equivalent of *n*-BuLi in THF led to the quantitative formation of the corresponding anion, which was fully characterized in solution by ^{1}H, ^{13}C, ^{11}B and ^{31}P NMR spectroscopy. Importantly, the ^{6}Li as well as the ^{31}P NMR spectra, performed at different temperatures, showed the absence of P–Li coupling. In order to examine whether the lithium cation coordinates to the hydrides (BH_3), a HOESY ^{6}Li-^{1}H NMR experiment was performed. It revealed a strong correlation between the boron hydrides and the lithium cation, demonstrating that the lithium coordinates to the hydrides in an η^3-manner in solution state [18].

The aggregation state of the lithium diphenyl phosphido-borane (**170a**) was determined on the basis of a ^{1}H-DOSY NMR experiment in THF.

In previous investigations, Willard et al. have shown that it is possible to employ DOSY NMR with internal references for the determination of formula weights of lithium derivatives by diffusion coefficient-formula weight (D-FW) correlation analysis. The formula weight of an unknown complex is deduced from a linear correlation of the logarithms of NMR-determined diffusion coefficients against the known formula weights of the references (for interesting investigations on DOSY-NMR, see [113–116]).

Plot of logD against log (FW) gives a linear correlation from which a molecular weight of 370 has been derived. This molecular weight corresponds to the structure of a monomeric lithium phosphido-borane complex in which two molecules of THF coordinate to the lithium cation (Fig. 10).

Gaumont, Gérard, Maddaluno et al. have studied the reactivity of the pre-generated lithium diphenylphosphido-borane (**170a**) towards carbonyl derivatives in THF and

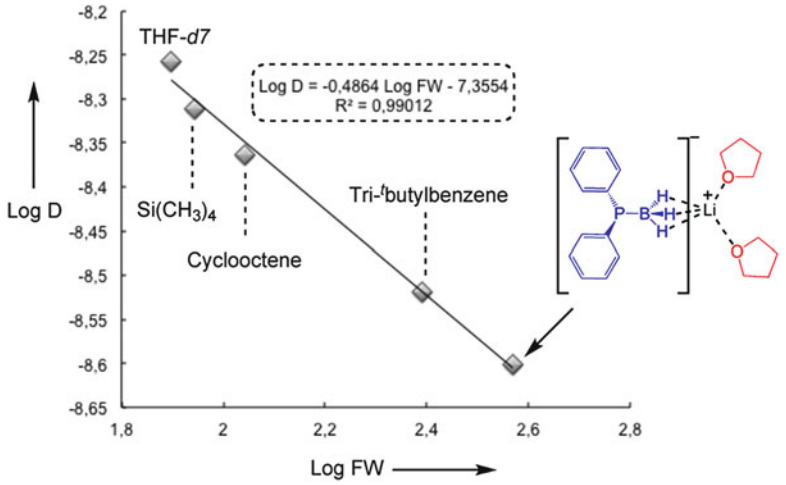
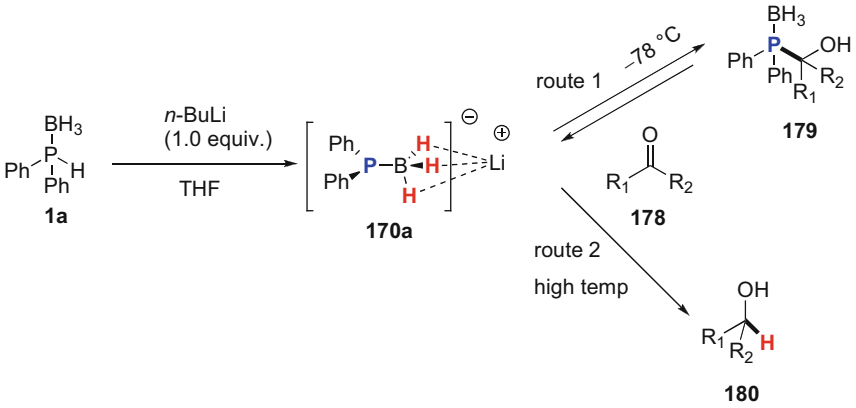


Fig. 10 Plot of the diffusion coefficients vs molecular weight



Scheme 62 Reactivity of lithium diphenylphosphido-borane (**170a**) with carbonyl compounds

they have shown that this anion possesses an ambident reactivity. It reacts as phosphorus nucleophile with carbonyl derivatives **178** at low temperature (−78°C) to yield the phosphination product **179** after acidic workup with HCl or H_2O (route 1), and it acts as a hydride nucleophile with the same electrophiles at high temperature (60°C) to give rise to the corresponding alcohol **180** (route 2) (Scheme 62).

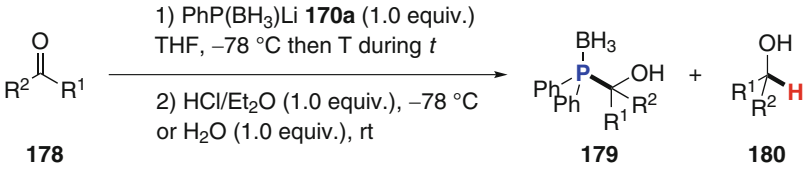
Table 6 summarizes the results obtained when lithium diphenylphosphido-borane (**170a**) was combined with aldehydes or ketones in THF at different temperatures. One can clearly see that quantitative formation of either the phosphination or the reduction adducts can be achieved upon temperature control.

This observation led the authors to postulate that the P-adduct **179** was formed reversibly under kinetic control, whereas the alcohol **180** was the thermodynamic product.

To prove the reversibility of the phosphination step, the benzaldehyde derived P-adduct **179a** was combined with 1 equiv. of *n*-BuLi in the presence of the highly electrophilic *para*-cyanobenzaldehyde **178b** in THF at −68°C. The mixture was warmed up to +5°C and then cooled to −68°C before quenching with HCl in diethylether to yield the *p*-cyanobenzaldehyde derived P-adduct **179b** in 63% yield along with benzaldehyde **178a** (Scheme 63).

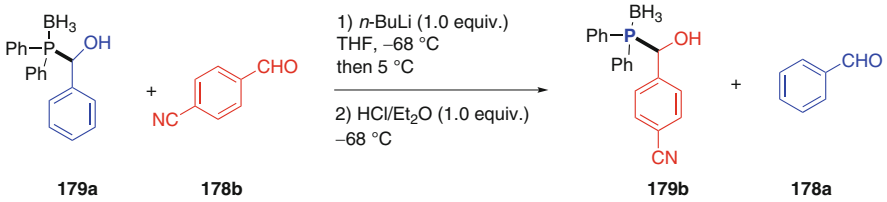
To gain more insight into the mechanism of the reaction of the phosphido-borane with carbonyl derivatives, DFT calculations have been performed at the B3LYP/6-31G++ level. Figure 11 shows the free energy profile for the reaction of formaldehyde and the solvated phosphido-borane $[H_2P(BH_3)Li][OMe_2]_2$ **170d**. As can be

Table 6 Reactivity of lithium diphenylphosphido-borane (**170a**) with carbonyl derivatives **178** at different temperatures (°C)



Entry	Substrate	*T* (°C)	*t* (min)	179/180[a]	Yield (%)
1	Benzaldehyde (**178a**)	−78	1	100/0	91
2	Benzaldehyde (**178a**)	60	10	0/100	79
3	*p*-Cyanobenzaldehyde (**178b**)	−78	1	100/0	90
4	*p*-Cyanobenzaldehyde (**178b**)	60	45	0/100	87
5	Cyclohexanone (**178c**)	−78	1	100/0	89
6	Cyclohexanone (**178c**)	60	60	0/100	81
7	2-Heptanone (**178d**)	−78	1	100/0	91
8	2-Heptanone (**178d**)	60	90	0/100	82

[a]Determined from ^{1}H NMR ratio



Scheme 63 Reaction of phosphination product **179a** with *p*-cyanoaldehyde (**178b**) in THF in the presence of *n*-BuLi

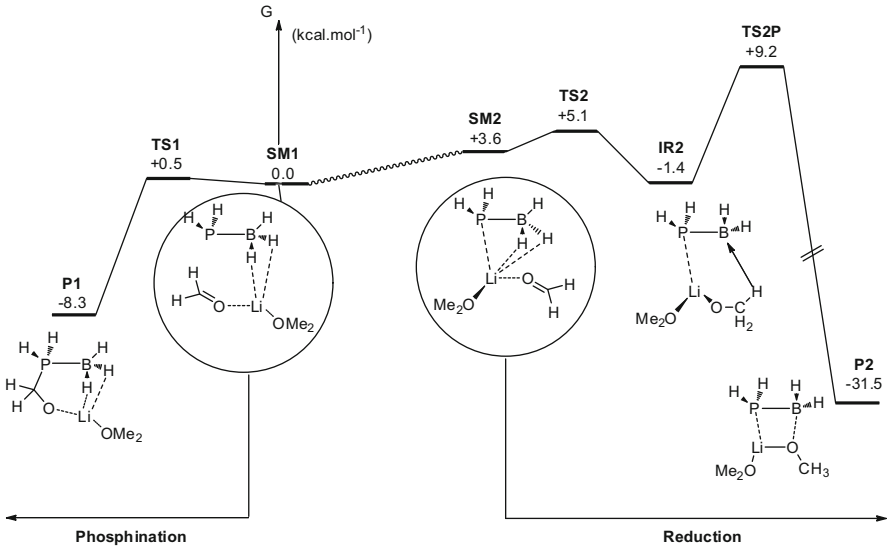


Fig. 11 Free energy profile for the reaction of the lithium phosphido-borane with formaldehyde

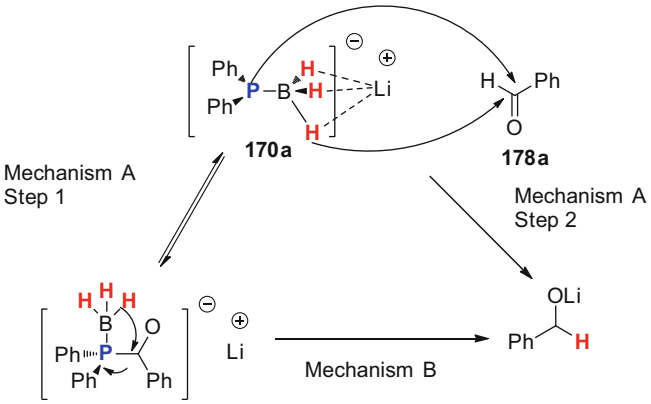
seen, the phosphorus attack at the carbonyl was controlled by the diffusion rate ($\Delta G^{\#} \approx 0.5$ kcal mol^{-1}). The transition state **TS1** shows that the lithium cation acts as a Lewis acid to activate the carbonyl moiety and might be responsible in part for the fast reaction calculated. Moreover, the diagram shows that the P-adduct (P1) lies about 8.3 kcal mol^{-1} below the starting material, which means that the phosphination reaction is probably going to be reversible.

Investigation of the reduction pathway shows that the process begins with a reorganization of the nucleophile-electrophile in such a way that the π_{CO} bond can interact with the lithium cation to lead to a more reactive ground state (**SM2**). The subsequent step consists of a hydride transfer to the aldehyde to yield the alkoxide (**IR2**), which is then rearranged to form the thermodynamically stable heterodimer (**P2**).

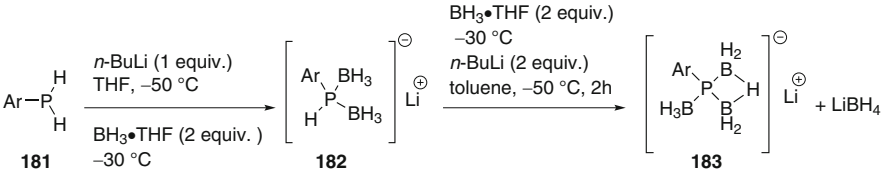
On the basis of the DFT calculations, it was demonstrated that the phosphination adduct is converted to the reduction product through mechanism A (Scheme 64), i.e. a reversible and fast phosphination step followed by an irreversible hydride transfer. However, mechanism B, where a direct intramolecular hydride transfer occurs followed by the departure of the phosphorus moiety, could not be ruled out as calculations have failed to locate the transition state.

3.1.3 Phosphido-bis(borane) Complexes of Alkali Metals

It has been shown that the treatment of primary arylphosphine **181** by 1 equiv. of *n*-BuLi followed by the addition of 2 equiv. of BH_3 at low temperature (−50°C) leads to the formation of lithium phosphido-bis(borane) **182** [110]. The X-ray



Scheme 64 Two possible pathways for the reaction of phosphido-borane **170a** with benzaldehyde (**178a**)



Scheme 65 Formation of lithium phosphido-(bis)borane **182** and dimer **183**

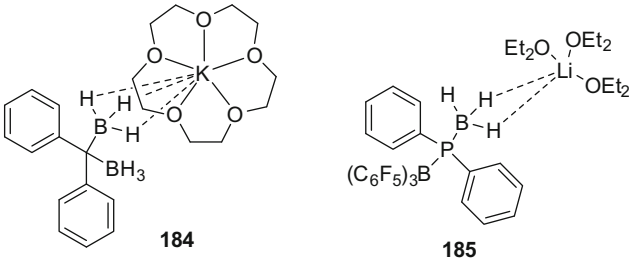
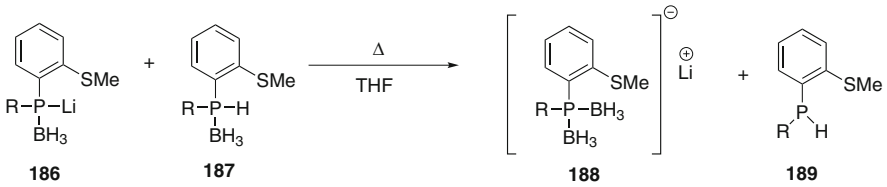


Fig. 12 Structures of phosphido-(bis)boranes **184** and **185**

structure of **182** reveals that the lithium counterion is coordinated to the borane fragment via an η^2-interaction. Treatment of **182** by an excess of *n*-BuLi and BH_3•THF at low temperature yielded the dimer **183** (Scheme 65). The X-ray structure of **183** shows the presence of a four-membered heterocyclic ring involving a hydride interaction between the two BH_2 groups.

On the basis of the seminal work of Wagner et al. on the synthesis of the first phosphido-bis(borane) coordinated to a heavier metal **184**, in which the potassium ion is bound to the hydrides (Fig. 12) [117], Lancaster et al. synthesized various phosphido-bis(borane) complexes bearing (pentafluorophenyl)borane groups **185** [118].



Scheme 66 Borane redistribution reaction between lithium phosphido-borane complex **186** and phosphine-borane **187** in THF

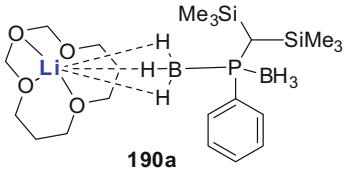


Fig. 13 Structure of lithium phosphido-bis(borane) **190a**

For instance, complex **185** was found to exist as a monomer in the solid state and showed an η^2-type coordination of the counterion (Li^+) with the hydrides (Fig. 12).

Recent developments in the field have been reported by Izod et al. [110, 112] who found an unexpected borane redistribution reaction between lithium phosphido-borane complex **186** and secondary phosphine-borane **187**, giving rise to phosphido-bis(borane) complex **188** along with the free secondary phosphine **189** (Scheme 66). The alkali metal phosphine-bis(borane) complex has unambiguously been characterized by NMR spectroscopy.

Izod et al. reported that phosphido bis(borane) complex [{$(Me_3Si)_2CH$}(Ph)P$(BH_3)_2$]Li **190** could be obtained as a pure material upon treatment of lithium phosphido-borane **175** with 1 equiv. of BH_3•SMe_2 in THF. Although Izod et al. were unable to crystallize this bis(borane) complex, they have shown that treatment of a solution of the complex in toluene with 1 equiv. of 12-crown-4 gave the adduct [{$(Me_3Si)_2CH$}(Ph)P$(BH_3)_2$]Li(12-crown-4) **190a** as a crystalline material, which was characterized by X-ray analysis (Fig. 13).

Sodium and potassium phosphido-(bis)boranes were also investigated as crown-ether complexes and it has been suggested that these anions may adopt a monodendate BH_3-donor mode or a variety of chelating/bridging modes, depending on the nature of the metal center [112].

3.1.4 Transition Metal-Phosphido-Borane Complexes

Much effort has been devoted during the last decade to isolate and characterize structures of phosphido-borane complexes derived from transition metals (Fig. 14) [119].

A few phosphido-boranes derived from palladium, platinum, iron, rhodium and molybdenum have been prepared either via metathesis reactions of an alkali metal

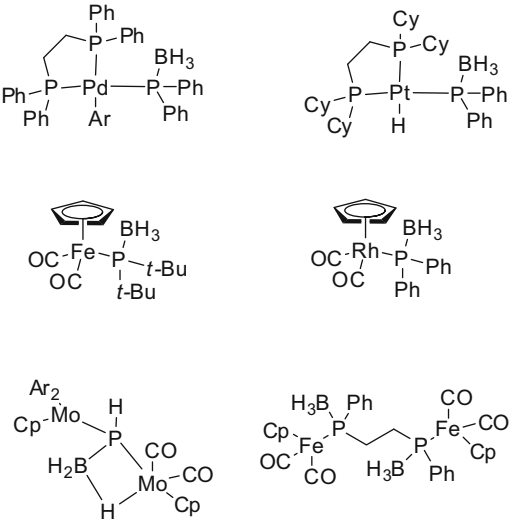


Fig. 14 Structures of phosphido-borane transition metal complexes

phosphido-borane with a transition metal halide or through an oxidative addition of a phosphine-borane to a transition metal complex.

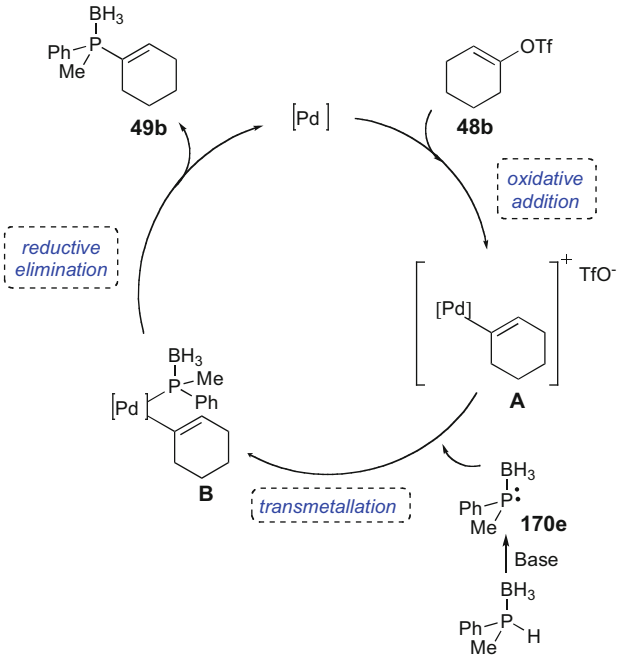
The first phosphido-borane transition metal complex was isolated in 1999 by Gaumont, Brown et al. when studying the mechanism of Pd-catalyzed cross coupling reaction between phosphine-boranes and aryl or alkenyl derivatives [120].

Recently, Gaumont et al. investigated the reaction mechanism of the palladium-catalyzed asymmetric phosphination of cyclohexenyl triflate (Sect. 2.2.4, Scheme 18) [121] through the characterization of the key intermediates involved in the process.

On the basis of these investigations, the proposed catalytic cycle begins with an oxidative addition of the alkenyl triflate to the Pd(0) complex to form the cationic complex **A** (Scheme 67). The next step is the transmetallation with phosphido-borane anion **170e**. Finally, the resulting transmetallation adduct **B** undergoes reductive elimination, affording the alkenylphosphine-borane **49b** and regenerating the Pd(0) catalyst. According to the mechanistic investigation, both Pd–P and P–C bond formation proceeds with retention of configuration and no interconversion occurs between both enantiomers of phosphido-borane anion, suggesting that the observed enantioselectivity results from a kinetic resolution, one enantiomer reacting faster than the other.

Gaumont et al. also reported copper-catalyzed C_{sp}–P bond formation for the synthesis of alkynylphosphines from secondary phosphine-boranes with 1-bromoalkynes (Scheme 15, Sect. 2.2.4) [38].

As part of their effort to elucidate the mechanism of this reaction, they investigated the structure of copper phosphido-borane species [$Ph_2P(BH_3)$Cuphen] **191** resulting from the treatment of diphenylphosphine-borane (**1a**) with a stoichiometric amount of BuLi, followed by the addition of CuI (1 equiv.) and phenanthroline (1 equiv) [122]. While the copper complex **191** was fully characterized in solution by



Scheme 67 Postulated catalytic cycle for the Pd-catalyzed P-alkenylation with vinyl triflates

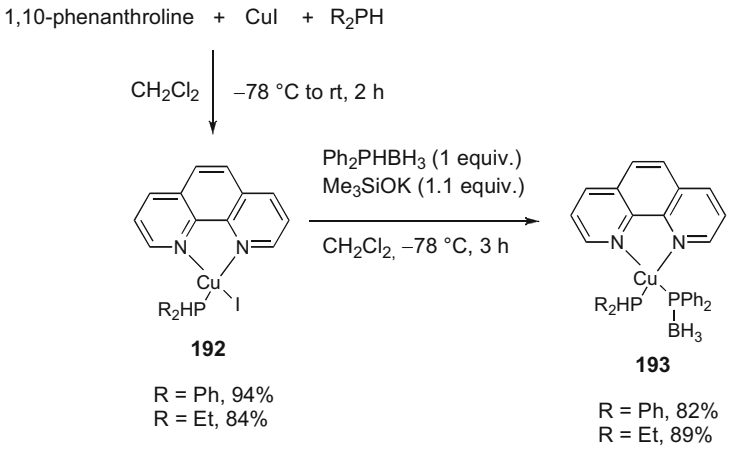
NMR spectroscopy, it was found to be unstable. The authors reasoned that the introduction of an additional electron-donating ligand, a secondary phosphine (R_2PH), into the coordination sphere of the metal would increase the stability of the copper complex.

To this end, the reaction of potassium diphenylphosphido-borane with copper complexes **192** was performed. The resulting well-defined complexes **193** are the first examples of isolable neutral copper-phosphido-borane complexes. They were characterized in the solid state (X-ray analysis) and in solution (NMR spectroscopy) (Scheme 68).

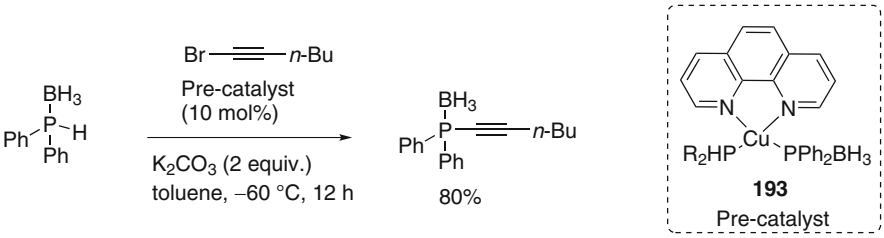
Importantly, complexes **193** can serve as pre-catalysts for the *P*-alkynylation of secondary phosphine-boranes with 1-bromoalkynes (Scheme 69), supporting the hypothesis of the involvement of a copper(I) phosphido-borane in the catalytic reaction.

3.2 Phosphinous Acid-Boranes

In contrast to phosphinite-boranes and chlorophosphine-boranes, which have been investigated extensively during the last decades, little was known about phosphinous acid boranes until very recently. For instance, a literature survey



Scheme 68 Synthesis of copper-phosphido-borane **193**



Scheme 69 Copper-phosphido-borane complex **193** as a catalyst for C_{sp}–P bond formation

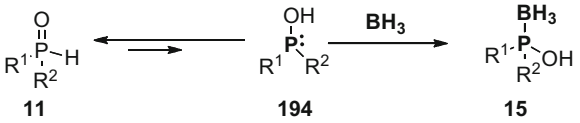
shows that only four phosphinous acid-borane structures had been published before 2003. This is quite surprising given the rich chemistry that phosphinous acid-boranes could exhibit through phosphorus, oxygen, or boron centers [24].

In fact, the main problem related to the access to these molecules by direct boration of phosphinous acid. This reaction was found to be difficult to achieve as phosphinous acids exist predominantly in the form of their tetracoordinate tautomers, in which the phosphorus lone pair is not accessible to react with BH_3 (Scheme 70). This drawback has probably hampered the use of phosphinous acid-boranes in synthesis for many years.

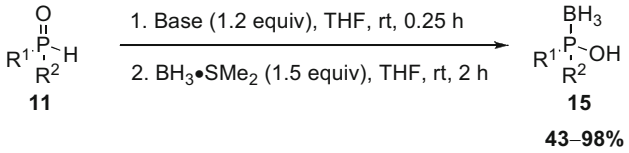
Stankevič and Pietrusiewicz have overcome this problem by showing that treatment of phosphine oxides **11** with a base (1.2 equiv.) followed by the addition of BH_3•SMe_2 gave the desired phosphinous acid-boranes **15** in good to excellent yield (Scheme 71) [123].

The same group has explored the reactivity of these complexes for the synthesis of phosphinite-boranes, tertiary phosphine-boranes, chlorophosphine-boranes, etc. [24].

In order to extend the reactivity of phosphinous acid-boranes to enantioselective synthesis, the same authors have recently described a facile resolution of racemic *tert*-butylphenylphosphinous acid-borane (**15a**). Given the relatively high acidities



Scheme 70 Formation of phosphinous acid-boranes **15** from secondary phosphine oxides **11**



Scheme 71 Synthesis of phosphinous acid-boranes **15**

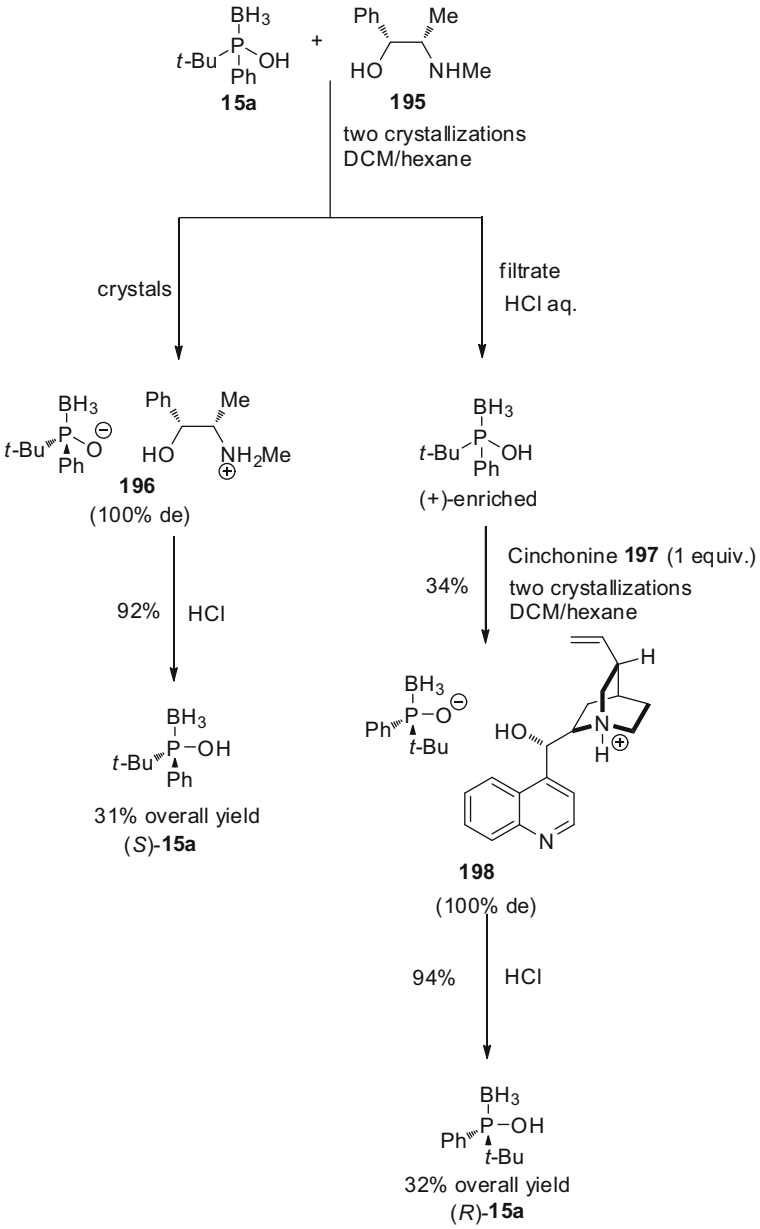
of phosphinous acid-boranes ($3.58 \leq pK_a \leq 5.88$), Pietrusiewicz et al. separated them via the formation of diastereomeric salts with enantiopure amines [23]. Thus, treatment of racemic *tert*-butylphenylphosphinous acid-borane (**15a**) with an equimolar amount of (−)-ephedrine hemihydrate (**195**) in a CH_2Cl_2-hexane mixture furnished, after two crystallizations, the ephedrine salt **196** with high diastereomeric purity. Subsequent acidic work-up in aqueous HCl afforded the enantiomerically pure (*S*)-(−)-**15a** in 31% overall yield (Scheme 72).

The enantiopure (*R*)-(+)-**15a** was recovered from the mother liquor and treated with an equimolar amount of cinchonine **197** to yield the cinchonine salt **198**, which was crystallized and analyzed by X-ray analysis. Acidic work-up of this salt with aqueous HCl furnished the enantiomerically pure (*R*)-(+)-**15a** in 32% overall yield. The assignment of the absolute configuration of the resolved enantiomers of **15a** was unambiguously confirmed by single-crystal X-ray diffraction of the cinchonine salt.

Having the resolved (*S*)-phosphinous acid-borane in hand, Stankevič and Pietrusiewicz have employed this chiral substrate for the synthesis of enantiopure organophosphorus derivatives. Phosphinite-boranes, boranatophosphinous-sulfonic anhydrides, secondary phosphine-boranes, tertiary phosphine-boranes, secondary phosphine oxides and phosphinic halides were efficiently prepared from this versatile building block in enantioenriched form (Scheme 73).

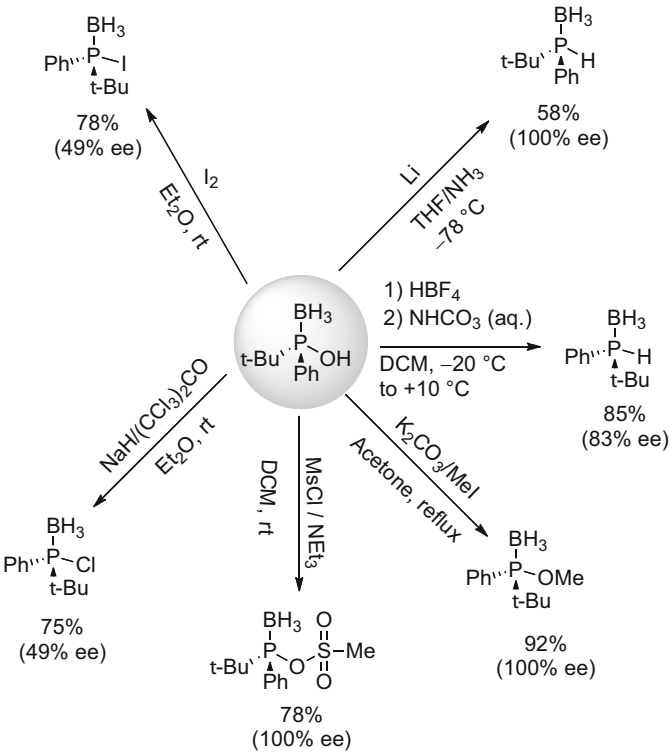
In 2008, Buono et al. described a one-pot synthesis of enantioenriched phosphinous acid-boranes from (R_p)-(−)menthyl hydrogenophenylphosphinate (**199**) [124]. As depicted in Table 7, the reaction consists of the addition of 2 equiv. of organolithium **200** to (R_p)-(−)-menthyl hydrogenophenylphosphinate. While the first equivalent of RLi serves as a base to abstract the phosphine oxide proton, the second equivalent acts as a nucleophile to substitute the menthyloxy group. In line with Pietrusiewicz's report [123], lithium phosphinate **201** reacts quantitatively with BH_3•SMe_2 to furnish the desired phosphinous acid-boranes **15** in good yields.

While good to excellent enantioselectivities were obtained with aryllithium and *n*-BuLi, *t*-BuLi and 1-furyllithium gave modest *ee*s. As the enantioselectivity of lithium phosphinate **201** has previously been measured by Buono et al. to be around



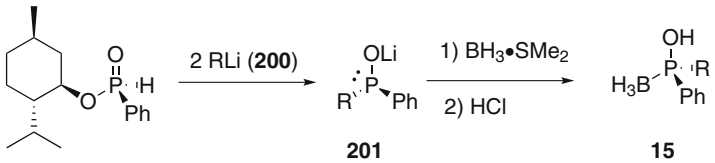
Scheme 72 Resolution of racemic phosphinous acid-borane **15a**

84% and remained unchanged after 3 days, the authors concluded that the loss of enantiopurity occurred in the boration step. This again is in good agreement with the Stankevič and Pietrusiewicz report, who noticed that the deprotonation of



Scheme 73 Multi-reactivity of phosphinous acid-borane **15a**

Table 7 Synthesis of phosphinous acid-boranes from **201**



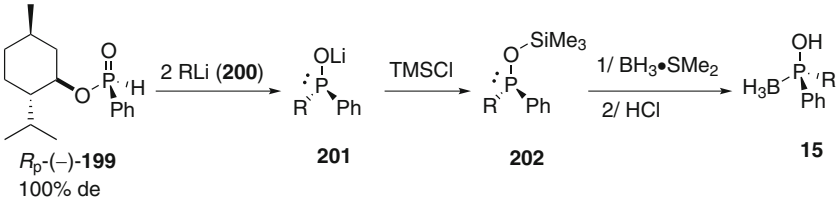
R-(–)-**199**
100 % de

201 **15**

Entry	R	Product	Yield[a] (%)	*ee*[b] (%)
1	Me	*S*-(−)-**15d**	78	95
2	*n*-Bu	(−)-**15e**	84	89
3	*t*-Bu	*S*-(−)-**15a**	82	60
4	2-MeC_6H_4	(+)-**15f**	93	98
5	2-PhC_6H_4	(−)-**15 g**	84	93
6	1-Naphthyl	*R*-(−)-**15 h**	88	91
7	1-Furyl	(+)-**15i**	92	72

[a]Isolated yields
[b]Determined by chiral HPLC

Table 8 Synthesis of phosphinous acid-boranes from *O*-silylated **202**



Entry	R	Product	Yield[a] (%)	*ee*[b] (%)
1	Me	*S*-(−)-**15d**	78	95
2	*n*-Bu	(−)-**15e**	70	89
3	*t*-Bu	*S*-(−)-**15a**	70	84
4	2-MeC_6H_4	(+)-**15f**	75	97
5	2-PhC_6H_4	(−)-**15g**	85	95
6	1-Naphthyl	*R*-(−)-**15h**	75	99
7	1-Furyl	(+)-**15i**	72	80

[a]Isolated yields
[b]Determined by chiral HPLC

resolved enantiopure *tert*-butylphenyl phosphine oxide, followed by the addition of BH_3 led to **15a** with only 74% *ee* [23, 24].

In order to improve the enantioselectivities of the phosphinous acid-boranes, the authors have slightly modified their first approach by the addition of Me_3SiCl to lithium phosphinate **201** to form the *O*-silylated product **202**. The latter was then protected with BH_3•SMe_2 and, finally, desilylated by the addition of HCl. By using this methodology, most of the enantioselectivities have been improved ($80\% \leq ee \leq 99\%$) (Table 8).

In 2011, Gatineau, Giordano and Buono reported the use of chiral phosphinous acid-boranes for the synthesis of optically pure hindered secondary phosphine-boranes, which were further converted to the corresponding tertiary phosphine boranes [25].

Three enantiopure phosphinous acid-boranes **15** (Fig. 15) have been synthesized by following the above-mentioned protocol.

The first attempts to access the secondary phosphine-borane starting from the phosphinous acid-borane **15b** by using the method described by Pietrusiewicz et al. met with failure. Indeed, treatment of enantiopure **15b** with mesyl chloride in the presence of triethylamine in dichloromethane gave a complex mixture in which the desired product was contaminated by undesired side-products (Scheme 74).

Interestingly, the use of mesyl anhydride instead of mesyl chloride led to the suppression of byproducts. The mixed anhydride (***S*****$_p$**)-**18b** resulting from the addition of mesyl anhydride to enantiopure phosphinous acid-borane **15b**, was then reduced by $NaBH_4$ in ethanol to yield the desired secondary phosphine-borane (***S*****$_p$**)-**17b** in good yield (90%) (Scheme 74). This protocol was found to be applicable to the three phosphinous acid-boranes **15a–c** leading to the expected bulky secondary phosphine-boranes in good yields.

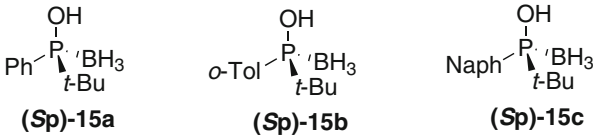
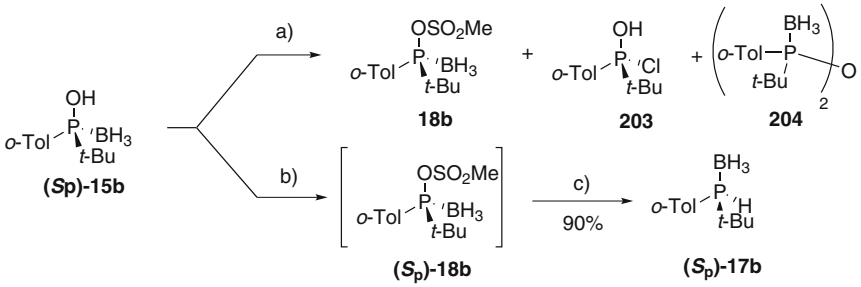


Fig. 15 Enantiopure phosphinous acid-boranes investigated by Buono



Reagents and conditions: a) $MeSO_2Cl$, Et_3N, 0 °C, CH_2Cl_2;
b) $(MeSO_2)_2O$, Et_3N, –15 °C, CH_2Cl_2; c) $NaBH_4$, 0 °C to rt, EtOH

Scheme 74 Synthesis of enantiopure secondary phosphine-borane **17b** from phosphinous acid-borane **15b**

3.3 Aminophosphine-Boranes

3.3.1 Synthesis of Primary and Secondary Aminophosphine-Boranes

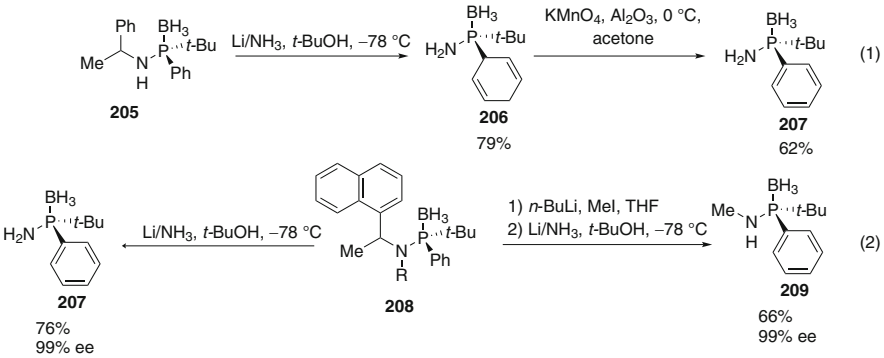
As described in Sect. 3.2, secondary phosphine oxides exist in equilibrium with their tri-coordinate forms. The corresponding nitrogen analogues, i.e. aminophosphines, behave similarly and this might explain their scarce use in organic synthesis. Even less popular are primary aminophosphines, which are known to dimerize at rt with evolution of ammonia [125].

In 2003, Kolodiazhnyi et al. demonstrated that aminophosphine-boranes are stable and can easily be obtained as pure diastereoisomers from chiral secondary amines such as 2-phenylethylamine [126].

Based on this seminal work, and on the fact that chiral aminophosphine-boranes have never been employed as ligands in metal catalysis, Riera and Verdaguer have developed a concise synthesis of primary and secondary aminophosphine-boranes [127].

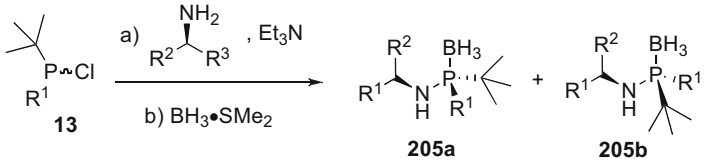
As shown in Scheme 75, treatment of the Kolodiazhnyi reagent **205** with lithium in ammonia led to the cleavage of the phosphorus benzyl ligand to furnish the unexpected Birch-reduced compound **206**. The latter was converted into the desired product **207** by oxidation with $KMnO_4$ (Scheme 75, (1)).

Cleverly, the authors circumvent the Birch-type reduction by employing the naphthyl derivative **208** instead of the phenyl analogue. As expected from their reduction potentials measured by Meerhozl and Heinze [128], the naphthyl



Scheme 75 Synthesis of primary and secondary aminophosphine-boranes

Table 9 Diastereoselective synthesis of aminophosphine-boranes

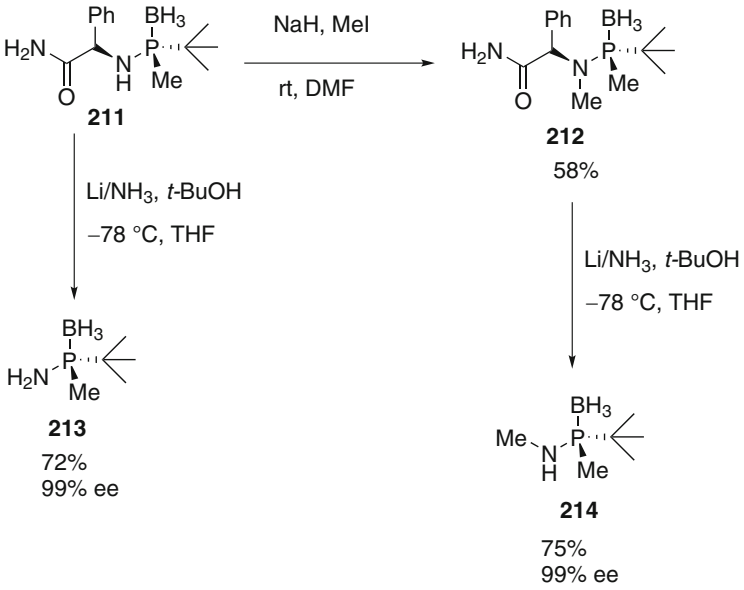


Entry	R^1	R^2, R^3	**210**	Yield (%)	dr (**205a**:**205b**)
1	Ph	Ph, Me	**210a**	87	5:1
2	Ph	1-naph, Me	**210b**	91	6:1
3	Ph	*p*-tol, Me	**210c**	88	4:1
4	Ph	*p*-$MeOC_6H_4$, Me	**210d**	90	4:1
5	Ph	*p*-ClC_6H_4, Me	**210e**	88	4.5:1
6	Ph	Ph, $CONH_2$	**210f**	95	1:1
7	Me	Ph, Me	**210g**	91	1:2
8	Me	1-naph, Me	**210h**	90	1:3
9	Me	Ph, $CONH_2$	**210i**	98	1.5:1

compounds do not undergo Birch reduction and deliver under the above-mentioned conditions the expected primary (**207**) as well as secondary aminophosphine-boranes (**209**) in good yields and outstanding enantioselectivities (Scheme 75, (2)).

With the optimized hydrogenolysis procedure in hand, the authors then developed a simple and useful route toward the diastereoselective synthesis of aminophosphine-boranes. This methodology is based on the dynamic kinetic resolution of (±)-*t*-BuPhPCl (**13a**) and (±)-*t*-BuMePCl (**13b**) with various chiral amines **210** (Table 9).

1-Naphthylethylamine (**210b**) gives the best selectivity among the various chiral amines used (Table 9, entries 2 and 8). It should be mentioned that, although the



Scheme 76 Synthesis of enantiopure primary **213** and secondary **214** aminophosphine-boranes

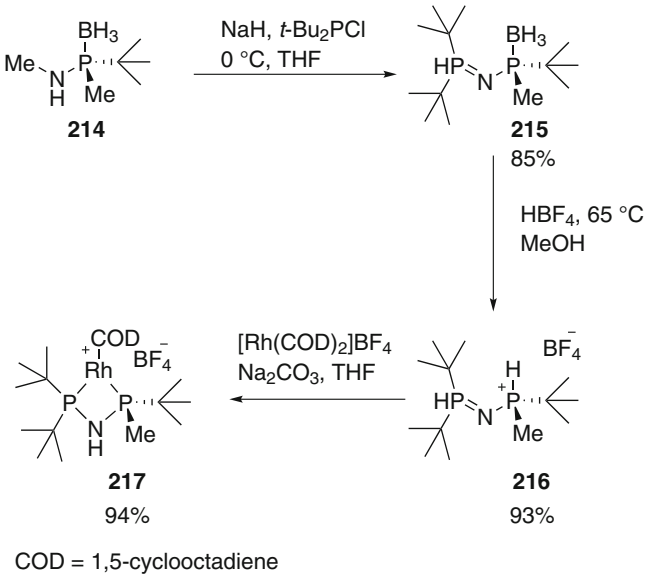
diastereoselectivities are low, it was possible to separate both sets of diastereoisomers through column chromatography.

Phenylglycinamide **210i** (Table 9, entry 9) was used as a resolving agent for the preparation of primary as well as secondary aminophosphine-boranes. The latter (**214**) were obtained as enantiopure materials upon methylation of **211** followed by treatment with Li/NH_3 (Scheme 76).

3.3.2 Synthesis of Aminodiphosphines

Enantiopure aminophosphine-boranes have been converted to the corresponding aminodiphosphines (PNP) following the synthetic strategy given in Scheme 77. It starts with the reaction of the optically pure aminophosphine-borane **214** with bulky *t*-Bu_2PCl (**13c**) to give bisphosphinamine **215**, which was found to exist exclusively as its P–H tautomer. A subsequent borane decomplexation with HBF_4 in MeOH at 65°C gave the phosphonium salt **216**, which was then combined with $[Rh(COD)_2]BF_4$ in the presence of sodium carbonate to yield the corresponding cationic complex **217** [127].

While aminodiphosphines bearing the chiral nitrogen center (PN*P) have previously been used as ligands in transition metal catalysis [129], the P*NP or P*NP* analogues have been less employed, although their abilities to induce chirality should be superior as the chiral center is closer to the metal center (Fig. 16).



Scheme 77 Synthesis of cationic rhodium complex **217**

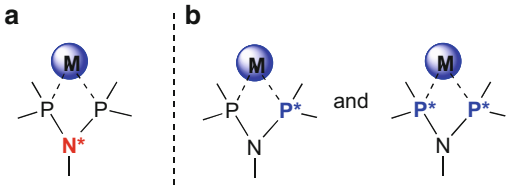


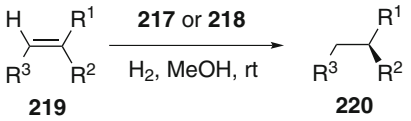
Fig. 16 Coordination of the metal centre (M) to PN*P, PNP* and P*NP* ligands

The Rh cationic complex **217**, as well as the active ligand–metal species **218** generated in situ by mixing $[Rh(COD)_2]BF_4$ (**217**), and an organic base have been used as catalysts in the asymmetric hydrogenation of enamides. As shown in Table 10, both catalysts enable enantioselective hydrogenation with outstanding enantioselectivity (≥99%), thus showing the efficiency of the P*NP as chiral ligands [127].

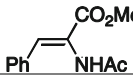
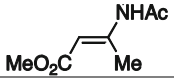
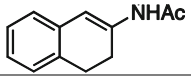
3.3.3 Stereoselective Synthesis of *P*-Stereogenic Aminophosphine-Boranes from Ring Opening of Bulky Borane Oxazaphospholidines

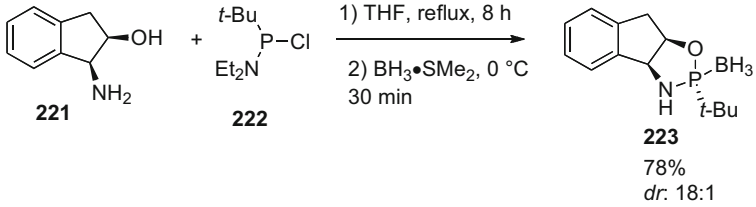
Although the synthesis of bulky aminophosphine-boranes through dynamic kinetic resolution (DKR) of racemic chlorophosphines with chiral amines has been shown to be successful, leading to optically pure material (≥99% *ee*), it suffers from low diastereoselectivity in the DKR step.

Table 10 Enantioselective hydrogenation of enamides **219**



219 **220**

Entry	Substrate	Cat. (mol%)	H_2 (bar)	*ee* (%)
1		**217** (0.3)	3	99
2		**218** (1.0)	3	99
3		**217** (0.3)	3	99
4		**218** (3.0)	10	99



221 **222** **223**

78%

dr: 18:1

Scheme 78 Synthesis of oxazaphospholidine-borane **223** by condensation of (−)-(*1S,2R*)-*cis*-1-amino-2-indanol (**221**) with *tert*-butylphosphine derivative **222**

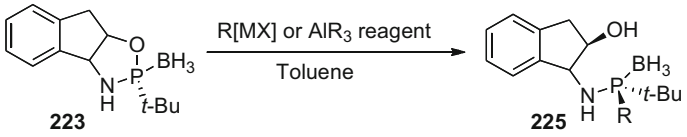
In order to overcome this limitation, Riera and Verdaguer have developed a more efficient synthesis of chiral aminophosphine-boranes [130]. This approach is based on the synthesis of chiral oxazaphospholidine-boranes and their diastereoselective ring opening to yield chiral aminophosphine-boranes.

First the authors focused on the synthesis of oxazaphospholidines by condensation of (*1S,2R*)-*cis*-1-amino-2-indanol (**221**) with various *tert*-butylphosphine chloride derivatives (Scheme 78).

Among all chlorophosphines tested, the racemic chloro-*tert*-butyl (diethylamino)-phosphine **222** was found to be the best substrate, providing the desired oxazaphospholidine-borane **223** in good yield and high diastereoselectivity (18:1) (Scheme 78). The major diastereoisomer was separated by crystallization and analysed by X-ray analysis.

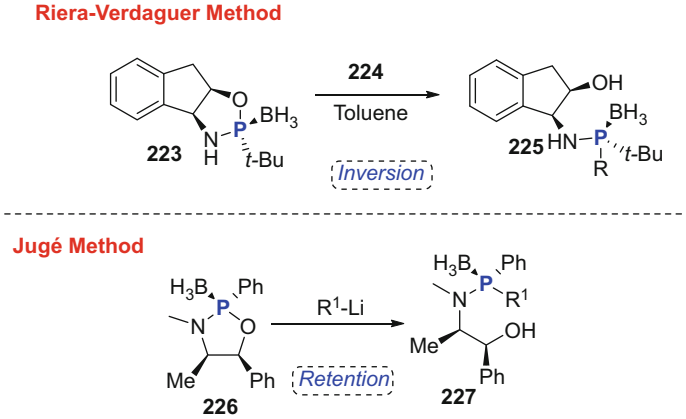
The ring opening of the enantiopure borane oxazaphospholidine **223** with different organometallic reagents was next investigated. As shown in Table 11, the reaction of **223** with MeLi **224a** takes place in toluene at 40°C, to give the product **225** in good yield and excellent stereoselectivity.

Table 11 Reactions of oxazaphospholidine-borane **223** with organometallic reagents **224a–f** in toluene



Entry	R[MX] or AlR_3[a]	*T* (°C)	Yield	dr
1	MeLi (**224a**)	40	76	≥96:4
2	MeMgBr (**224b**)	100	91	≥99:1
3	PhMgBr (**224c**)	100	96	≥96:4
4	2-MeOPhMgBr (**224d**)	100	94	≥96:4
5	Me_3Al (**224e**)	80	90	≥93:7
6	Et_3Al (**224f**)	100	88	≥90:10

[a]Organometallic reagents were used in excess (between 2.2 and 4.5 equiv.) with respect to **223**



Scheme 79 Riera-Verdaguer's vs Jugé's methods for the synthesis of *P*-stereogenic tertiary phosphines

Because of their low nucleophilicity compared to MeLi, Grignard reagents **224b–d** react with **223** at higher temperature (100°C) to furnish the targeted aminophosphine-boranes **225** diastereoselectively. Aluminium reagents **224e, f** are also effective in this reaction, but less selective than the corresponding organomagnesium ones.

Remarkably, X-ray analyses of **225** revealed an inversion of configuration at the phosphorus atom upon nucleophilic ring opening. This result is unexpected if we refer to the seminal work of Jugé et al., who demonstrated that nucleophilic ring opening of ephedrine **226** occurs with retention of configuration at the phosphorus atom to yield the aminophosphine-borane **227** (Scheme 79) [34, 131, 132].

Scheme 80 Proposed mechanism for the ring opening of oxazaphospholidine **223** with organometallic reagents **224**

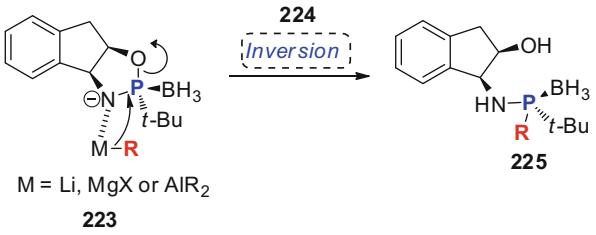
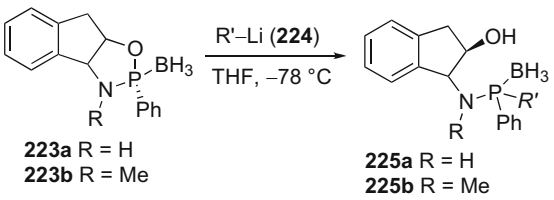


Table 12 Reactions of (+)-*cis*-1-amino-2-indanol (**223**) derived phenyl oxazaphospholidines with organolithium reagents



Entry		R	R′	Yield (%)	dr	Abs. Conf
1	**223a**	H	Me	89	≥ 95:5	(S_p)
2	**223b**	Me	Me	89	≥ 95:5	(R_p)
3	**223a**	H	*o*-An[a]	73	≥ 95:5	(R_p)
4	**223b**	Me	*o*-An[a]	88	≥ 95:5	(S_p)

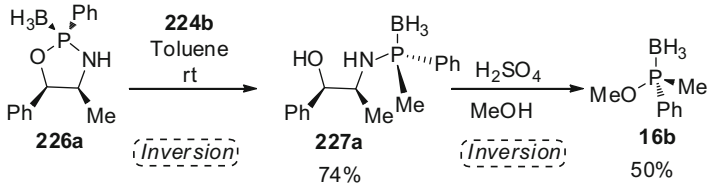
[a]*o*-An = *ortho*-anisyl (2-methoxyphenyl)

As the organometallic reagent was used in excess over the oxazaphospholidine-borane, it was assumed that the first equivalent of MeLi served as a base to abstract a proton from the N–H to furnish the amide anion. The latter coordinates to the counterion of the second MeLi equivalent to direct its attack at the phosphorus center (Scheme 80).

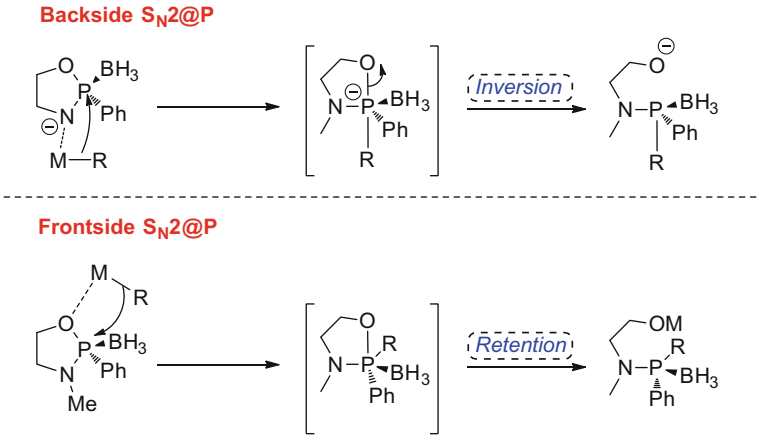
Further evidence of the key role of the N–H group on the stereochemical outcome of the S_N2 reaction was obtained by comparing the reactions of the NH-phenyloxazaphospholidines derived from (+)-*cis*-1-amino-2-indanol (**223**) with organolithium reagents, which took place with inversion of configuration at the phosphorus center, and the reaction of the N–Me oxazaphospholidine analogues which occurred with retention of the configuration at phosphorus, although the same nucleophiles were used (Table 12).

Importantly, it was further shown that treatment of ephedrine **226a** with MeMgBr (**224b**) at rt furnished diastereoselectively the ring-opening product **227a**. Methanolysis of **227a** gave (+)-(R_p)-**16b** in 96% *ee*, which confirms that ring opening of the norephedrine occurs with inversion at the phosphorus center (Scheme 81).

These results clearly show that the substituent at the nitrogen atom of the heterocycle is the only factor controlling the stereodivergent ring opening of oxazaphospholidines.



Scheme 81 Ring opening of norephedrine with methyl magnesium bromide



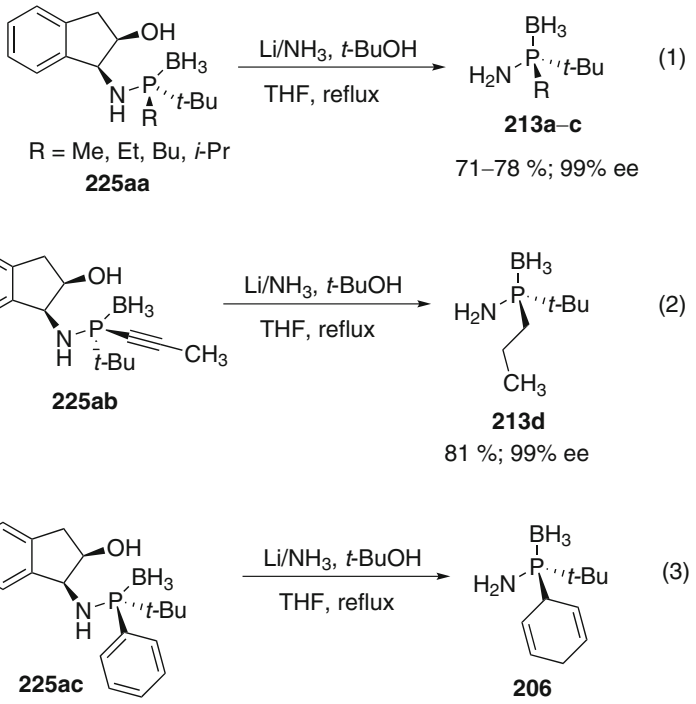
Scheme 82 Proposed reaction pathways for the ring-opening of N–Me and N–H borane oxazaphospholidines

As a conclusion, the reactions of organolithium reagents with the N–H borane oxazaphospholidines take place via backside S_N2 at the phosphorus center (S_N2@P) with inversion of configuration at the phosphorus, while the reactions with the *N*-methylated borane oxazaphospholidines occur via frontside S_N2@P with retention of configuration at phosphorus, as previously demonstrated by Jugé et al. This is because of the interaction between the oxygen and the nucleophile counterion, which assists the attack of the nucleophile by the frontside (Scheme 82).

These hypotheses have been confirmed by DFT calculations through detailed analyses of the stereochemical course of both processes [133].

The previously obtained open chain products **225** were submitted to reductive cleavage conditions at the benzylic position by using lithium in ammonia in the presence of *t*-BuOH (Scheme 83).

While the reaction has been found to be stereospecific, leading to the expected primary aminophosphine-boranes in good yields and excellent enantioselectivities ($\geq$99% *ee*) in the cases of **213a–c** (R=Me, Et, Bu and *i*-Pr) and to the fully reduced *tert*-butyl-*n*-propylaminophosphine (**213d**) in 81% yield, it gives the Birch type product **206** in the case of phenyl-derived borane oxazaphospholidine **225ac** instead of the expected aminophosphine-borane (Scheme 83, (3)).



Scheme 83 Synthesis of primary aminophosphine-boranes from the ring opened compounds **225a**

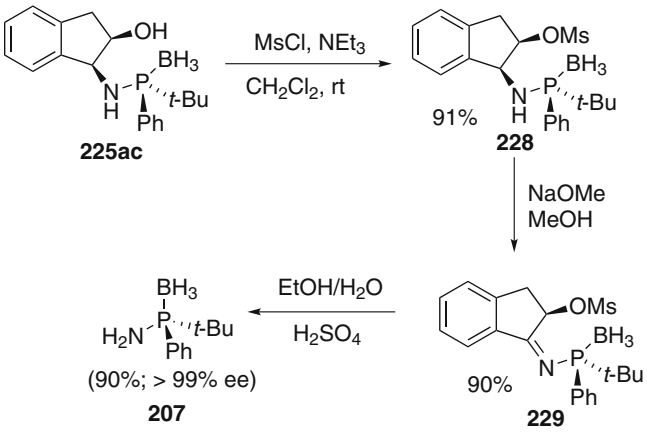
In order to circumvent this problem, i.e. the access to arylaminophosphines, the authors have developed an elegant method, which consists of transforming the alcohol function in **225** into a mesylate one (**228**). Conversion into iminophosphine **229** was then performed in good yield under basic conditions. The latter was finally hydrolysed under acidic conditions to afford the desired primary arylamino-phosphine boranes **207** in excellent yields (Scheme 84).

Remarkably, no racemization at the phosphorus center occurred during the whole process and arylaminophosphines were isolated in >99% *ee*.

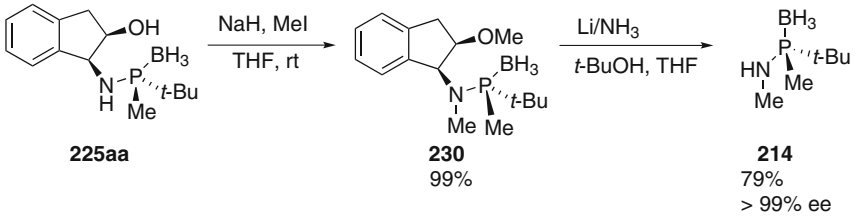
Secondary aminophosphine-boranes have also been successfully synthesized by methylation of both the alcohol and the secondary amine functions. The resulting adduct was then treated with Li/NH_3 to give the secondary aminophosphine-borane **214** in good yield and excellent enantioselectivity (Scheme 85).

3.4 Phosphonite-Borane Complexes

In contrast to secondary phosphine-boranes and their corresponding anions, which have extensively been used for C–P bond formation (Sect. 2), the reactivity of the dialkoxyphosphine-boranes was completely unknown until very recently. Indeed,



Scheme 84 Hydrolytic cleavage of aryl aminophosphines



Scheme 85 Synthesis of secondary aminophosphine-boranes from **225aa**

although the synthesis of $(MeO)_2PH(BH_3)$ was achieved in the 1970s by Centofanti et al., it was shown that this phosphonite-borane is pyrophoric and hard to purify [134].

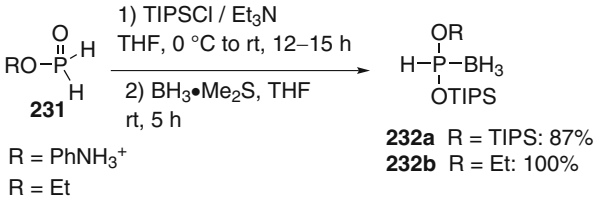
In 2008, Montchamp et al. took the challenge of synthesizing dialkoxyphosphine-boranes [135, 136]. To this end, they disclosed a straightforward synthesis of novel borane complexes of H_3PO_2 in their P(III) tautomeric form (Scheme 86). The synthesis simply consists of the silylation of **231** followed by a borane complexation to furnish **232** in excellent yields.

Having the bench-stable phosphonite-boranes in hand, Montchamp et al. have nicely explored their reactivity in different reactions [137].

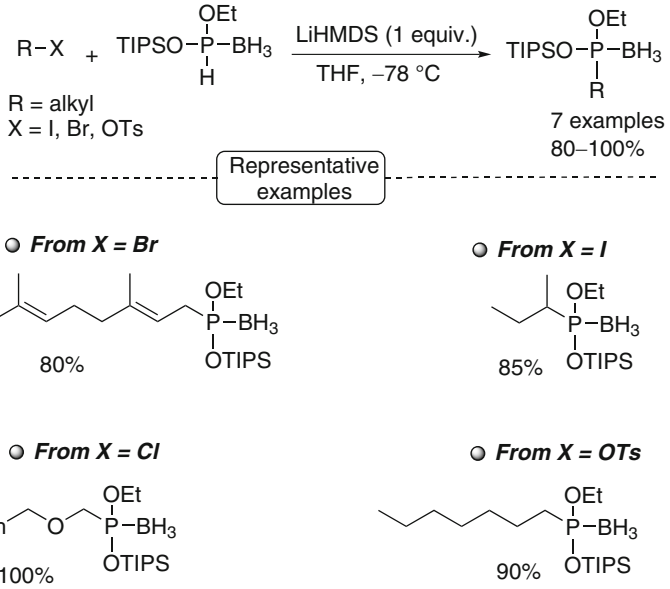
Because of the low acidity of **232**, a relatively strong base, LiHMDS, was used to generate the corresponding anions, which were then combined with various alkyl halides to give the alkylated products in good to excellent yields (Scheme 87).

Phosphonite-borane anions have also been employed as phosphorus nucleophiles toward aldehydes in acetonitrile and under reflux to yield the phosphination products in good yield (Scheme 88).

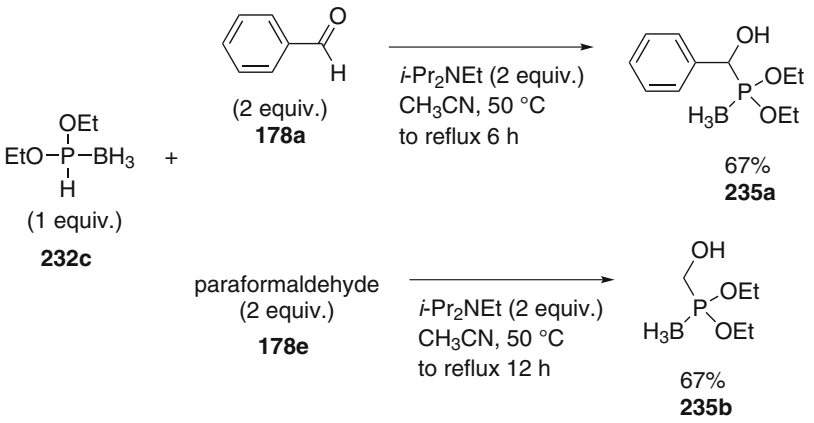
Phosphonite-boranes have also been investigated in free radical reactions. As shown in Scheme 89, while AIBN was found to be unsuccessful in initiating the



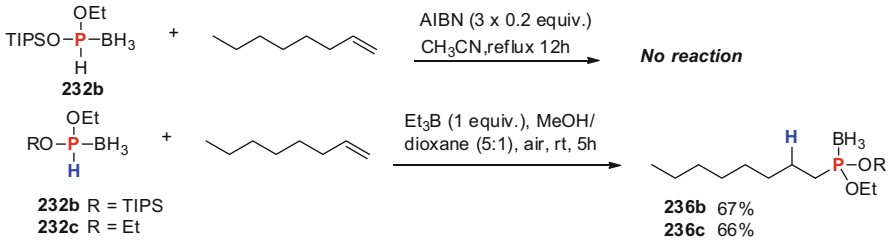
Scheme 86 Montchamp's synthesis of dialkoxyphosphine-boranes



Scheme 87 Alkylation of the anion of phosphonite-borane



Scheme 88 Phosphonite-boranes as nucleophiles with aldehydes



Scheme 89 Hydrophosphination of alkene under radical conditions using phosphonite-boranes as hydrophosphinating agents

reaction of the phosphonite-borane **232b** with 1-octene, Et_3B/air permitted the formation of the P-centered radical, thus allowing the reaction to take place and yielding the hydrophosphination product (**236**) in good yield [138].

Inspired from the pioneering work of Montchamp, Crich et al. have recently shown that diethyl phosphonite-borane could be used as a valuable precursor for the synthesis of P-chiral gluco- and manno-phosphonite-borane complexes [139, 140]. Moreover, phosphonite-boranes have been employed by Wada et al. for the synthesis of boron-containing nucleotide analogues [141].

4 Conclusions

In this chapter the main contributions since 2007 in the field of synthesis and applications of BH_3-phosphorus complexes are reported. Recent advances deal with the development of original synthetic methodologies allowing simple and concise access to functionalized and/or optically active phosphine-boranes. Although phosphine-borane complexes have been known since the pioneering work of Imamoto in the 1980s and have been widely used as phosphine surrogates, new families of borane complexes have emerged recently. They have shown versatility for the preparation of various types of enantioenriched phosphorus derivatives and have paved the way to the discovery of original reactivities. Such are metal phosphido-boranes, which were previously only considered as in situ intermediates in the P-functionalization of secondary phosphine-boranes. They were recently fully characterized in the solid state and in solution and it has been shown that they were powerful phosphinating agents as expected, but also valuable reducing agents toward carbonyl derivatives, depending on the control imposed to the media, as well as key intermediates in transition metal-catalyzed C–P bond formation. Besides phosphido-boranes, the development of new powerful routes toward optically active phosphinous-acid boranes and their esters has allowed efficient access to enantiopure *P*-stereogenic secondary and tertiary phosphine-boranes. *P*-stereogenic aminophosphine-boranes were studied and used as a new class of chiral ligands. Lastly, phosphonite-borane complexes, only available since

the recent work of Montchamp, have offered an efficient access to functionalized *H*-phosphinates, compounds of difficult access. Not to be forgotten is the key work, which has been developed these last few years in the field of phosphine-borane complexes. Moreover, beyond the scope of this review, they can serve as non-transition metal compounds capable of activating small and rather inert molecules such as H_2 through the concept of Frustrated Lewis Pairs (FLP). Phosphorus-borane derivatives are still in their infancy but have already been recognized as powerful and innovative reagents. Thus, there is no doubt that the future should offer new fascinating results in this field.

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Synthesis of Non-racemic α-Hydroxyphosphonates via Asymmetric Phospho-Aldol Reaction

Christopher D. Spilling and Raj K. Malla

Abstract It has been more than 50 years since the first phospho-aldol reactions of dialkyl phosphites were reported. These efficient P–C bond-forming reactions have become the cornerstone of methods for the synthesis of α-hydroxyphosphonates and, by numerous available substitution reactions, the synthesis of other α- and γ-substituted phosphonates and phosphonic acids. Much of the interest in α- and γ-substituted phosphonates and phosphonic acids has been stimulated by reports of their biological activity, which is often dependent upon their absolute and relative stereochemistry. In this chapter, we review diastereoselective and enantioselective additions of dialkyl phosphites to aldehydes and ketones, otherwise called the phospho-aldol, Pudovik or Abramov reactions.

Keywords Abramov reaction • Asymmetric • Catalysis • Diastereoselective • Enantioselective • Phospho-aldol • Phosphonylation • Pudovik reaction • α-Hydroxyphosphonates

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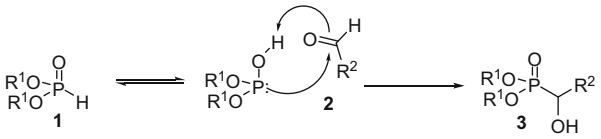
Abbreviations

A	Adenosine
ALB	Aluminum lithium binaphthoxide
AraC	Cytosine arabinoside
Bn	Benzyl
Bz	Benzoyl
C	Cytidine
CALB	*Candida antarctica* lipase B
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP	4-Dimethylaminopyridine
DMEDA	*N*,*N*′-Dimethylethylenediamine
DMT	Dimethyl tartrate
DMTr	4,4′-Dimethoxytrityl
HIV	Human immunodeficiency virus
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
LLB	Lithium lanthanum binaphthoxide
MntOH	(1*R*,2*S*,5*R*)-Menthol
NHC	*N*-Heterocyclic carbene
Piv	Pivolate
PMEA	9-[2-(Phosphonomethoxy)-ethyl]adenine
Py	Pyridine
T	Thymidine
TBDMS	*tert*-Butyldimethylsilyl
TBDSP	*t*-Butyldiphenylsilyl
THF	Tetrahydrofuran
Tr	Trityl
U	Uridine

1 Introduction

There are several reported examples of biologically active α-hydroxyphosphonates and phosphonic acids [1–3]. Furthermore, α-hydroxyphosphonates have proven to be useful intermediates for the synthesis of other α- and γ-substituted phosphonates and phosphonic acids [4–13]. Since many of the transformations of the hydroxyl

Scheme 1 The phospho-aldol reaction



group into other useful moieties are stereospecific, asymmetric approaches to non-racemic α-hydroxyphosphonates have been of great interest. Amongst the various methods available for the synthesis of non-racemic α-hydroxyphosphonates, asymmetric P–C bond formation is one of the most efficient. In particular, the phospho-aldol reaction has received much attention. This chapter focuses on the synthesis of chiral, non-racemic α-hydroxyphosphonates via the asymmetric phospho-aldol reaction of dialkyl phosphites with aldehydes and ketones. The discussion builds on several earlier reviews [14–19], including a chapter authored by Kee and Nixon in a previous addition of this series [20].

The phospho-aldol reaction is the addition of a dialkyl phosphite **1** to an aldehyde **2** (or ketone) resulting in the formation of a phosphorus–carbon bond and the creation of a new chirality center (Scheme 1). In the early 1950s, papers and patents from several groups reported the formation hydroxyphosphonates by the base-promoted addition of dialkyl phosphites to aldehydes (and ketones). Fields patented a "process of preparing substituted hydroxymethylphosphonic esters" by the Et_3N-promoted addition dialkylphosphites to aldehydes and ketones [21]. Similarly, Pudovik [22] and Abramov [23, 24] independently published a series of papers employing catalytic sodium methoxide to promote reaction. Indeed, the addition of phosphite to carbonyl is often referred to as the Pudovik or the Abramov reaction [25]. However, there have been many subsequent investigations which demonstrate that reaction can be promoted thermally [26] and by a large range of both acid and base catalysts [25, 27].

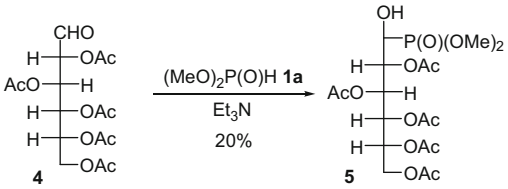
The wide range of conditions available for promoting the phospho-aldol reaction opens up a wealth of possibilities for developing asymmetric variants from metal complexes to organocatalysts.

2 Diastereoselective Phospho-Aldol Reactions

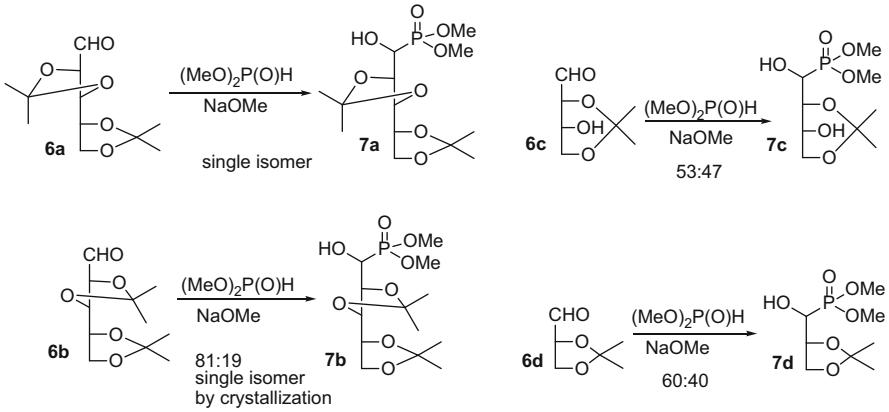
2.1 Diastereoselective Addition of Dialkyl Phosphites to Chiral Aldehydes

2.1.1 Carbohydrate-Derived Aldehydes and Ketones

It wasn't long after the first reports of the phospho-aldol reaction that it was employed in the synthesis of phosphonate derivatives of carbohydrates. In search for insecticidal phosphonates, Alexander and Barthel [28] reported the Et_3N-promoted addition of dimethyl phosphite **1a** to *aldehydo*-D-glucose pentaacetate **4** (Scheme 2). However, neither the diastereoselectivity of the reaction or the stereochemistry at the new chirality center in the pure product **5** (isolated by crystallization) were determined.



Scheme 2 The reaction of dimethyl phosphite with *aldehydo*-D-glucose pentaacetate [28]



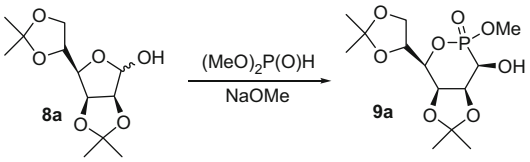
Scheme 3 The reaction of dimethyl phosphite with various carbohydrate-derived aldehydes [29–31]

About a decade later, Paulsen published a series of articles on the addition of dialkyl phosphites to carbohydrate-derived aldehyde and ketones [29–31]. Isopropylidene-protected aldehydo carbohydrates **6** were reacted with dialkyl phosphites using sodium methoxide to give hydroxyphosphonates **7** with poor to excellent diastereoselectivity (Scheme 3). The reaction of dialkyl phosphites with protected glyceraldehydes was studied in more detail by Wroblewski and Balcerzak. They looked at other reaction promoters (KF, LDA, Et_3N), but observed little change in the diastereoselectivity [32].

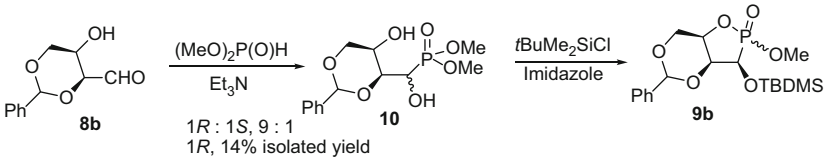
Several research groups have used the addition of dialkyl phosphites to carbohydrate-derived aldehydes (e.g., **8a** and **8b**) as the pivotal reaction in the synthesis of phostones (e.g., **9a** and **9b**) and related cyclic phosphonates (Schemes 4 and 5) [31, 33, 34]. However, in other syntheses of cyclic phosphonates (phostones), trialkyl phosphites [$P(OMe)_3$/AcOH] appear to be the preferred phosphorus nucleophiles [35, 36].

A component of Paulsen's early work on the addition of dialkyl phosphites to carbohydrates [29] involved phosphonylation of pyranose-derived ketones (e.g., **11a** and **11b**) (Scheme 6). In general, purification results in the isolation of a single isomer of the tertiary hydroxyphosphonates (e.g., **12a** and **12b**).

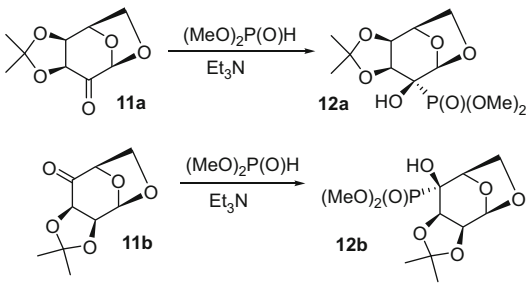
Related phosphonylation reactions of furanose aldehydes and ketones have become important in the development of non-hydrolysable phosphonate mimics of bioactive carbohydrate phosphates, especially modified nucleosides. Wiemer et al. [37, 38]



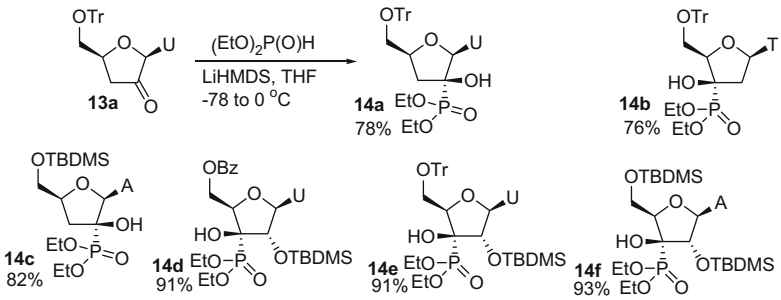
Scheme 4 Synthesis of a pyranose phostone [31]



Scheme 5 Synthesis of a furanose phostone [33, 34]

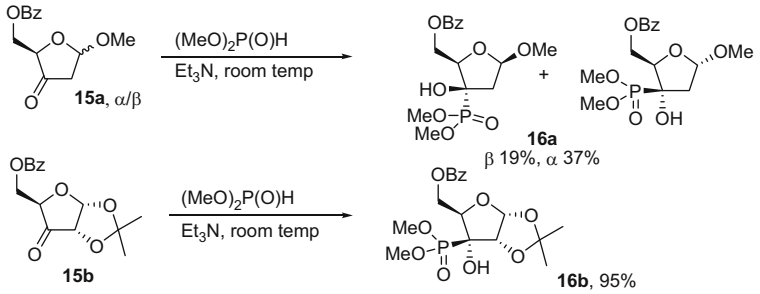


Scheme 6 Reaction of dimethyl phosphite with carbohydrate-derived ketones [29]

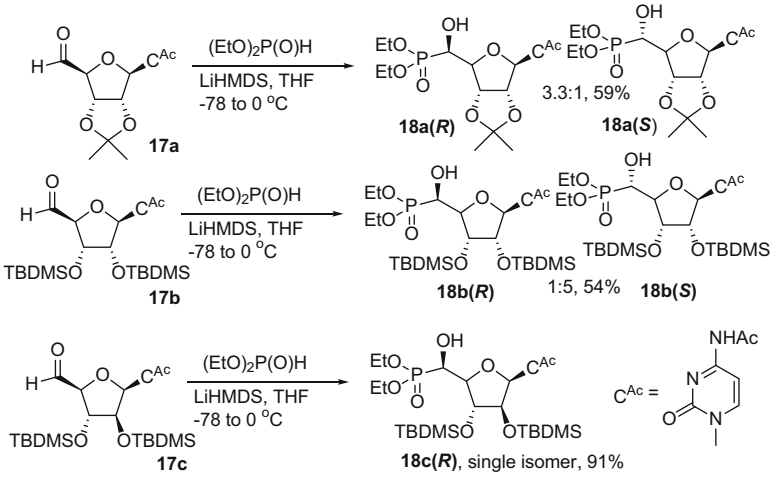


Scheme 7 Addition of lithium salt of diethyl phosphite to 2-keto- and 3-keto furanoses [37, 38]

showed that the addition of lithium salt of diethyl phosphite to 2-keto- and 3-keto furanoses (e.g., **13a**) resulted in the formation of a single diastereoisomer of the tertiary hydroxyphosphonates **14a–f** (Scheme 7). In a further transformation, the hydroxyl was converted to a chloride, which was subsequently reductively removed.



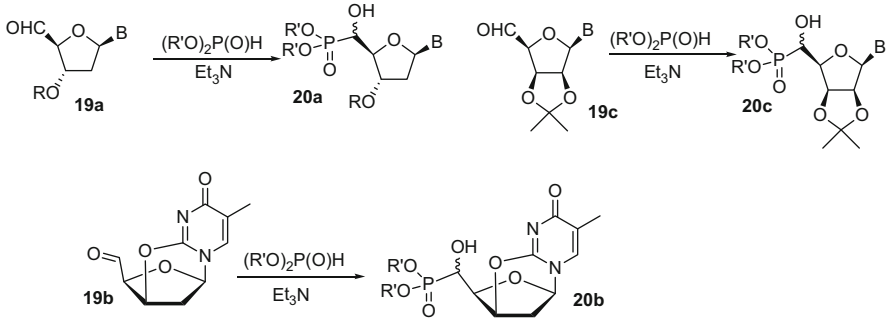
Scheme 8 Et_3N-promoted addition of dimethyl phosphite to deoxyribose- and xylose-derived ketones [39]



Scheme 9 Phosphonylation of furanose-derived aldehydes with lithium dimethyl phosphite [40]

Similarly, Montero et al. reported [39] the Et_3N-promoted addition of dimethyl phosphite to deoxyribose- **15a** and xylose- **15b**-derived ketones (Scheme 8). In the case of the deoxyribose-derived ketone **15a**, the phosphite nucleophile approach from the face opposite to the anomeric methoxy group to give a mixture of diastereoisomers **16aα** and **16aβ**. In the reaction of xylose-derived ketone **15b**, the isopropylidene controls the approach of the phosphite leading to a single isomer **16b**.

Wiemer and coworkers [40] prepared a series of Ara-C hydroxyphosphonate analogs. Ara-C is an important anti-leukemia compound. Resistance developed during the clinical use of Ara-C has been attributed to decreased activity in deoxycytidine kinase, which converts Ara-C to the monophosphate. Wiemer et al. rationalized that compounds containing a phosphonate mimic of the phosphate metabolite should display activity similar to Ara-C. The phosphonylation of the furanose-derived aldehydes **17** with lithium dimethyl phosphite gave the corresponding hydroxyphosphonates **18** in good yield. The diastereoselectivity depended on the carbohydrate structure and ranged from 3.3:1 to 100:0 (Scheme 9).



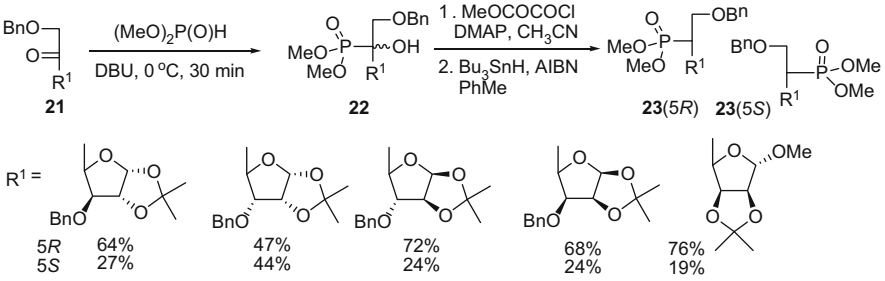
Scheme 10 Et_3N-promoted phosphonylation of nucleoside aldehydes with dialkyl phosphites [41, 42]

Table 1 Et_3N promoted phosphonylation of nucleoside aldehydes **19** with dialkyl phosphites [41, 42]

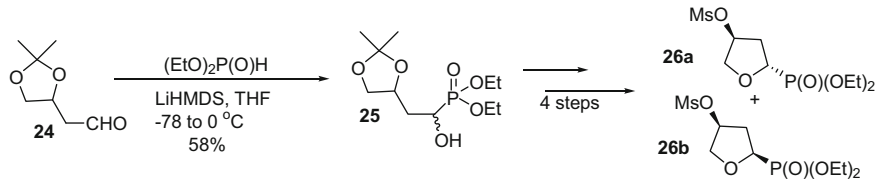
Sugar	R	R′	Base (B)	R/S ratio	Yield (%)
19a	TBDPS	Me	T	21/79	78
19a	TBDPS	Et	T	19/81	77
19a	TBDPS	*i*Pr	T	13/87	67
19a	TBDMS	Me	T	20/80	71
19a	Bz	Me	T	42/58	52
19a	Bz	Et	T	50/50	58
19a	Piv	Et	T	33/67	54
19a	DMTr	Me	T	19/81	60
19a	TBDPS	Me	C^{Bz}	15/85	84
19a	TBDPS	Me	G^{Bz}	34/66	82
19a	TBDPS	Me	G^{iBu}	40/60	76
19a	TBDPS	Me	A^{Bz}	25/75	69
19a	DMTr	Me	A^{Bz}	22/78	80
19b	–	Me	T	37/73	34
19c	–	Et	U^{MeM}	30/70	31
19c	–	Et	U	45/55	46
19c	–	Et	C^{Bz}	43/57	57
19c	–	Me	G^{Bz}	40/60	66
19c	–	Et	A^{Bz}	33/67	32
19c	–	Me	A^{Bz}	17/83	42

Again, because of their stability toward hydrolysis by phosphomonoesterases, Rosenberg [41, 42] studied the phosphonylation of a wide range of nucleoside 5-aldehdyes (Scheme 10, Table 1). The Et_3N-promoted phosphonylation of aldehydes **19a–c** in CH_2Cl_2 with dimethyl-, diethyl-, or diisopropyl phosphite gave hydroxyphosphonates **20a–c** in low to high yield and with diastereoselectivities ranging from1:1 to 4:1, favoring the 5*S* isomer in all cases.

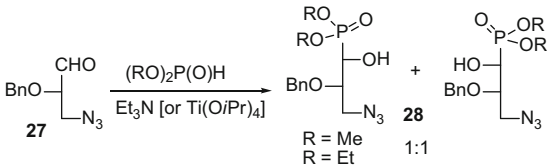
Hanaya [43, 44] investigated different routes to phosphono sugars via the DBU-promoted addition of dimethyl phosphite to hexofuranose ketones **21** (Scheme 11). The hydroxyphosphonates **22** were formed in high yield and with



Scheme 11 DBU promoted addition of dimethyl phosphite to hexofuranose ketones [43, 44]



Scheme 12 Phosphonylation of an isopropylidene protected aldehyde using lithio diethyl phosphite [45]



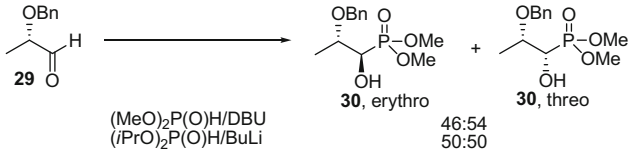
Scheme 13 Phosphonylation of a protected hydroxy aldehyde [46]

diastereoselectivities ranging from 1:1 to 3:1 favoring the 5*R* isomer. The hydroxyphosphonates were deoxygenated using a two-step protocol affording mixtures of the diastereoisomeric phosphonates **23**.

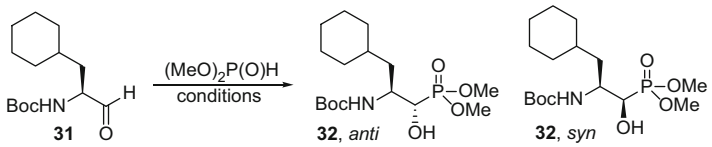
2.1.2 Protected α-Hydroxy Aldehydes

Interested in cyclic analogs of the anti-HIV compound PMEA, Nair [45] phosphonylated the isopropylidene protected aldehyde **24** using diethyl phosphite and LiHMDS (Scheme 12). The corresponding diastereoisomeric hydroxyphosphonates **25** were formed in 58% yield. The diastereoisomers could not be separated and the ratio was not reported. Further reactions (protection, hydrolysis, mesylation, and cyclization) led to the formation of tetrahydrofurans **26a** and **26b** with overall yields of 30% and 16%, respectively.

Studies on the phosphonylation of relatively simple protected hydroxy aldehydes (**27** and **29**) by Wroblewski (Scheme 13) [46] and Hammerschmidt



Scheme 14 Phosphonylation of a protected lactaldehyde [47]



Scheme 15 Addition of dimethyl phosphite to a Boc protected α-amino aldehyde

Table 2 Addition of dimethyl phosphite to a Boc-protected α-amino aldehyde

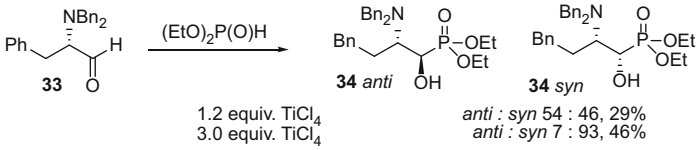
Base, solvent	Ratio (*anti*:*syn*)
DBU, DMF	1.2:1
NMM, DMF	7.0:1
iPr_2NEt, DMF	6.3:1
iPr_2NEt, MeOH	4.0:1
iPr_2NEt, CH_2Cl_2	7.0:1
KF, DMF	12.0:1
KF, MeOH	7.0:1
KF, CH_2CI_2	4.0:1

(Scheme 14) [47] showed little or no control over the diastereoselectivity. However, the hydroxyphosphonates still proved to be useful in the synthesis of their intended target molecules.

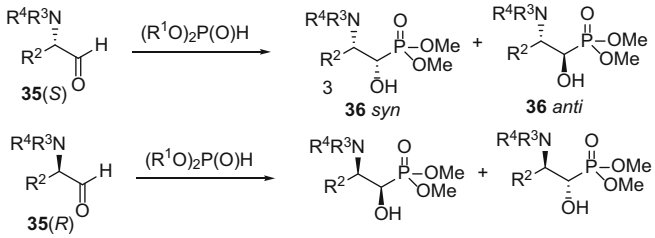
2.1.3 Protected α-Amino Aldehydes

The phosphonylation of α-amino aldehydes has become a rich source of structurally diverse and biologically interesting hydroxy phosphonates. Various phosphorus nucleophiles, including dialkyl phosphites and trialkyl phosphites, have been employed. In keeping with the theme of this chapter, some examples of the reactions of dialkyl phosphites with protected α-amino aldehydes are discussed below.

As part of a synthesis of human renin inhibitors, Patel et al. [1, 48, 49] investigated the addition of diethyl- or dimethyl phosphite to the Boc-protected α-amino aldehyde **31** using various bases and solvents (Scheme 15, Table 2). In all cases the *anti* isomer was favored with diastereoselectivities ranging from 1:1 to



Scheme 16 Reaction an *N*,*N*-dibenzyl protected amino aldehyde with diethyl phosphite [50]



Scheme 17 Addition of phosphites to various *N*-protected amino aldehydes [51–57]

12:1. The addition of dimethyl phosphite using KF in DMF provided the best diastereoselectivity.

The reaction the *N*,*N*-dibenzyl-protected amino aldehyde **33** with diethyl phosphite and $TiCl_4$ gave a diastereoisomeric mixture of hydroxyphosphonates **34** in modest yield (Scheme 16). The diastereoselectivity was dependent on the ratio of $TiCl_4$, with 3 equiv. giving an *anti*:*syn* ratio of 7:93 [50].

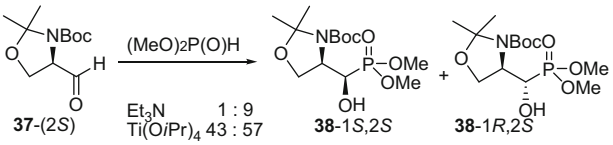
Interested in preparing phosphonic acid analogs of α-hydroxy-β-amino acids such as those found in taxol or paclitaxel, Wroblewski et al. [51–55] investigated the addition of phosphites to various *N*-protected amino aldehydes **35** (Scheme 17, Table 3). Boc-protected phenyl glycinal gave predominantly the *syn* hydroxy phosphonatein at around a 3:1 ratio with either Et_3N, KF, or the lithium phosphite. In a related study, addition of dimethyl or diethyl phosphite to (*S*)-*N*,*N*-dibenzyl-phenylglycinol usingEt_3N resulted in a 4:1 selectivity. In comparison, little selectivity was observed with the Li^+ or Mg^{2+}phosphite salts. Additional examples of the fluoride-promoted addition of dialkyl phosphites to *N*-Boc-protected α-amino aldehydes were reported by and Larcheveque [56] and Kafarksi [57] (Scheme 17, Table 3).

Wroblewski and Balcerzak [58] also studied the phosphonylation of Garner's aldehyde **37** (Scheme 18). The Et_3N promoted addition of dimethyl phosphite was quite selective, giving the hydroxyphosphonate **38** in a 1:9 ratio. In comparison, the same reaction promoted with $Ti(OiPr)_4$ gave almost equal amounts of the two diastereoisomers.

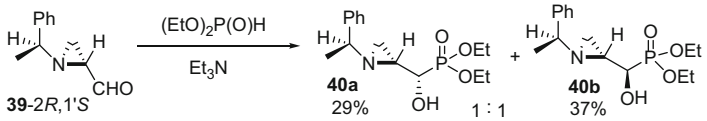
Phospho-aldol reaction (Scheme 19) of diethyl phosphite with the aziridinyl aldehyde **39** proceeded in good yield, but was unselective, giving the diastereoisomeric phosphonates **40** in a 1:1 ratio.[59] The diastereoisomers were separated by column chromatography.

Table 3 Addition of phosphites to various *N*-protected amino aldehydes [51–57]

R^2	R^3, R^4	Phosphite, R^1	Conditions	Yield (%)	Ratio (syn/anti)
Ph (±)	Boc, H	Et	Et_3N, neat, r.t.	80	75:25
Ph (±)	Boc, H	Et	KF, DCM, r.t.	ND	73:27
Ph (±)	Boc, H	Et	(LDA/n-BuLi), THF, −60°C	90	70:30
Ph (±)	Bz, H	Et	Et_3N, neat, r.t.	74	65:35
Ph (±)	Bz, H	Et	$(EtO)_2P(O)Li$	43	54:46
Ph (±)	Bz, H	Et	$(EtO)_2P(O)Na$	ND	78:22
Ph (±)	Bz, H	Et	$Ti(OiPr)_4$	80	46:54
Ph (*S*)	Bn, Bn	Me	Et_3N	ND	22:78
Ph (*S*)	Bn, Bn	Et	$E_{t3}N$	ND	20:80
Ph (*S*)	Bn, Bn	Me	$(MeO)_2P(O)Li$	ND	43:57
Ph (*S*)	Bn, Bn	Et	$(EtO)_2P(O)Li$	ND	49:51
Ph (*S*)	Bn, Bn	Et	$Ti(OiPr)_4$	ND	28:72
Bn	Boc, H	Et	CsF, neat, 0°C	92	73:27
Bn	Boc, H	Et	KF, DMF, 0°C	75	82:18
$tBuOC_6H_4CH_2$	Boc, H	Et	KF, DMF, 20°C	82	80:20
C_3H_7	Boc, H	Et	KF, DMF, 20°C	76	87:13
$(CH_3)_2CHCH_2$	Boc, H	Et	KF, DMF, 20°C	74	81:19
$(CH_3)_3CH$	Boc, H	Et	KF, DMF, 20°C	68	78:22
CH_3	Boc, H	Me	KF, DMF, r.t.	78	80:20
$(CH_3)_2CHCH_2$	Boc, H	Me	KF, DMF, r.t.	81	88:12
$CH_3CH_2(CH_3)CH$	Boc, H	Me	KF, DMF, r.t.	82	83:17

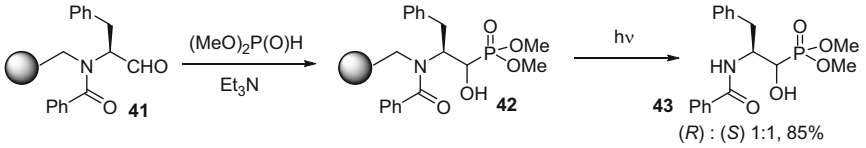


Scheme 18 Phosphonylation of Garner's aldehyde [58]

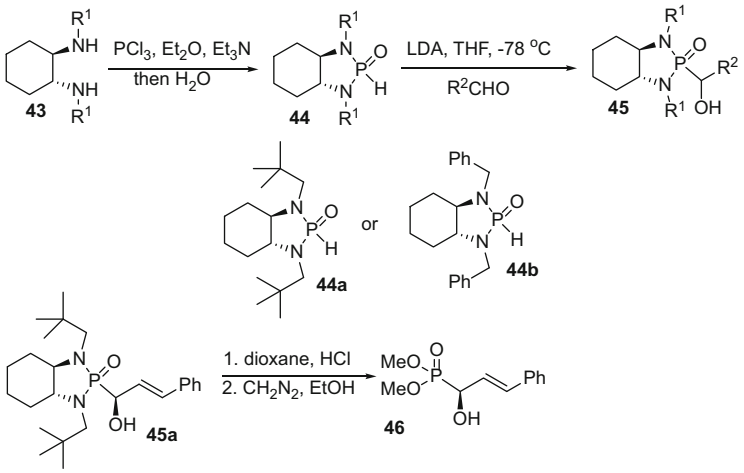


Scheme 19 Reaction of diethyl phosphite with an aziridinyl aldehyde [59]

As part of a solid phase method for the synthesis of potential aspartic protease inhibitors, Dolle and co-workers [60] performed the phospho-aldol reaction on a resin-bound protected amino aldehyde (Scheme 20). However, the Et_3N addition of dimethyl phosphite was found (after the adduct was released from the resin) to be high yielding, but was not selective.



Scheme 20 Phospho-aldol reaction of a resin bound protected amino aldehyde [60]



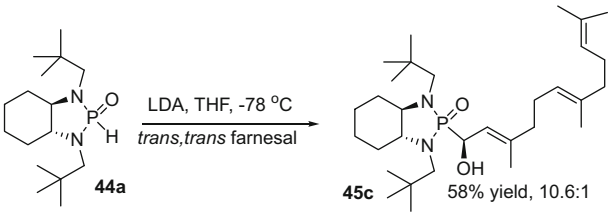
Scheme 21 Synthesis and phospho-aldol reactions of phosphorous acid diamides [61, 62]

2.2 *Diastereoselective Addition of Chiral Phosphites to Aldehydes*

In common with many asymmetric reactions, chiral reagents have been used successfully in controlling the stereochemistry of P–C bond formation in the phospho-aldol reaction. Spilling et al. prepared a series of chiral phosphorous acid diamides **44** [61, 62]. Deprotonation of the phosphorous acids **44** with LDA followed by addition of the corresponding anion to aldehydes gave hydroxyphosphonamides **45** (Scheme 21). The best stereoselectivities were observed with the *N*-neopentyl derivative **44a** (3.4:1 to 29:1), although the *N*-benzyl compound **44b** was selective with some aldehydes (Table 4). In most cases, the phosphonamides **45** were crystalline and recrystallization gave diastereoisomerically pure materials. Hydrolysis of the phosphonamides **45** with HCl in dioxane and methylation with diazomethane gave the hydroxyphosphonates **46** without racemization. The configuration of the new chirality center (C-1) was assigned both by X-ray crystallography of hydroxyphosphonamides [63–65] and comparison of the optical rotation of the hydroxyphosphonates with literature values. The *R*,*R* diamide gave the (*S*)-hydroxyphosphonate.

Table 4 Phospho-aldol reactions of phosphorous acid diamides [61, 62]

Aldehyde	Phosphorous acid diamide	Yield (%)	Ratio
PhCHO	$CH_2C(Me)_3$	49	25:1
α-NaphthCHO		91	29:1
β-NaphthCHO		58	14:1
PhCH=CHCHO		68	7.9:1
CH_3CH=CHCHO		91	6.9:1
n-C_6H_{13}CHO		80	4:1
PhCHO	CH_2Ph	77	1:1
α-NaphthCHO		93	2:1
β-NaphthCHO		89	1:1
PhCH=CHCHO		94	4:1
CH_3CH=CHCHO		71	5.6:1
n-C_6H_{13}CHO		62	2.4:1

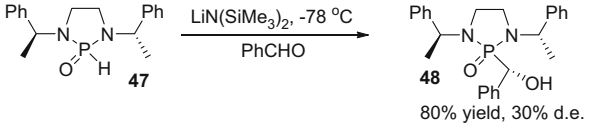


Scheme 22 Reaction of a phosphorous acid diamide with farnesal [66]

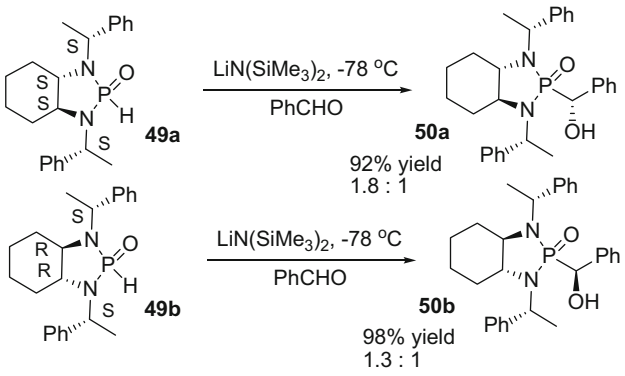
Wiemer et al. attempted to apply the chiral phosphorous acid diamide **44a** to the synthesis of a hydroxyfarnesylphosphonic acid [66]. Although the addition step was successful, giving the hydroxyphosphonamides **45c** in 58% yield with a diastereoselectivity of >10:1 (Scheme 22), the hydrolysis conditions proved too harsh for this substrate and led to decomposition.

Kee and Devitt prepared phosphorous acid diamides **47** with the chirality moved out of the ring and onto the nitrogen substituents [67]. Again, deprotonation with a strong base and addition of the resulting anion to benzaldehyde at low temperature resulted in formation of two hydroxyphosphonamide diastereoisomers **48** in 1.8:1 ratio (30% d.e.) and 80% yield (Scheme 23).

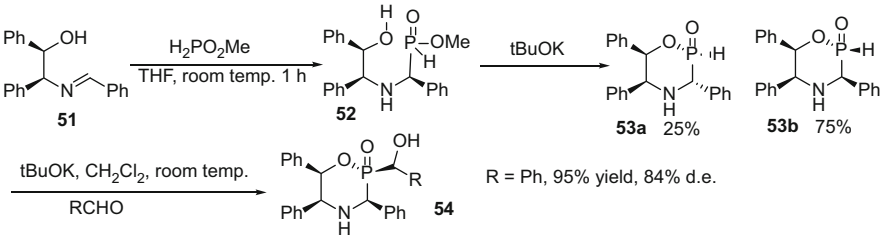
Phosphorous acid diamides **49** with the chirality both in the ring and on the nitrogen substituent have also been prepared [68]. Reaction of the corresponding anions with benzaldehyde gave two diastereoisomeric hydroxyphosphonamides **50** (Scheme 24). Phosphorous acid **49a** (1*S*,2*S*,1′*S*,1″*S*) formed phosphonamides **50a** in 92% yield in a 1.8:1 ratio, favoring the (*R*) configuration at C1, whereas the



Scheme 23 Phospho-aldol reaction of a phosphorous acid diamide with chirality on the nitrogen substituent [67]



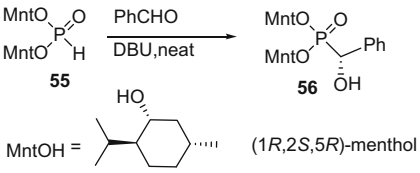
Scheme 24 Phosphorous acid diamides with the chirality both in the ring and on the nitrogen substituent [68]



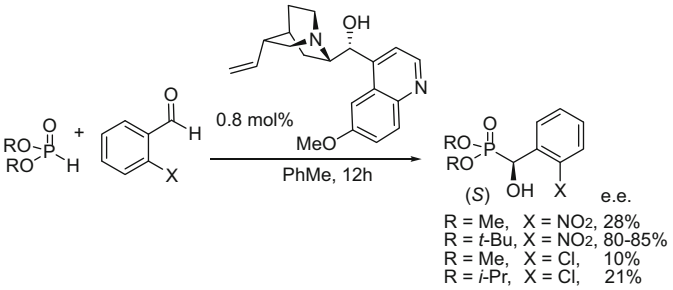
Scheme 25 Synthesis and phospho-aldol reaction of anoxazaphosphinane [69]

phosphorus acid **49b** (1*R*,2*R*,1′*S*,1″*S*) gave phosphonamides **50b** in 98% yield and 1.3:1 ratio, favoring the (*S*) configuration at C1. There does appear to be an additive effect of the multiple chiral centers.

Although somewhat outside the scope of this review, it is interesting to compare the reactions of oxazaphosphinanes **53** with the phosphorous acid diamides **44**. These structurally intriguing compounds are prepared by reaction of imine **51** with methyl hypophosphite, followed by base-induced ring closure to give a 3:1 ratio of **53a** and **53b** [69]. Reaction of the major diastereoisomer **53b** with benzaldehyde using *t*BuOK as base gave the hydroxyalkyl adduct **54** in 95% yield with 84% d.e. (Scheme 25).



Scheme 26 Phospho-aldol reaction of dimenthyl phosphite with benzaldehyde [70]



Scheme 27 The quinine catalyzed addition of dialkyl phosphites to *o*-substituted benzaldehydes [71]

Phospho-aldol reaction of dimenthyl phosphite **55** with benzaldehyde gave the (*R*)-hydroxyphosphonate **56** as a pure diastereoisomer after recrystallization from hexane [70]. The reaction was performed using DBU as the catalyst neat at room temperature (Scheme 26).

3 Catalysis

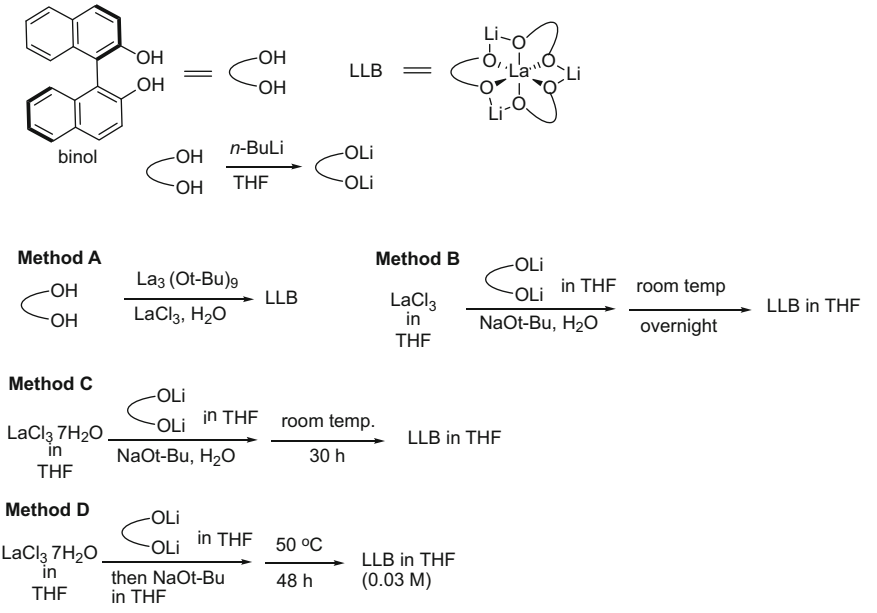
The first catalytic asymmetric phospho-aldol reaction was carried out in 1983. Wynberg and Smaardijk reported the quinine catalyzed addition of dialkyl phosphites to *o*-substituted benzaldehydes [71] (Scheme 27). The reaction used catalytic amounts of quinine (0.8 mol%), but was generally slow and required *o*-electron-withdrawing substituents to achieve acceptable reaction rates. Useful levels of enantiopurity are obtained with di-*tert*-butyl phosphite. Although the methyl esters are formed initially with low selectivity, they could be crystallized to enantiopurity because they crystallize as conglomerates. The products derived from the quinine-catalyzed reactions were assigned as (*S*)-enantiomers, whereas quinidine gave the (*R*)-enantiomer with nearly identical selectivity [72]. Not only was this the first reported example of a catalytic asymmetric phospho-aldol reaction, but it was also the first "organocatalytic" method. It took almost a decade for the next articles on catalytic asymmetric phospho-aldol reactions to appear in the literature, but these early findings paved the way for future researchers.

3.1 Lanthanide Catalysts

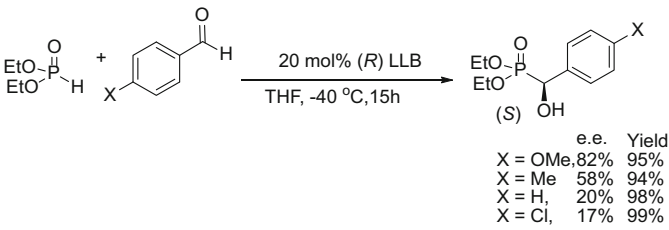
In 1993 there was renewed activity in the area of catalytic asymmetric phospho-aldol reactions. Shibuya and coworkers recognized [73] that the lithium lanthanum binaphthoxide (LLB) catalyst, originally developed by Shibasaki for nitro-aldol condensations [74, 75], was effective in the phospho-aldol reaction (Scheme 28). The catalyst is prepared by from either lanthanum alkoxide and binaphthol (Method A) or lanthanum trichloride and lithium binaphthoxide (Methods B, C, and D) [74–77].

Reaction of diethyl phosphite with aromatic aldehydes using 20 mol% of the $LaCl_3$ H_2O-derived catalyst (Method C) at −40°C for 15 h gave (*S*)-hydroxyphosphonates with enantiomeric excesses of between 17% and 82% and chemical yields of >90% (Scheme 29). The highest selectivity was observed with aromatic aldehydes bearing an electron-releasing substituent in the *para* position. The effect of the *para* substituent was demonstrated using a linear Hammet plot (OMe, Me, H, and Cl), which showed a large ρ value of −1.30 ($r = 0.92$).

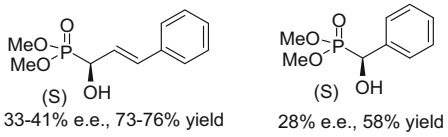
Spilling et al. also recognized the need for a catalytic asymmetric phospho-aldol reaction and, in an independent publication [78], showed that reaction of dimethyl phosphite with cinnamaldehyde using (*R*) LLB (Method C) gave the (*S*)-hydroxyphosphonate with enantiomeric excess of 33–41% and chemical yield of >70% (Scheme 30). The (*S*) stereochemistry was proven unequivocally by a crystal structure determination on an *o*-methyl mandelate derivative [79]. Addition of dimethyl phosphite to benzaldehyde gave (*S*)-hydroxyphosphonate with 28% *ee* in 58% yield, which is consistent with Shibuya's observations [73]. Batch-to-batch variation in the reaction selectivity was observed, demonstrating the sensitive nature of the catalyst preparation.



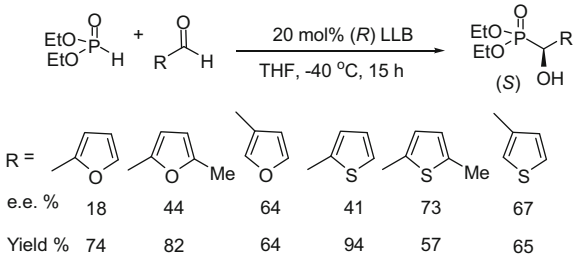
Scheme 28 Methods for the preparation of LLB [74–77]



Scheme 29 LLB catalyzed phosphonylation reaction of aromatic aldehydes [73]



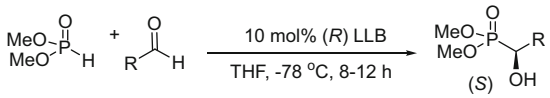
Scheme 30 LLB catalyzed phosphonylation reaction of cinnamaldehyde and benzaldehyde [78]



Scheme 31 LLB catalyzed phosphonylation reaction of heteroaromatic aldehydes [80]

In a follow-up paper, Shibuya and coworkers examined several additional lanthanide alkoxides including La-Na-(*R*)-binol (LSB), Eu-Li-(*R*)-binol (EuLB), and Sm-Li-(*R*)-binol (SmLB) [80]. Although all of the complexes showed good catalytic activity, they were significantly less selective than the original LLB. This study included an expansion of the substrate scope for the LLB-catalyzed reaction to include several heteroaromatic aldehydes (Scheme 31).

The results with LLB clearly demonstrated that enantioselective asymmetric variants of the phospho-aldol reaction were possible using chiral metal complexes. However, low enantioselectivity, tricky catalyst preparation, relatively high catalyst loading (20 mol%), and the need to maintain a reaction temperature of −40°C or below for 15 h reduces the appeal of this catalyst system. Shibasaki addressed the problem of low enantioselectivity with an improved catalyst preparation [81]. Catalyst prepared by reaction of $LaCl_3$ $7H_20$ with binol dilithium salt and NaO*t*Bu in THF at 50°C (Method D) resulted in remarkable improvements in enantioselectivity. Further improvements were observed with slow addition of the aldehyde to a solution of the catalyst and phosphite (Scheme 32, Table 5).

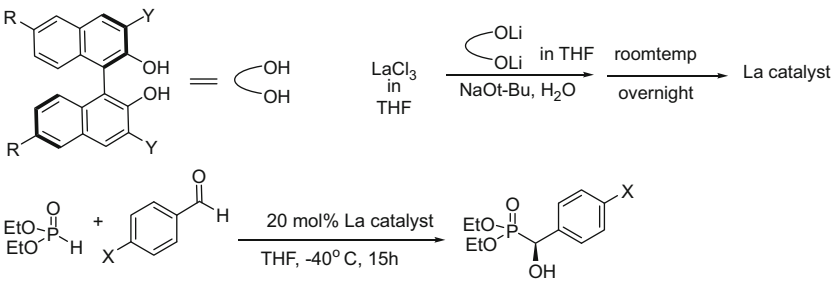


Scheme 32 LLB catalyzed phosphonylation reaction of various aldehydes using an improved LLB preparation [81]

Table 5 LLB catalyzed phosphonylation reaction of various aldehydes using an improved LLB preparation [81]

Aldehyde[a]	Yield (%)	*ee* (%)
4-$O_2NC_6H_4CHO$	85	36
PhCHO	88	79
4-$MeOC_6H_4CHO$	83	88
PhCH=CHCHO	90	84
C_3H_7CH=CHCHO	63	75
n-$C_5H_{11}CHO$	88	61

[a]Selected examples



Scheme 33 The influence of binol substituents on the LLB catalyzed phosphonylation reactions [82]

Qian et al. examined the influence of binol substituents on the LLB-catalyzed reaction [82]. They prepared a series of five new catalysts from binols substituted at the 3 and/or 6 positions using the older method of preparation (Method C) (Scheme 33). Some improvements in the selectivities were observed with 6-phenyl substituted binols. For example, the reaction of diethyl phosphite improved from 20% *ee* (with LLB) to 39% with the substituted catalyst (Table 6). Since Shibasaki had already shown that a more reliable method of catalyst preparation (Method D) led to improved selectivity, it is possible that the 6-substituted binol-derived catalysts (prepared using Method D) might be even more selective than the published values.

Walsh et al. [83] published an in-depth study of the nature of Shibasaki's heterobimetallic catalysts (LLB and related structures). The study included several X-ray crystal structures of the complexes. Complexes were also prepared by displacing THF with dimethyl ethylene diamine (DMEDA). Reaction of dimethyl phosphite and benzaldehyde employing LLB and the corresponding DEMDA complex as catalysts gave virtually identical yields and stereoselectivities [79% e.e (88%) and 78% e.e (92%), respectively].

Table 6 The influence of binol substituents on the LLB catalyzed phosphonylation reactions [82]

Catalyst	R	Y	Aldehyde	Yield (%)	*ee* (%)
I	H	H	X=H	93	20 (21)[b]
I			X=Me	93	55 (58)[b]
II	H	$CH_3OCH_2CH_2$-	X=H	83	21
II			X=Me	89	53
III	Ph	H	X=H	82	39
III			X=Me	93	69
III			X=OMe[a]	89	74
III			X=Cl	95	52
IV	Ph	$CH_3OCH_2CH_2$-	X=H	87	30
IV			X=Me	89	62
V	H	Me_3Si	X=H	93	0
V			X=Me	92	0

[a]Reaction at −78°C
[b]Literature values [73]

Complexes derived from chiral *N*,*N*′-dioxide ligands **57** and lanthanide triflates catalyzed the addition of diethyl phosphite to aldehydes to give hydroxyphosphonates in good yield [84]. The combination of ytterbium and ligand **57a** gave the most selective catalyst (Scheme 34, Table 7). Both the reaction yield and stereoselectivity were improved by the addition of pyridine. Yields ranged from 68% to 99% and stereoselectivities from 70% to 80% *ee*.

3.2 Titanium Catalysts

Titanium complexes featured in the early stages of the resurgence in the asymmetric phospho-aldol reaction. In 1993, Shibuya and co-workers reported the first application of chiral titanium complexes in the phospho-aldol reaction [85]. A 1:1 mixture of titanium isopropoxide and diisopropyl tartrate (Sharpless catalyst) catalyzed the addition of diethyl phosphite to benzaldehyde to afford the α-hydroxyphosphonate with 75% yield and 53% enantiomeric excess (Scheme 35). Etheral solvents (Et_2O, THF) resulted in more selective reactions than halogenated (CH_2Cl_2) or hydrocarbon (PhMe) solvents.

Inspired by the findings of Shibuya with the Sharpless catalyst, Spilling and coworkers examined iterative structural modifications, beginning with tartrate esters and ultimately arriving at cyclohexane diol [86]. The ligands **58** (20 mol%) were complexed with titanium isopropoxide (20 mol%) in Et_2O and screened using dimethyl phosphite and cinnamaldehyde at −10°C as the standard reaction (Scheme 36). The selectivity improved from 13% *ee* with diisopropyl tartrate to 70% *ee* with cyclohexanediol **58e**.

The cyclohexanediol/titanium isopropoxide complex was quite general for a range of aldehydes. Typically, reaction of dimethyl phosphite with various

Scheme 34 Asymmetric phosphonylation-catalyzed chiral lanthanide complexes of *N*,*N*′-dioxide [84]

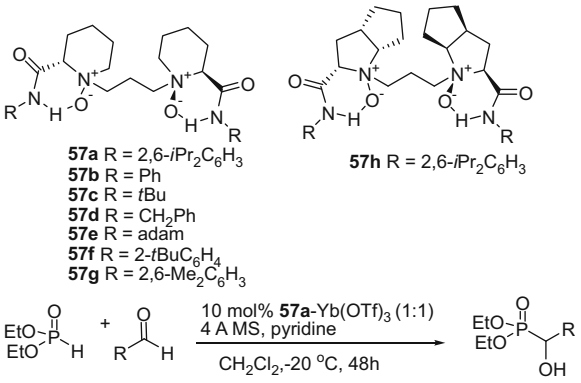
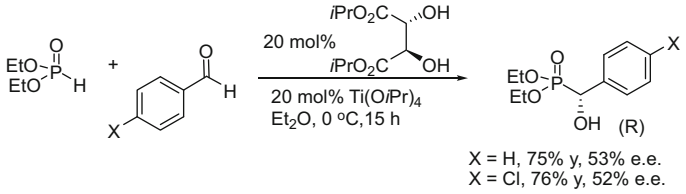


Table 7 Asymmetric phosphonylation catalyzed chiral lanthanide complexes of *N*,*N*′-dioxide [84]

Aldehyde[a]	Yield (%)	*ee* (%)
4-FC_6H_4CHO	94	71
3-ClC_6H_4CHO	72	71
4-ClC_6H_4CHO	85	71(*R*)
PhCHO	90	78(*R*)
4-$MeOC_6H_4CHO$	94	82(*R*)
4-$CH_3C_6H_4CHO$	89	80
2-$CH_3C_6H_4CHO$	99	76
3-ClC_6H_4CHO	72	71
PhCH=CHCHO	68	70
2-Furyl	87	80(*R*)

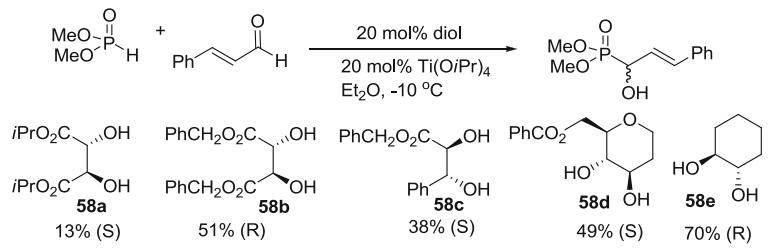
[a]Selected examples



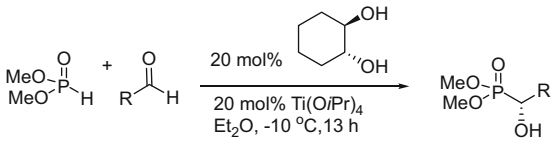
Scheme 35 Phosphonylation of aromatic aldehydes catalyzed titanium isopropoxide and diisopropyl tartrate [85]

aldehydes using 20 mol% of (1*S*,2*S*)-cyclohexanediol and titanium isopropoxide in Et_2O at −10°C gave (*R*)-hydroxyphosphonates in yields of 48–82% and enantioselectivities of 42–70% *ee* (Scheme 37, Table 8).

As part of the general investigation into tartrate esters, Spilling et al. [87, 88] examined the complex formed between dimethyl tartrate (DMT) and titanium isopropoxide. This complex was a surprisingly effective and quite general catalyst. Reaction of dimethyl phosphite with aldehydes using 20 mol% of L-dimethyl tartrate and titanium isopropoxide in Et_2O at −15°C gave (*R*)-



Scheme 36 Phosphonylation of cinnamaldehyde catalyzed chiral titanium alkoxides [86]



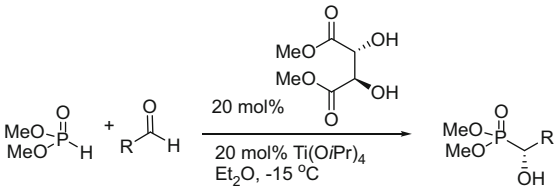
Scheme 37 Phosphonylation of aldehydes catalyzed titanium isopropoxide and cyclohexane diol [86]

Table 8 Phosphonylation of aldehydes catalyzed titanium isopropoxide and cyclohexane diol [86]

Aldehyde	Yield (%)	*ee* (%)
4-$O_2NC_6H_4CHO$	58	52
PhCHO	51	64
4-$MeOC_6H_4CHO$	65	57
4-MeC_6H_4CHO	69	64
4-FC_6H_4CHO	44	62
PhCH=CHCHO	45	70
n-$C_5H_{11}CH$=CHCHO	44	60
CH_3CH=CHO	72	65
n-$C_5H_{11}CH\equiv$CHCHO	82	49
c-$C_6H_{11}CHO$	48	42

hydroxyphosphonates in moderate to high yields of 68–98% and enantioselectivities of 32–74% *ee* (Scheme 38, Table 9). For all but aliphatic aldehydes, the yields and selectivities with dimethyl tartrate are more consistent and somewhat improved over cyclohexanediol.

A closer look at the reaction uncovered an interesting property. The reaction of benzaldehyde and dimethyl phosphite was run using 20 mol% catalyst and aliquots were taken throughout the reaction. The conversion and enantiomeric excess of the product were measured (by HPLC and NMR). At low conversion the enantiomeric excess is low. However, as the reaction proceeds the enantiomeric excess improves, finally leveling off at about 70% *ee* (Fig. 1) (Spilling and Smith, unpublished results). Similar results were observed with acrolein and cinnamaldehyde. This phenomenon is known as asymmetric autoinduction [89] and has been observed



Scheme 38 Phosphonylation of aldehydes catalyzed titanium isopropoxide and dimethyl tartrate [87, 88]

Table 9 Phosphonylation of aldehydes catalyzed by titanium isopropoxide and dimethyl tartrate [87, 88]

Aldehyde	Yield (%)	*ee* (%)
PhCHO	80	70
CH_2=CHCHO	71	70
PhCH=C(Me)CHO	70	73
2-furyl-CH=CHCHO	98	67
PhCH=CHCHO	71	73
n-C_5H_{11}CH=CHCHO	98	69
CH_3CH=CHO	68	64
n-C_5H_{11}CH≡CHCHO	82	74
c-C_6H_{11}CHO	77	32

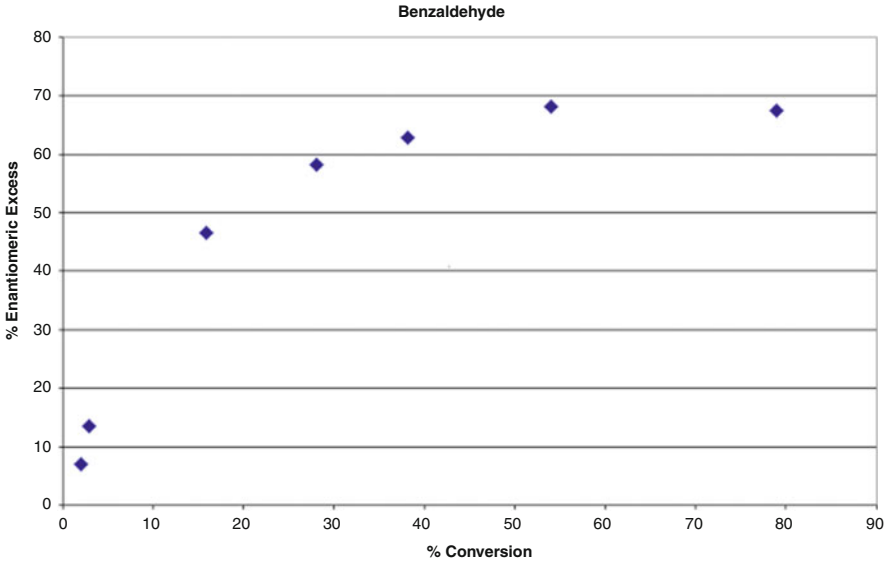
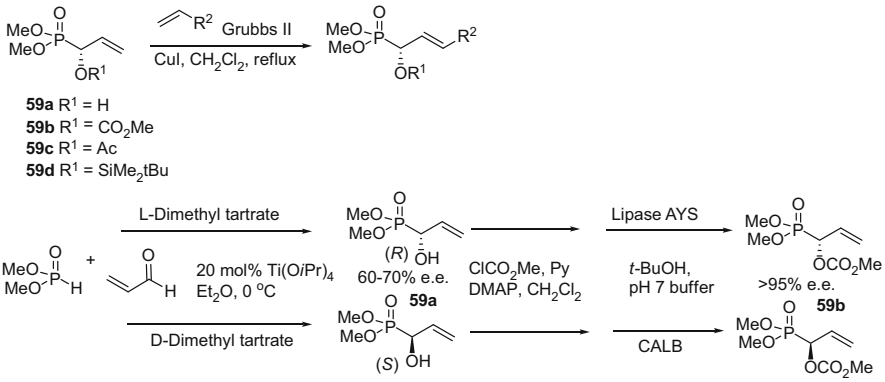


Fig. 1 Graph of *ee* vs conversion for the phosphonylation of benzaldehyde catalyzed titanium isopropoxide and dimethyl tartrate

with titanium alkoxide-based asymmetric catalysts in other reactions [90]. It has been proposed that the product is incorporated into the titanium complex to produce a new and more selective catalyst.



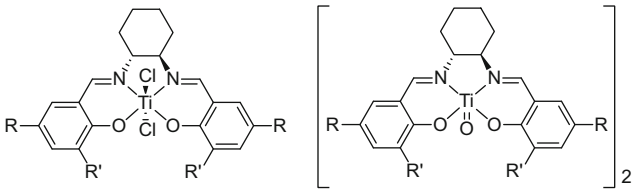
Scheme 39 Formation and cross metathesis of the acrolein-derived phosphonates

The DMT/Ti(O*i*Pr)$_4$ system has some advantages and some disadvantages. On the plus side, DMT is a crystalline solid available as both enantiomers. Both DMT and Ti(O*i*Pr)$_4$ are inexpensive. However, the reaction is moisture sensitive and the enantioselectivities are not yet at a useful level.

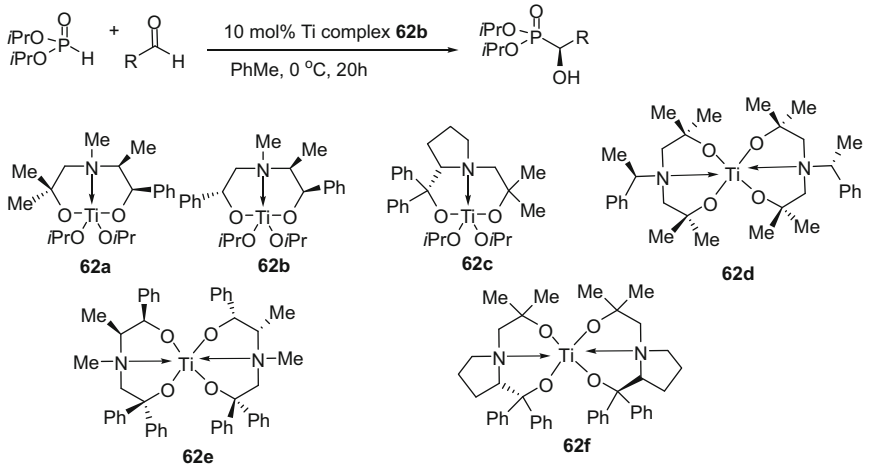
The acrolein-derived hydroxyphosphonate **59a**, and the derivatives **59b–d** in particular, are good substrates for alkene cross metathesis reactions (Scheme 39). Reaction of types I and II alkenes with the phosphonates, using 10 mol% Grubbs second generation catalyst and 10 mol% copper(I) iodide as co-catalyst, gave the substituted phosphonates in good yield and without eroding the stereochemistry [12, 91].

The metathesis results stimulated the search for effective methods for the large scale formation of the acrolein-derived hydroxyphosphonate **59a** and its derivatives in high enantiomeric excess. Spilling showed that the application of sequential asymmetric reactions would lead to hydroxyphosphonates in good overall yield and with high enantiomeric excess [88]. In particular, DMT/Ti(O*i*Pr)$_4$-catalyzed phosphonylation followed by lipase-catalyzed hydrolysis of the corresponding acetates gave hydroxy (or acetoxy) phosphonates with excellent enantiopurity. Thus, the methyl carbonate **59b**, which is an important intermediate, is formed in high enantiomeric excess in three steps (Scheme 39). The phosphonylation reaction can be run on a 1-L scale in a jacketed reactor, and the product hydroxyphosphonate (**59a**, 70% *ee*) can be isolated by fractional distillation under high vacuum. Reaction of the hydroxyphosphonate with methyl chloroformate gives the carbonate **59b**, which can also be purified by distillation. Lipase-catalyzed hydrolysis of the minor enantiomer increases the enantiomeric excess of the carbonate (>95% *ee*) and can be run in 1- to 10-g batches. The appropriate selection of enzyme combined with hydroxy phosphonate, produced using either D- or L-dimethyl tartrate, yields either the (*S*) or (*R*) enantiomer [13].

After a brief hiatus, titanium complexes made a reappearance in 2004. Kee and coworkers prepared some dichlorotitanium **60** and dioxotitanium **61** complexes from cyclohexanediamine-derived Schiff's bases [92]. The complexes were characterized using X-ray crystallography. Unfortunately, the dioxotitanium complexes



Scheme 40 Schiff's base titanium complexes [92]



Scheme 41 Phosphonylation catalyzed by titanium isopropoxide complexes of aminodiols [93]

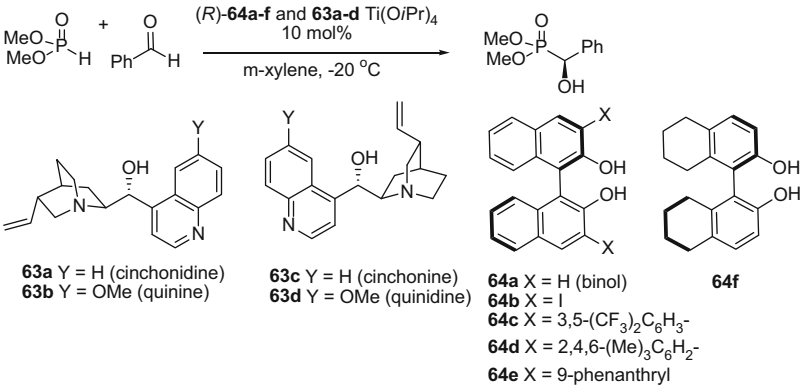
61 (Scheme 40) were only weakly catalytically active in the phospho-aldol reaction between dimethyl phosphite and benzaldehyde, and the product hydroxyphosphonate was racemic.

Kaitsev et al. prepared and characterized (by X-ray crystallography) a series of chiral and achiral titanium isopropoxide complexes of aminodiols [93]. The chiral complexes **62** were investigated as potential catalysts for the asymmetric phospho-aldol reaction (Scheme 41). Reactions of dimethyl, diethyl, and diisopropyl phosphite with benzaldehyde in toluene at 0°C using 10 mol% catalyst were examined. The enantioselectivities ranged from 10% to 38%, with complex **62b** and diisopropyl phosphite giving the best result. Using complex **62b**, diisopropyl phosphite was reacted with some additional aldehydes to give (*S*)-hydroxyphosphonates in chemical yields of 68–84% and enantioselectivities of 14–56% *ee* (Scheme 41, Table 10).

You and coworkers explored the synergy between chiral tertiary amines, in the form of chinchona alkaloids, and titanium binaphtholate complexes [94]. The combinations of six different binols **64a–f** and four alkaloids **63a–d** (10 mol%) were complexed with titanium isopropoxide (20 mol%) in *m*-xylene and screened

Table 10 Phosphonylation catalyzed by titanium isopropoxide complexes of aminodiols [93]

Aldehyde	Yield (%)	*ee* (%)
2-BrC_6H_4CHO	84	14
4-FC_6H_4CHO	76	40
PhCHO	81	50
4-$MeOC_6H_4CHO$	76	35
3-$O_2NC_6H_4CHO$	76	52
2-Thiophenyl	68	56



Scheme 42 Phosphonylation catalyzed by chinchona alkaloids and titanium binaphtholate complexes [94]

Table 11 Phosphonylation catalyzed by chinchona alkaloids and titanium binaphtholate complexes [94]

Binol	Alkaloid	Yield (%)	*ee* (%)
64a	63a	99	66
64f	63a	64	24
64b	63a	99	99
64c	63a	78	69
64d	63a	23	49
64e	63a	30	60
64b	63b	98	94
64c	63b	76	62
64b	63c	34	78
64b	63d	32	20

using dimethyl phosphite and benzaldehyde at −20°C as the standard reaction. The yields of hydroxyphosphonate varied from 32% to 99% and the enantioselectivities ranged from 20% to 99% (Scheme 42, Table 11). The configuration of both the quinuclidine nitrogen and the C9 hydroxyl on alkaloid were shown to be crucial to the catalytic performance.

The combination of cinchonidine **63b** and (*R*)-3,3′-diiodobinaphthol **64b** gave hydroxy phosphonate with the highest yield and enantioselectivity. The

Scheme 43 Phosphonylation catalyzed by cinchona alkaloids and titanium binptholate complexes [96]

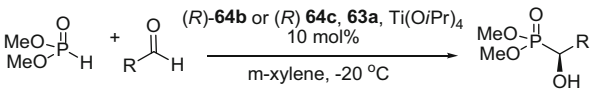
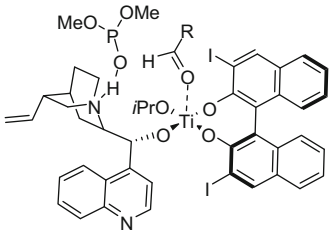


Table 12 Phosphonylation catalyzed by cinchonidine and titanium binaphtholate complexes [94]

Aldehyde[a]	Binol	Yield (%)	*ee* (%)
PhCHO	63b	99	99
m-ClC_6H_4CHO	63b	99	94
p-ClC_6H_4CHO	63b	99	92
p-$CH_3C_6H_4CHO$	63b	96	97
2-$MeOC_6H_4CHO$	63b	98	98
p-CNC_6H_4CHO	63b	99	91
1-Naphthyl	63b	99	99
PhCH=CHCHO	63b	97	89
Cyclohexyl	63c	95	92
n-Octyl	63c	97	94

[a]Selected examples

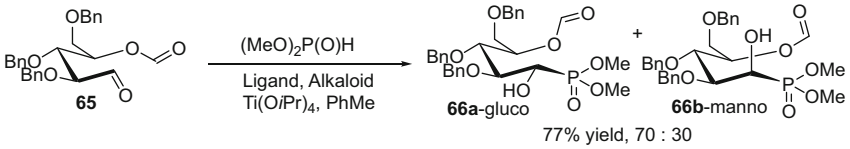
Scheme 44 Proposed reaction complex



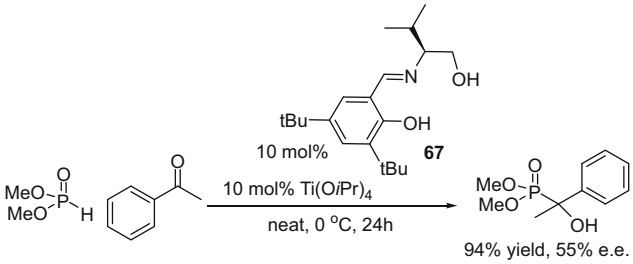
combination of cinchonidine/binol **64b** and Ti(O*i*Pr)$_4$ was further examined in the reaction of dimethyl phosphite with several aldehydes to give the (*S*)-hydroxyphosphonate (Scheme 43, Table 12). The product yields and enantioselectivities were generally excellent, especially with aromatic aldehydes.

The authors proposed a model (Scheme 44) wherein the alkaloid and the binol are complexed with titanium. The Lewis basic aldehyde coordinates to titanium and the phosphite hydrogen bonds via the P(III) tautomer to the amine. Given the propensity of titanium alkoxides to oligomerize and their dynamic nature, this is probably an over-simplification of the actual events taking place in solution, but the model does allow the stereochemistry (*Si* face attack) of the hydroxyphosphonate to be rationalized.

Crich and coworkers used the You catalyst system to control the diastereoselectivity in the addition of dimethyl phosphite to the carbohydrate-derived aldehyde **65** [95]. A combination of ligand (*R*)-**63b** and cinchonidine gave a 10:90 mixture, favoring the manno phosphonate **66b** in 57% yield (Scheme 45). In contrast, (*R*)-**63a** and cinchonidine favored the gluco phosphonate **66a** (70:30) in 77% yield. The phosphonates are precursors to phostones.



Scheme 45 Phosphonylation of a carbohydrate-derived aldehyde [95]



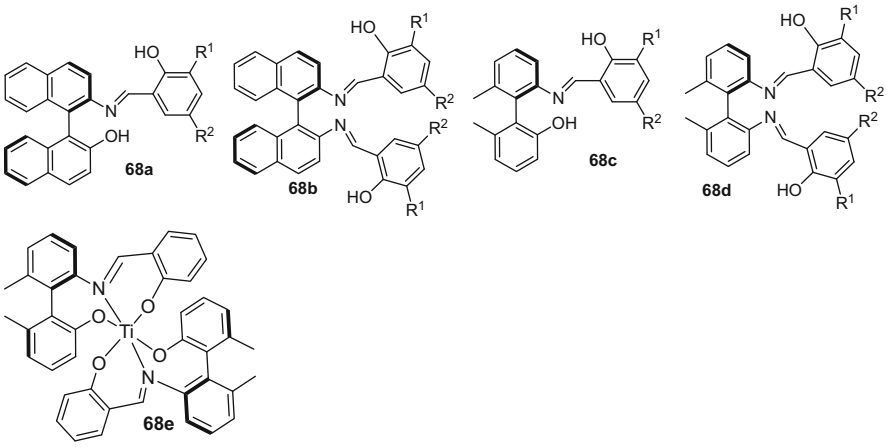
Scheme 46 Phosphonylation of acetophenone catalyzed by a titanium Schiff's base complex [96]

After studying the reaction of dimethyl phosphite with aryl methyl ketones (acetophenones) using metal alkoxides and triflates as catalyst, Feng and coworkers reported a single example as an asymmetric variant [96]. A combination of the valinol-derived Schiff's base ligand **67** and titanium isopropoxide catalyzed the addition of dimethyl phosphite to acetophenone in a neat mixture to give the tertiary hydroxyphosphonate in 94% yield and 55% *ee* (Scheme 46).

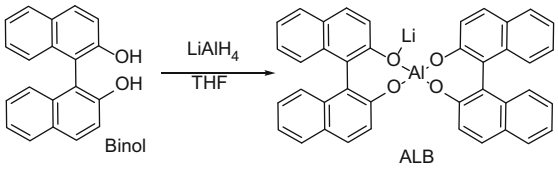
Zi et al. prepared a series of 12 binaphthylamine-derived Schiff base ligands **68** [97]. The ligands **68** were complexed with Ti(O*i*Pr)$_4$ in 1:1 and/or 2:1 ratios to give LTi(O*i*Pr)$_2$, LTi(O*i*Pr), and L$_2$Ti complexes. Most of the complexes were characterized by X-ray crystallography (Scheme 47). The potential of the complexes to act as catalysts in the phospho-aldol reaction was tested using the addition of dimethyl phosphite to benzaldehyde in toluene at 20°C as a standard reaction. Complex **68e** gave hydroxyphosphonate in 88% yield with 27% *ee*. The enantioselectivity improved to 45% on switching to THF as solvent. The reaction of other aromatic aldehydes with dimethyl phosphite under similar conditions resulted in phosphonates with similar levels of enantioselectivity (40–66%).

3.3 Aluminum Catalysts

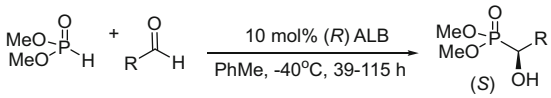
Shortly after the independent reports by Spilling and Shibuya that the lanthanum heterobimetallic catalyst LLB promoted the asymmetric phosphonylation of aldehydes, Shibasaki began the search for a more effective complex. After examining various binol–lanthanide–alkali metal combinations, he found a related catalytically active aluminum complex (ALB) [98]. The ALB complex is prepared by



Scheme 47 Binaphthylamine-derived Schiff base ligands and related structures [97]



Scheme 48 Preparation of ALB [98]



Scheme 49 Phosphonylation of aldehydes catalyzed by ALB [100]

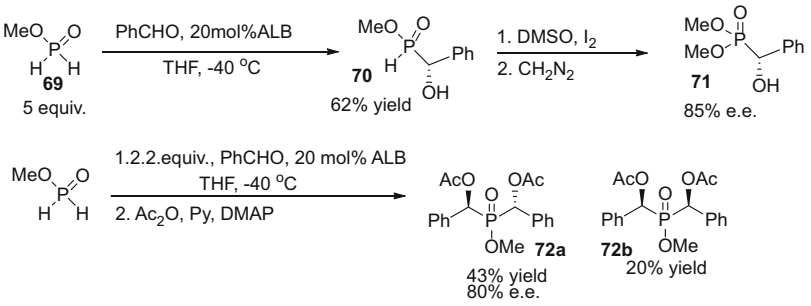
Table 13 Phosphonylation of aldehydes catalyzed by ALB [100]

Aldehyde[a]	Yield (%)	*ee* (%)
p-$O_2NC_6H_4CHO$	88	78
p-ClC_6H_4CHO	80	83
PhCHO	90	85
p-$MeOC_6H_4CHO$	88	78
PhCH=CHCHO	85	82
C_3H_7CH=CHCHO	53	55

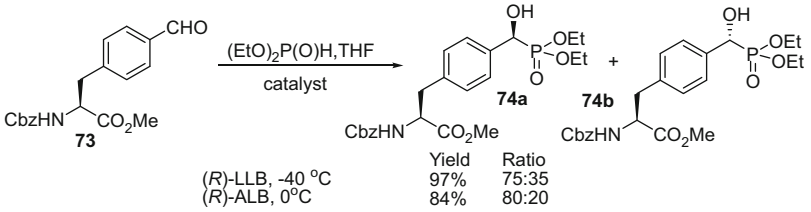
[a]Selected examples

reaction of 2 equiv. of binol with lithium aluminum hydride in THF (Scheme 48). The dried complex is redissolved in toluene.

Reaction of dimethyl phosphite with aldehydes using 10 mol% of ALB in toluene at −40°C gave hydroxyphosphonates in yields of 39–90% and enantioselectivities of 55–90% *ee* (Scheme 49, Table 13). ALB was superior to LLB for



Scheme 50 Hydrophosphinylation of aldehydes catalyzed by ALB [99]



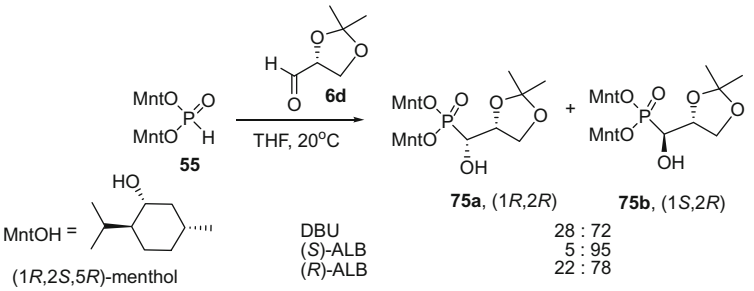
Scheme 51 Phosphonylation of a tyrosine-derived aldehyde [102]

aromatic aldehydes bearing electron-withdrawing substituents. (*R*)-ALB results in the (*S*)-phosphonate.

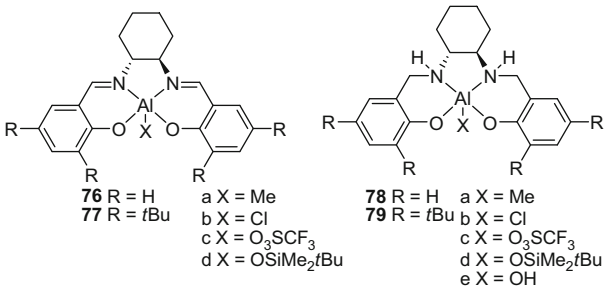
The application of ALB has been extended to hydrophosphinylation (Scheme 50) [99]. The ALB-catalyzed reaction of an excess of methyl phosphinate **69** with benzaldehyde in THF at −40°C gave the H-phosphinate **70** in 62% yield. The enantioselectivity (85% *ee*) was determined by oxidation to the phosphonate **71**. Alternatively, the ALB-catalyzed reaction of methyl phosphinate **69** with excess benzaldehyde followed by acetylation of the product gave the diastereoisomeric *anti***72a** and *syn***72b** α,α′-diacetoxyphosphinates in a 2:1 ratio. The enantiomeric excess of the major *anti*-diastereoisomer **72a** was determined to be 80% by conversion to the dihydroxyphosphinate (Dibal) and Mosher ester formation.

As part of an investigation into the synthesis of fluorophosphonate mimics of tyrosine phosphate, Shibuya [100] employed both LLB and ALB in the phosphonylation of the tyrosine-derived aldehyde **73**. Both catalysts resulted in the formation of hydroxyphosphonates **74** in good yield and modest diastereoisomeric ratios (Scheme 51). Unfortunately, conversion of the hydroxyl to fluoro using DAST resulted in epimerization of the stereocenter.

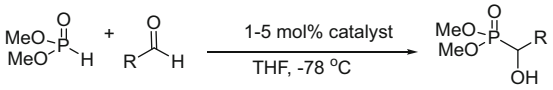
Kolodiazhnyi [101] studied the effect of ALB with a chiral phosphite and a chiral aldehyde as an example of triple asymmetric induction. The phospho-aldol reaction of di(1*R*,2*S*,5*R*)menthyl phosphite **55** with the (2*R*)-isopropylidine protected glyceraldehyde **6d** gave the (1*R*) and (1*S*) diastereoisomeric hydroxyphosphonates **75a** and **75b**. The reaction performed using DBU gave a 28:72 ratio



Scheme 52 Reaction of a chiral phosphite and a chiral aldehyde catalyzed by ALB [101]



Scheme 53 Aluminum complexes derived from salcyen and salcyan ligands [102–106]



Scheme 54 Phosphonylation of aldehydes catalyzed by aluminum complexes derived from salcyen and salcyan ligands [102–106]

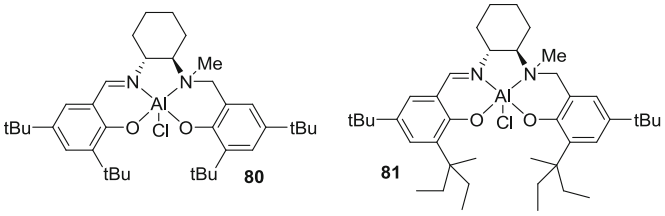
(*R*:*S*). No improvement was observed with (*R*)-ALB; however, with (*S*)-ALB the ratio improved to 5:95 (*R*:*S*) (Scheme 52). In the latter case, the inherent diastereoisomeric preference for the addition of dimenthyl phosphite to (*R*)-isopropylidene-protected glyceraldehyde **6d** was enhanced by the preference of ALB to form the (*R*)-hydroxyphosphonate. However, it is expected, based on Shibasaki's work, that this enhancement would be observed with (*R*)-ALB not (*S*)-ALB. There are conflicting statements in the abstract and the main text of this paper leading to confusion about the actual result.

In a series of papers, Kee et al. [102–106] reported preparation and characterization of aluminum complexes derived from salcyen and salcyan ligands as catalysts for the phospho-aldol reaction (Scheme 53). The complexes were formed by reaction of the parent ligand with trialkylaluminum or dialkylaluminum chloride. When the remaining substituent (X) is an alkyl, this group can be substituted by further reaction, e.g., with *t*BuMe$_2$SiOH. The complexes **76a** and **79e** catalyzed the addition of dimethyl phosphite to aromatic aldehydes (Scheme 54, Table 14). The

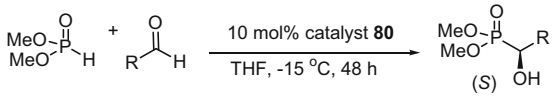
Table 14 Phosphonylation of aldehydes catalyzed by aluminum complexes derived from salcyen and salcyan ligands [102–106]

Aldehyde[a]	Catalyst	Conv (%)	*ee* (%)
PhCHO	**76a**	ND	41(*R*)
p-$BrFC_6H_4CHO$	**76a**	ND	24(*R*)
p-$CH_3C_6H_4CHO$	**76a**	ND	49(*R*)
p-$MeOC_6H_4CHO$	**76a**	ND	46(*R*)
p-$NO_2C_6H_4CHO$	**76a**	ND	17(*R*)
p-ClC_6H_4CHO	**76a**	ND	28(*R*)
PhCHO	**79e**	95	59(*S*)
p-$BrFC_6H_4CHO$	**79e**	85	42(*S*)
p-$CH_3C_6H_4CHO$	**79e**	88	53(*S*)
p-$MeOC_6H_4CHO$	**79e**	91	47(*S*)
p-$NO_2C_6H_4CHO$	**79e**	64	18(*S*)

[a]Selected examples



Scheme 55 Aluminum complexes of hybrid salen-type ligands [108–109]



Scheme 56 Phosphonylation of aldehydes catalyzed by aluminum complexes of hybrid salen-type ligands [108]

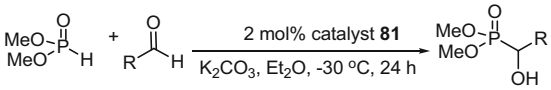
enantioselectivities were highest for aldehydes with *para* electron releasing groups topping out at 59% *ee*. The imine complex **76a** gave hydroxyphosphonates with the opposite configuration from the amine complex **79e** derived from the same diamine.

Katuski and Saito [107, 109] employed a hybrid salen-type ligand **80** with one imine and one tertiary amine in the phospho-aldol reaction (Scheme 55). They observed remarkable improvements in enantioselectivity over those observed by Kee [102–106]. Reaction of dimethyl phosphite with aldehydes in THF at 15°C using 10 mol% catalyst took 48 h and gave (*S*)-hydroxyphosphonates in 61–96% yield and with 83–94% *ee* (Scheme 56, Table 15). Aromatic aldehydes with *para* electron-withdrawing substituents gave the best selectivities. However, it is results with aliphatic aldehydes that make this catalyst useful.

In a follow-up paper, Katuski and coworkers [109] optimized the ligand structure **81** by the inclusion of the more sterically demanding tertiary hexyl group. However, the most important observation was that the addition of inorganic bases,

Table 15 Phosphonylation of aldehydes catalyzed by aluminum complexes of hybrid salen-type ligands [108]

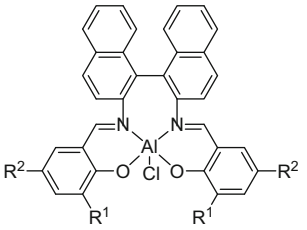
Aldehyde	Yield (%)	*ee* (%)
p-$NO_2C_6H_4CHO$	95	94
p-ClC_6H_4CHO	88	88
PhCHO	87	90
p-$MeOC_6H_4CHO$	87	81
o-ClC_6H_4CHO	96	91
PhCH=CHCHO	77	83
$PhCH_2CH_2CHO$	94	91
$(CH_3)_2CHCHO$	89	89
CH_3CH_2CHO	61	89



Scheme 57 Phosphonylation of aldehydes catalyzed by aluminum complexes of hybrid salen-type ligands [109]

Table 16 Phosphonylation of aldehydes catalyzed by aluminum complexes of hybrid salen-type ligands [109]

Aldehyde	Yield (%)	*ee* (%)
4-$NO_2C_6H_4CHO$	98	98
4-ClC_6H_4CHO	95	98
PhCHO	99	97
4-$MeOC_6H_4CHO$	98	93
2-ClC_6H_4CHO	94	97
PhCH=CHCHO	97	95
$PhCH_2CH_2CHO$	93	97
$(CH_3)_2CHCHO$	96	96
$nC_7H_{15}CHO$	90	96

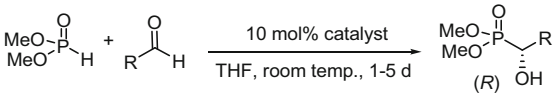


82a, $R^1 = R^2 = F$
82b, $R^1 = t$Bu, $R^2 = NO_2$
82c, $R^1 = R^2 = t$Bu
82d, $R^1 = t$Bu, $R^2 = H$
82e, $R^1 = t$Bu, R^2 = Br
82f, $R^1 = t$Bu, R^2 = I
82g, $R^1 = t$Bu, R^2 = OMe

Scheme 58 Aluminum complexes of binaphthylamine-derived Schiff's base ligands [110]

such as potassium carbonate, led to significant enhancements in both rate and enantioselectivity (Scheme 57, Table 16).

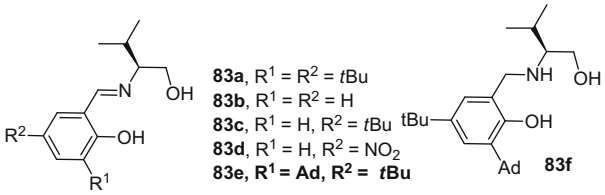
Katsuki et al. [110] also prepared a series of binaphthylamine Schiff's base aluminum complexes **82a–g** (Scheme 58). The reactivity and selectivity of the aluminum complexes was explored using the addition of dimethyl phosphite to



Scheme 59 Phosphonylation of aldehydes catalyzed by aluminum complexes of binaphthylamine-derived Schiff's base ligands [110]

Table 17 Phosphonylation of aldehydes catalyzed by aluminum complexes of binaphthylamine-derived Schiff's base ligands [110]

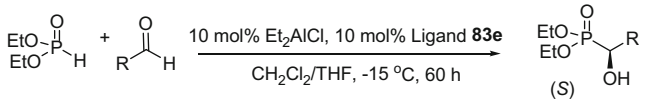
Aldehyde	Yield (%)	*ee* (%)
PhCHO	62	79
4-FC_6H_4CHO	69	82
4-$MeOC_6H_4CHO$	55	79
4-$CH_3C_6H_4CHO$	82	80
2-FC_6H_4CHO	69	80
2-$CH_3C_6H_4CHO$	79	75
$PhCH_2CH_2CHO$	71	83
Cyclohexyl	86	86
n-Hexyl	79	86
PhCH=CHCHO	82	64



Scheme 60 Valinol-derived Schiff's base ligands [111]

p-chlorobenzaldehyde as a standard reaction. Complex **82e** gave the best selectivity and was examined further. Reaction of dimethyl phosphite with aldehydes in THF at room temperature using 10 mol% catalyst **82e** took 1–5 days and gave (*R*)-hydroxyphosphonates in 55–86% yield and with 64–86% *ee* (Scheme 59, Table 17). Although complex **82e** gives decent selectivities with aliphatic aldehydes, it is probably not the best choice for aromatic or unsaturated aldehydes and the reactions times are long.

Feng and coworkers [111] prepared series of valinol-derived Schiff's base ligands **83a–e** (Scheme 60). These ligands were complexed with Et_2AlCl and the catalytic activity of the resulting complexes was explored using the addition of diethylphosphite to benzaldehyde as a probe reaction. The best results were achieved using ligand **83e** which was explored further. Reactions of an extensive range of aldehydes with diethyl phosphite with 10 mol% of catalyst and run in a mixture of THF and CH_2Cl_2 at −15°C took 60 h to go to completion and gave hydroxyphosphonates in 73–96% yield and 85–97% *ee* (Scheme 61, Table 18).

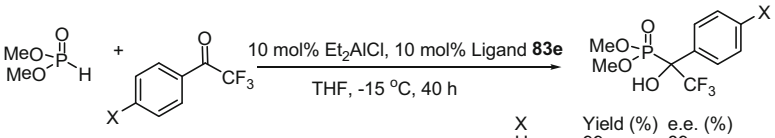


Scheme 61 Phosphonylation of aldehydes catalyzed by aluminum complexes of valinol-derived Schiff's base ligands [111]

Table 18 Phosphonylation of aldehydes catalyzed by aluminum complexes of valinol-derived Schiff's base ligands [111]

Aldehyde[a]	Yield (%)	*ee* (%)
4-FC_6H_4CHO	87	97
4-$NO_2C_6H_4CHO$	81	92
PhCHO	96	95
4-$MeOC_6H_4CHO$	94	97
4-$CH_3C_6H_4CHO$	89	97
2-$CH_3C_6H_4CHO$	93	96
PhCH=CHCHO	73	85
2-Furyl	89	94
$PhCH_2CH_2CHO$	93	87
*n*BuCHO	92	85
*t*BuCHO	73	91

[a]Selected examples



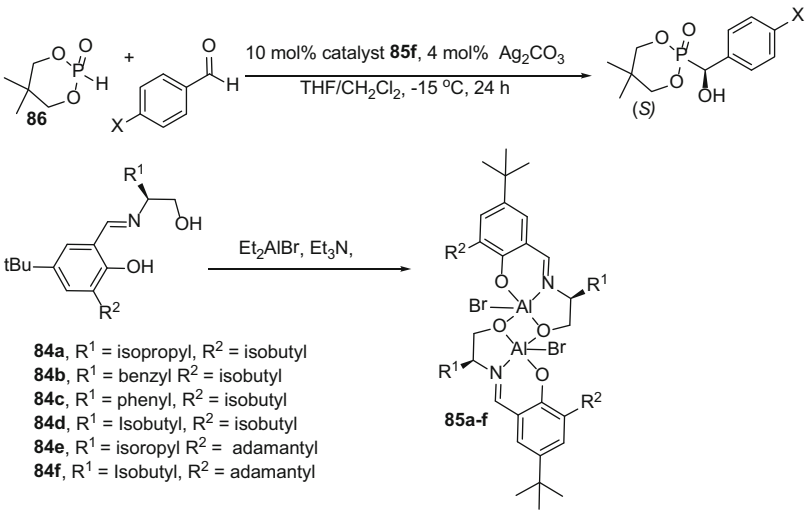
X	Yield (%)	e.e. (%)
H	99	89
Me	82	87
MeO	85	90
Br	87	85
Cl	96	85
F	93	86

Scheme 62 Addition of dimethyl phosphite to aryl trifluoromethyl ketones [112]

Interestingly, reaction using catalyst **83e** exhibited a nonlinear effect, which suggests that the complex is not monomeric.

The aluminum chloride complex derived from ligand **83e** was also shown [112] to be an effective catalyst for the addition of dimethyl phosphite to aryl trifluoromethyl ketones (Scheme 62). Reaction using 10 mol% of the complex in THF at −15°C gave the tertiary hydroxyphosphonates in good yield and with enantiomeric excesses in the mid- to high 80%s. Feng also used similar ligand architectures with some titanium complexes (see titanium section).

He et al. [113] prepared a series of six amino alcohol-derived Schiff's base ligands **84a–f** (Scheme 63) and their corresponding dimeric aluminum bromide complexes **85a–f**. These complexes **85** catalyzed the addition of cyclic phosphites



Scheme 63 Dimeric aluminum complexes from amino alcohol-derived Schiff's base ligands [113]

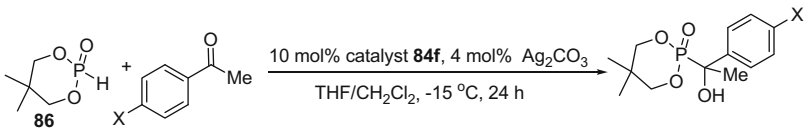
Table 19 Phosphonylation of aldehydes catalyzed by dimeric aluminum complexes [114]

Aldehyde[a]	Yield (%)	*ee* (%)
PhCHO	82	99
4-$CH_3C_6H_4CHO$	84	99
3-$CH_3C_6H_4CHO$	83	99
4-ClC_6H_4CHO	75	99
4-BrC_6H_4CHO	82	99
4-$MeOC_6H_4CHO$	79	99
2-Furyl	68	99
2-Thienyl	79	99

[a]Selected examples

86 to both aldehydes (Scheme 63, Table 19) and acetophenones (Scheme 64, Table 20) with good yields and enantioselectivities.

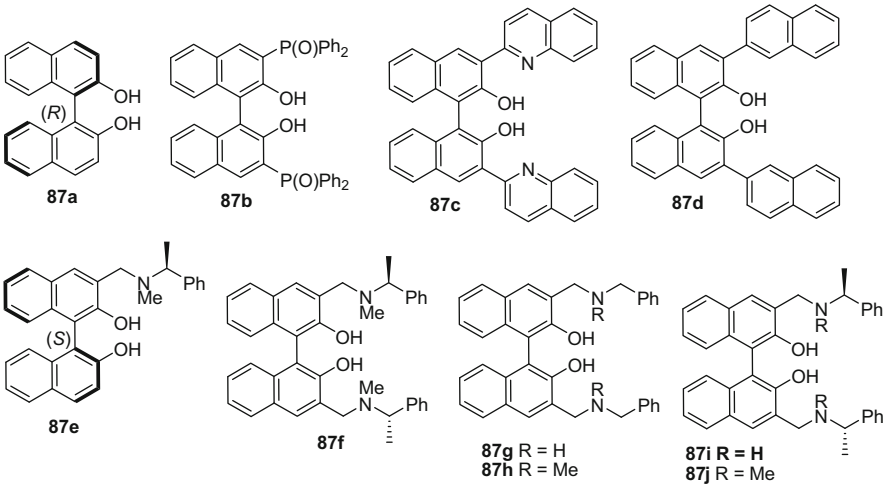
After selecting aluminum as the metal of choice, Feng and coworkers [115] screened a large array of binaphthol-based bifunctional ligands (Scheme 65). The screen was performed by reacting the ligand (10 mol%) in situ with Et_2AlCl (10 mol%) in THF to form the aluminum complex which was then used as catalyst in the reaction of diethyl phosphite with benzaldehyde at 0°C. Ligand **87j** gave the best combination of yield (85%) and enantioselectivity (70%). Reactions with ligand **87j** were optimized by variations in solvent, concentrations, aluminum source, and the addition of molecular sieves giving marginal improvement. Using the optimized reaction conditions (10 mol% ligand, 10 mol% Et_2AlCl, 10 mg 3-Å molecular sieves, THF, 0°C), diethyl phosphite was reacted with a range of aromatic, unsaturated, and aliphatic aldehydes (Scheme 66, Table 21) to give



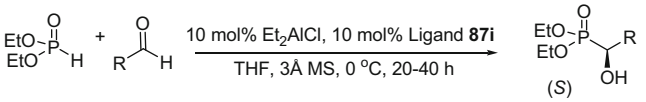
Scheme 64 Phosphonylation of acetophenones catalyzed by dimeric aluminum complexes [113]

Table 20 Phosphonylation of acetophenones catalyzed by dimeric aluminum complexes [113]

Acetophenone	Yield (%)	*ee* (%)
4-$ClC_6H_4C(=O)Me$	68	98
3-$ClC_6H_4C(=O)Me$	70	97
2-$ClC_6H_4C(=O)Me$	68	99
4-$BrC_6H_4C(=O)Me$	70	95
3-$BrC_6H_4C(=O)Me$	71	95
4-$FC_6H_4C(=O)Me$	70	96
4-$MeOC_6H_4C(=O)Me$	67	98
2-ThienylC(=O)Me	68	97



Scheme 65 Binaphthol-based bifunctional ligands [114]

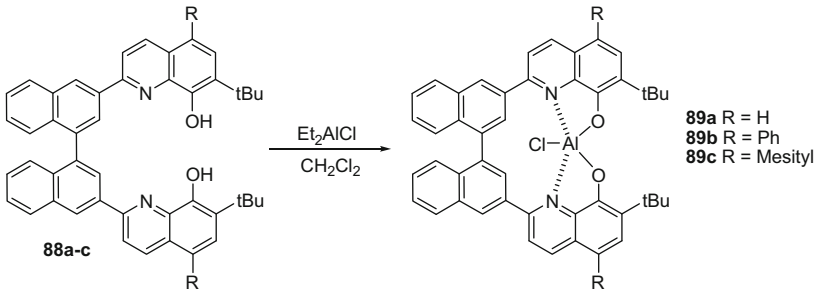


Scheme 66 Phosphonylation of aldehydes catalyzed by aluminum complexes of binaphthol-based bifunctional ligands [114]

Table 21 Phosphonylation of aldehydes catalyzed by aluminum complexes of binaphthol-based bifunctional ligands [114]

Aldehyde[a]	Yield (%)	*ee* (%)
PhCHO	88	75
4-$MeOC_6H_4CHO$	74	87
4-$MeOC_6H_4CHO$	71	81
4-$CH_3C_6H_4CHO$	91	83
4-ClC_6H_4CHO	88	65
4-FC_6H_4CHO	87	62
4-$NO_2C_6H_4CHO$	88	67
PhCH=CHCHO	86	63
2-Thienyl	75	45
$PhCH_2CH_2CHO$	99	75
nC_4H_9CHO	85	77

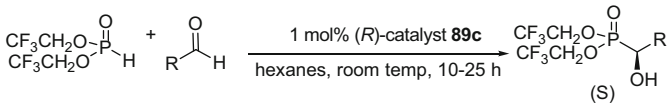
[a]Selected examples



Scheme 67 Tethered bis(8-quinolinao) (TBox) ligands [115]

hydroxyphosphonates in good to excellent yield (71–99%) and modest to good enantiomeric excess (45–83%). Reaction times varied from 20 to 40 h.

Yamamoto recognized [115] that ligand **88a**, developed in his lab for other reactions, had potential for the phospho-aldol reaction (Scheme 67). Using 10 mol % the corresponding aluminum chloride complex, reaction of a series of phosphites with benzaldehyde was studied. Typical phosphites (Me, Et, Ph) gave low selectivities and yields. In contrast, reaction of bis(trifluoroethyl)phosphite resulted in hydroxyphosphonate in 94% yield and with 78% *ee*. This result was rationalized on the basis that the first step in the reaction is deprotonation of the phosphite to give a more nucleophilic species. The deprotonation would be favored by electron-withdrawing groups, such as trifluoroethyl, on the phosphite. With the appropriate phosphite identified, ligand modification resulting in **88c** was used to improve both the reaction rate and selectivity. Finally, the reaction of bis(trifluoroethyl)phosphite with a range of aldehydes and 1 mol% catalyst in hexanes at room temperature gave hydroxyphosphonates in 91–95% and 82–97% *ee* (Scheme 68, Table 22). It was also demonstrated that the trifluoromethyl ester could be hydrolyzed to the phosphonic acid using conc. HCl in MeOH with racemization.



Scheme 68 Reaction of bis(trifluoroethyl)phosphite with aldehydes catalyzed by aluminum complexes of tethered bis(8-quinolinao) (TBox) ligands [115]

Table 22 Reaction of bis (trifluoroethyl)phosphite with aldehydes catalyzed by aluminum complexes of tethered bis(8-quinolinao) (TBox) ligands [115]

Aldehyde[a]	Yield (%)	*ee* (%)
PhCHO	95	96
2-Naphthyl	98	95
4-ClC_6H_4CHO	94	95
4-BrC_6H_4CHO	96	95
4-NO_2	93	95
4-$MeOC_6H_4CHO$	93	92
4-$CH_3C_6H_4CHO$	94	97
2-$MeOC_6H_4CHO$	93	94
2-$CH_3C_6H_4CHO$	93	95
PhCH=CHCHO	95	93
Cyclohexyl	95	82
n-Hexyl	91	82

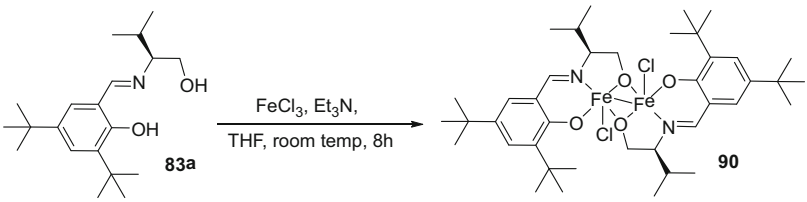
[a]Selected examples

Hu et al. [116, 117] performed computational studies on the mechanism of hydrophosphonylation of aldehydes catalyzed by Schiff's base and other aluminum complexes.

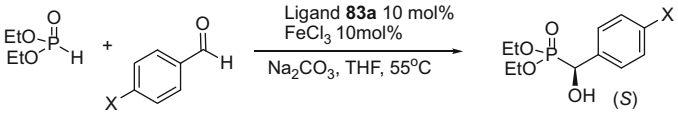
3.4 Iron Catalysts

There have been some recent reports of iron-based catalysts. Muthupandi and Sekar [118] prepared iron(III) complexes from 11 amino alcohol-derived Schiff's base ligands (Scheme 69). The best results were observed with complex **90**. Addition of diethyl phosphite to a series of aromatic aldehydes using 10 mol% ligand, 10 mol% $FeCl_3$, and sodium carbonate in THF at 55°C for 10–29 h gave (*S*)-hydroxyphosphonates in excellent yields, but with modest enantioselectivities (Scheme 70, Table 23). Both the selectivity and yield improved with the increased reaction temperature. In comparison to the corresponding Schiff's base aluminum catalyst, the iron complexes are less reactive (requiring elevated temperature) and much less selective.

Boobalan and Chen [119] prepared iron complexes from a series of camphor-based Schiff's base ligands (Scheme 71). These iron complexes (5 mol%) were examined as catalysts using the addition of diisopropyl phosphite to benzaldehyde



Scheme 69 Dimeric iron complexes from amino alcohol-derived Schiff's base ligands [118]

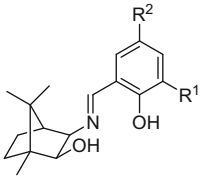


Scheme 70 Phosphonylation of aldehydes catalyzed by dimeric iron complexes [118]

Table 23 Phosphonylation of aldehydes catalyzed by dimeric iron complexes [118]

Aldehyde[a]	Yield (%)	*ee* (%)
4-$NO_2C_6H_4CHO$	96	64
4-FC_6H_4CHO	92	58
4-ClC_6H_4CHO	95	53
PhCHO	92	50
4-$CH_3C_6H_4CHO$	88	58
3-$CH_3C_6H_4CHO$	84	71
2-Furyl	78	52
2-Thienyl	81	68

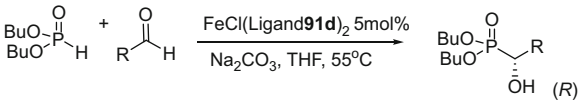
[a]Selected examples



91a $R^1 = R^2 = H$
91b $R^1 = R^2 = t$Bu
91c $R^1 = R^2 = Me$
91d $R^1 = Me$, $R^2 = H$
91e $R^1 = H$, $R^2 = Me$
91f $R^1 = t$Bu, $R^2 = H$
91g $R^1 = H$, $R^2 = t$Bu

Scheme 71 Dimeric iron complexes from camphor-derived Schiff's base ligands [119]

in THF at room temperature using sodium carbonate as a heterogeneous base. Ligand **91d** showed the best selectivity and was studied further by varying the phosphite, base, solvent, and temperature. Ultimately, dibutyl phosphite was reacted with a wide range of aldehydes using 5 mol% catalyst and Et_3N in THF at −25°C to give (*R*)-hydroxyphosphonates in excellent yield and good selectivity (79–95% *ee*) (Scheme 72, Table 24). In several cases the enantiopurity of the product could be improved by recrystallization.



Scheme 72 Phosphonylation of aldehydes catalyzed by camphor-derived dimeric iron complexes [119]

Table 24 Phosphonylation of aldehydes catalyzed by camphor-derived dimeric iron complexes [119]

Aldehyde[a]	Time (h)	Yield (%)	*ee* (%)
4-FC_6H_4CHO	48	90	83
4-BrC_6H_4CHO	48	90	85
PhCHO	35	99	93
4-$CH_3C_6H_4CHO$	60	99	88
3-$CH_3C_6H_4CHO$	60	99	85
4-MeO	72	90	95
2-Furyl	72	91	84
2-Thienyl	73	92	89
PhCH=C(Me)CHO	72	80	89
$(CH_3)_2CHCHO$	90	90	83

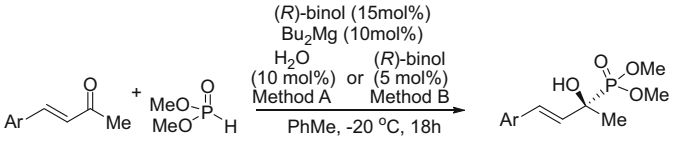
[a]Selected examples

3.5 Magnesium Catalysts

Phosphonylation of unsaturated ketones presents an interesting challenge. In theory, the phosphite nucleophile can undergo 1,4- or 1,2-addition. Furthermore, the tertiary hydroxyphosphonates formed by 1,2 addition are prone to phospha Brook rearrangement or retroreaction. Although magnesium binaphtholates catalyze 1,4-addition of diaryl phosphine oxides to unsaturated esters, the related reaction with dimethyl phosphite and unsaturated ketones gives the 1,2 addition products [120]. The catalyst is formed by reaction of dibutyl magnesium (10 mol%) with binol (15 mol%), followed by the addition of water (10 mol%, Method A) or more binol (5 mol%, Method B). Reaction of dimethyl phosphite with β-aryl-α,-β-unsaturated ketones in toluene at −20°C gave tertiary hydroxy phosphonates in 59–96% chemical yield and with 81–86% enantiomeric excess (Scheme 73, Table 25). In some cases the enantiopurity could be improved to >90% by a single crystallization.

3.6 Organocatalysts

Research on the catalytic asymmetric phospho-aldol reaction has come full circle, from the original work of Wynberg on quinine catalysis to the recent advent of new organocatalysts. However, Kee [121] should be recognized for his description of



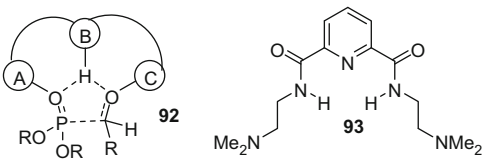
Scheme 73 Magnesium binaphtholate catalyzed addition of dimethyl phosphite to unsaturated ketones [120]

Table 25 Magnesium binaphtholate-catalyzed addition of dimethyl phosphite to unsaturated ketones [120]

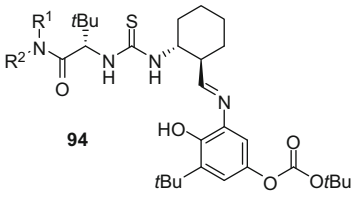
Ketone (Ar)	Method	Yield (%)	*ee* (%)
Ph	A	89	86
3-$CH_3C_6H_4$	A	77	86
3,5-$Cl_2C_6H_3$	A	96	81
3,5-$(MeO)_2C_6H_3$	A	81	85
2-Naphthyl	A	74	84
2-Furyl	A	79	83
3-Thienyl	A	63	82
4-ClC_6H_4	B	82	81
4-$MeOC_6H_4$	B	59	82

1,4/1,2 adduct 1:>99

Scheme 74 Amphoteric catalysts [121]



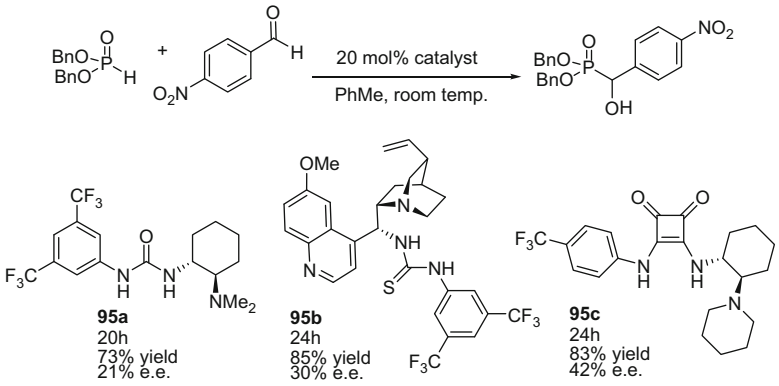
Scheme 75 An organocatalyst for the phosphonylation of imines [122]



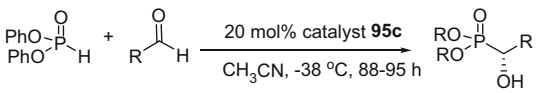
the "amphoteric receptor," where he described many of the key elements of modern organocatalysts which are effective in the phospho-aldol reaction (Scheme 74).

A catalyst for the addition of dialkyl phosphites to imines was described earlier in renaissance of organocatalysis [122]. However, such catalysts (e.g., **94** in Scheme 75) were ineffective for the corresponding addition to aldehydes.

It appears that efficient catalysis requires both hydrogen bond activation of the aldehyde and a tertiary amine base to help bind and tautomerize the phosphite. To this end, Herrera and co-workers [123] examined three catalysts using the addition of dibutyl phosphite to *p*-nitro benzaldehyde as the test reaction (Scheme 76). All



Scheme 76 Organocatalysts for the addition of dibutyl phosphite to *p*-nitro benzaldehyde [123]



Scheme 77 Phosphonylation of aldehydes catalyzed by squaric acid **95c** [123]

Table 26 Phosphonylation of aldehydes catalyzed by squaric acid 95c [123]

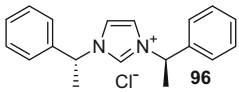
Aldehyde[a]	Yield (%)	*ee* (%)
4-$NO_2C_6H_4CHO$	88	98
4-$CH_3C_6H_4CHO$	80	81
1-Naphthyl	80	93
PhCHO	81	82
4-BrC_6H_4CHO	84	72
4-ClC_6H_4CHO	82	80
4-CNC_6H_4CHO	85	98
$PhCH_2CH_2CHO$	68	77
Cyclohexyl	75	98
*t*Bu	85	73

[a]Selected examples

three compounds were active catalysts and gave hydroxyphosphonate with low selectivity. The squaric acid derivative gave the most promising result and was studied further. A series of reactions to screen phosphite structures revealed that diphenyl phosphite gave the best results in terms of both selectivity and yield (83% yield, 46% *ee*). Further improvement (88% yield, 76% *ee*) was realized by switching to acetonitrile as solvent and running the reaction at low temperature (−38°C).

Using the best conditions (20 mol% catalyst **95c**, CH_3CN, −38°C), the reactions of diphenyl phosphite with a range of aromatic and aliphatic aldehydes were performed (Scheme 77, Table 26). The yield of (*R*)-hydroxyphosphonates ranged from 72% to 98% and the selectivity from 68% to 88% *ee*.

Scheme 78 An NHC catalyst [124]



96

Table 27 Reaction of dimethyl phosphite with methyl arylglyoxylaates catalyzed by 97a

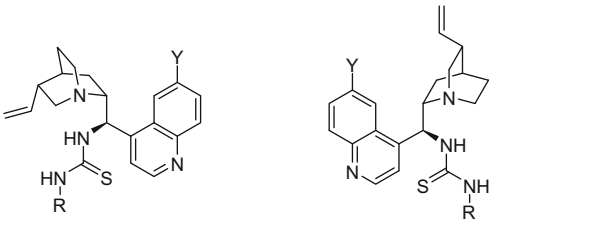
Aldehyde	Yield (%)	*ee* (%)
Ph	92	90
3-$CH_3C_6H_4$	92	90
4-$CH_3C_6H_4$	90	90
4-$MeOC_6H_4$	90	91
3-FC_6H_4	94	90
4-FC_6H_4	90	90
4-ClC_6H_4CHO	85	90
2-Thiophenyl	91	91
2-Naphthyl	86	88

Table 28 Reaction of dimethyl phosphite with methyl arylglyoxylates catalyzed by 87g

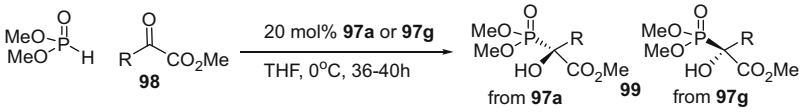
Aldehyde	Yield (%)	*ee* (%)
Ph	94	88
3-$CH_3C_6H_4$	91	90
4-$CH_3C_6H_4$	91	87
4-$MeOC_6H_4$	84	81
3-FC_6H_4	95	90
4-FC_6H_4	92	86
4-ClC_6H_4CHO	85	80
2-Thiophenyl	90	84
2-Naphthyl	86	84

NHCs were shown [124] to catalyze the phospho-aldol reaction using 10 mol% loading in CH_2Cl_2 at room temperature (Scheme 78). However, reaction of diethyl phosphite catalyzed chiral NHC (X=*t*BuOK) gave, after 48 h, racemic hydroxyphosphonate in 76% yield.

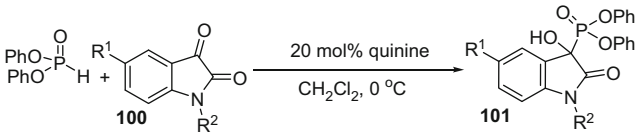
More reactive carbonyl substrates, such methyl phenyl glyoxylate, are excellent substrates for the organocatalytic phospho-aldol reaction. The cinchona alkaloid-derived organocatalysts **97** were screened for activity in the reaction of dimethyl phosphite to methyl phenyl glyoxylate [125]. Catalysts **97a** and **97g** in THF gave the best results in terms of yield and selectivity, giving hydroxyphosphonates with the opposite rotations (Schemes 79 and 80). The reaction of dimethyl phosphite with several methyl arylglyoxylates catalyzed by **97a** (Table 27) and **97g** (Table 28) in THF at 0°C were studied. In general, catalyst **97a** gave slightly higher selectivities with comparable yields. This reaction has been studied using computational methods [126].



Scheme 79 Cinchona alkaloid-derived thiourea organocatalysts [125]



Scheme 80 Phosphonylation of glyoxylates catalyzed by cinchona alkaloid-derived thioureas [125]



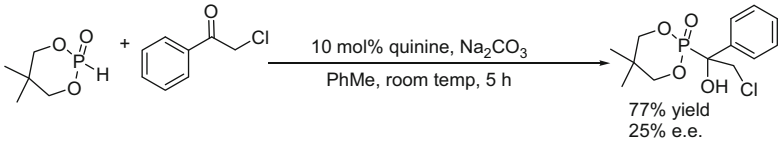
Scheme 81 Phosphonylation of isatins catalyzed by quinine [127]

Isatins are another example of alpha-dicarbonyl substrates which have been studied in the organocatalytic phospho-aldol reaction. Cinchona alkaloids, their corresponding thiourea derivatives, and the cyclohexane diamine-derived thioureas were screened as catalysts in the addition of phenyl phosphite to *N*-methyl isatin [127]. Surprisingly, quinine gave the best combination of good yield (53%) and good selectivity (59% *ee*). Solvent optimization identified CH_2Cl_2 as the best solvent, which resulted in significant improvement in yield (99%) and modest improvement in selectivity (67% *ee*). Final various *N*-protected isatins with substituents on the aromatic ring were reacted with diphenyl phosphite using 20 mol% quinine in CH_2Cl_2 at 0°C to give phosphonate in good to excellent yields (60–99%) and modest enantioselectivity (25–67% *ee*) (Scheme 81, Table 29).

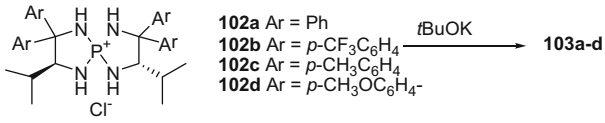
Quinine was also the catalyst of choice in the addition of cyclic phosphites to a α-chloroketones [128]. Reaction of the cyclic phosphite with 2-chloroacetophenone using 10 mol% quinine and sodium carbonate in toluene at room temperature gave the tertiary hydroxy phosphonate in 77% yield and 25% *ee* (Scheme 82). Attempts

Table 29 Phosphonylation of isatins catalyzed by quinine [127]

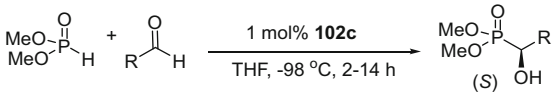
R^1	R^2	Yield (%)	*ee* (%)
H	CH_3	99	67
H	CH_3CH_2	96	64
H	$PhCH_2$	89	51
H	$BrCH_2CH_2$	99	36
H	$CH_2{=}CHCH_2$	98	48
CH_3	CH_3	88	62
F	CH_3	80	52
Cl	CH_3	70	25
Br	CH_3	60	44
CH_3	$PhCH_2$	93	58
F	$PhCH_2$	77	41



Scheme 82 Reaction of a cyclic phosphite with 2-chloroacetophenone catalyzed by quinine [128]



Scheme 83 Chiral phosphonium salts [129]



Scheme 84 Phosphonylation of aldehydes catalyzed by chiral phosphonium salts [129]

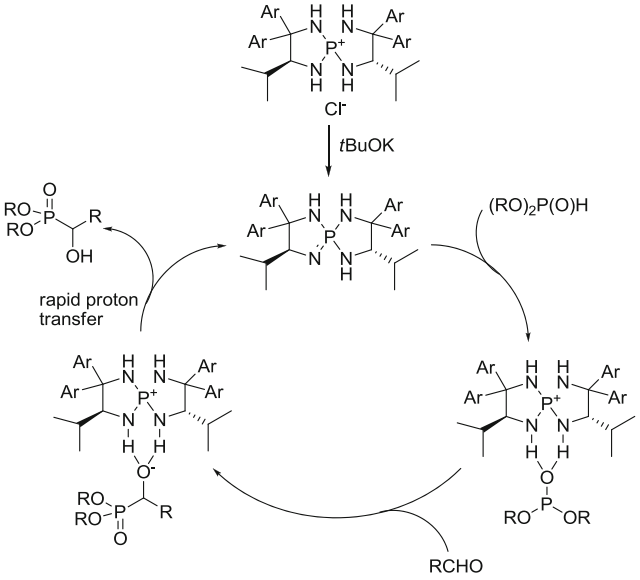
to optimize the reaction by varying added base, stoichiometry, and temperature gave some improvement in yield, but only a modest increases in selectivity.

In 2009 Ooi et al. reported [129] on the synthesis and application of one of the most remarkable catalysts to date. The catalysts (**103a–d**), prepared by treating the phosphonium salts (**102a–d**) with potassium *tert*-butoxide (Scheme 83), catalyzed the addition of dimethyl phosphite to a wide range of aldehydes to give hydroxyphosphonates in excellent yield with very high selectivity (Scheme 84, Table 30). The catalyst loading was as low as 1 mol%. However, the best selectivity was observed at −98°C, which was not a very practical temperature for long

Table 30 Phosphonylation of aldehydes catalyzed by chiral phosphonium salts [129]

Aldehyde[a]	Yield (%)	*ee* (%)
4-FC_6H_4CHO	97	97
2-FC_6H_4CHO	97	98
PhCHO	97	98
4-$MeOC_6H_4CHO$	99	94
4-$CH_3C_6H_4CHO$	91	96
2-$CH_3C_6H_4CHO$	98	96
3-BrC_6H_4CHO	98	98
PhCH=CHCHO	90	96
2-Furyl	90	98
$PhCH_2CH_2CHO$	99	91

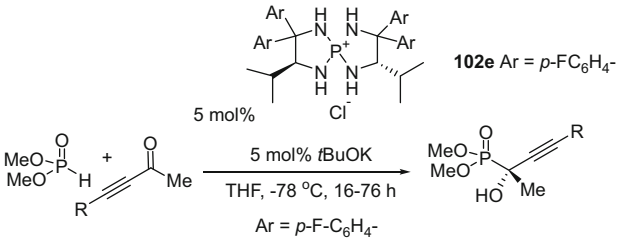
[a]Selected examples



Scheme 85 Proposed catalytic cycle for phosphonium salts [129]

reaction times (Scheme 84). A catalytic cycle was proposed (Scheme 85) for the phosphonylation reaction.

Further studies [130] demonstrated the application of these catalysts to the phosphonylation of enynes. The catalyst (**103e**, 5 mol%), prepared by treating the phosphonium salt (**102e**) with potassium *tert*-butoxide, catalyzed the addition of dimethyl phosphite in THF at −78°C to a wide range of ynones to give hydroxyphosphonates in excellent yield with very high selectivity (Scheme 86, Table 31).



Scheme 86 Phosphonylation of ynones catalyzed by chiral phosphonium salts [130]

Table 31 Phosphonylation of ynones catalyzed by chiral phosphonium salts [130]

Ynone, R =	Yield (%)	*ee* (%)
Et	73	90
$Me(CH_2)_8$	98	88
Cyclohexyl	96	90
Me_2CHCH_2	97	79
$BnOCH_2$	97	81
$tBuMe_2SiO(CH_2)_2$	96	87
$Me_3SiO(Me)_2C$	96	88
Me_3Si	96	91

4 Summary

The more than 50 years of phospho-aldol reaction of dialkyl phosphites has witnessed enormous growth in the interest and applications of this reaction. In this chapter we have demonstrated the evolution of the diastereoselective and enantioselective additions of dialkyl phosphites to aldehydes and ketones, otherwise called the phospho-aldol, Pudovik, or Abramov reactions.

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Recent Advances in *H*-Phosphonate Chemistry. Part 1. *H*-Phosphonate Esters: Synthesis and Basic Reactions

Michal Sobkowski, Adam Kraszewski, and Jacek Stawinski

Abstract This review covers recent progress in the preparation of *H*-phosphonate mono- and diesters, basic studies on mechanistic and stereochemical aspects of this class of phosphorus compounds, and their fundamental chemistry in terms of transformation of P–H bonds into P-heteroatom bonds. Selected recent applications of *H*-phosphonate derivatives in basic organic phosphorus chemistry and in the synthesis of biologically important phosphorus compounds are also discussed.

Keywords *H*-Phosphonates · Mechanism · Nucleotide analogues · Organic catalysis · Oxidative coupling · Stereochemistry

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Abbreviations

A, C, G, T, U	Adenosine, cytidine, guanosine, thymidine, uridine
AA	Amino acid
ACN	Acetonitrile
AIBN	2,2′-Azobis(isobutyronitrile)
AZT	3′-Azido-3′-deoxythymidine
BOPCl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
CE	2-Cyanoethyl
d4T	2′,3′-Didehydro-3′-deoxythymidine
DBU	1,8-Diazabicyclo [5.4.0]undec-7-ene
DCA	Dichloroacetic acid
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEP	Diethyl *H*-phosphonate, $(EtO)_2P(O)H$
DIPP	Diisopropyl *H*-phosphonate, $(i\text{-}PrO)_2P(O)H$
DMAP	*N*,*N*-Dimethylaminopyridine
DMP	Dimethyl *H*-phosphonate, $(MeO)_2P(O)H$
DMTr	4,4′-Dimethoxytrityl
DPCP	Diphenyl chlorophosphate
DPP	Diphenyl *H*-phosphonate, $(PhO)_2P(O)H$
Fm	(9*H*-Fluoren-9-yl)methyl
IL	Ionic liquid
NEPCl	2-Chloro-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (neopentylene chlorophosphate)
NTP	Nucleoside 5′-triphosphate
Nu	Nucleoside
PEG	Poly(ethylene glycol)
PIm_3	Tri(1*H*-imidazol-1-yl)phosphine
PU	Polyurethane
Pv	Pivaloyl
SET	Single electron transfer
TEA	Triethylamine
TFA	Trifluoroacetic acid
TMTr	4,4′,4″-Trimethoxytrityl
TPP	Triphenylphosphine

1 Introduction

Mono- and diesters of phosphonic acid (H_3PO_3), referred to as *H*-phosphonates, are four-coordinate compounds and contain a characteristic H–P=O structural motif, which governs their unique chemical properties.

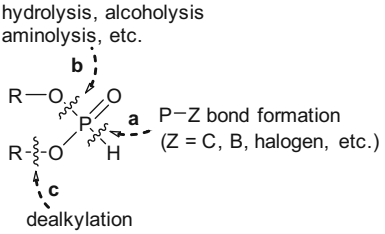


Fig. 1 Heterolytic bond breaking in *H*-phosphonates

Depending on the conditions and type of the reagents used, the reactions of *H*-phosphonate esters may involve (1) heterolytic breaking of the P–H bond which is instrumental for the formation of P–C, P–B, P–Cl, P–Br, P–I, P–metal bonds, etc. (path a), (2) P–O bond cleavage (as in hydrolysis, alcoholysis or transesterification, aminolysis, sulfhydrolysis, etc.) (path b), or (3) O–C bond scission, e.g., dealkylation (path c). These options are outlined in Fig. 1 and are valid both for mono- and diesters.

In addition to the above processes, homolytic bond breaking may generate reactive free radical species, and this topic will be discussed in Part 2 of this contribution, along with other reactions involving the P–H → P–C type transformations.

H-Phosphonate mono- and diesters differ noticeably in their chemical properties. The monoesters show considerable resistance to oxidation, base- and acid-catalyzed hydrolysis, or solvolysis. This stability is commonly attributed to the relatively high electron density in the vicinity of the phosphorus atom in their anionic form, $(RO)PHO_2^-$, which hampers a nucleophilic attack as well as abstraction of a P–H proton to form a tervalent, nucleophilic form [1, 2]. However, *H*-phosphonate monoester anions possess a nucleophilic oxygen atom, which can react rapidly with a range of condensing agents (e.g., acyl chlorides), producing highly reactive species bearing a good leaving group. Synthesis of *H*-phosphonate monoesters, their properties, and methods for their further esterification are important topics of studies in the chemistry of derivatives of biomolecules, while simple alkyl/aryl monoesters seem to attract less attention.

H-Phosphonate diesters, $(R^1O)(R^2O)P(O)H$, as neutral species, are significantly more reactive than the monoesters, since they are better targets for a nucleophilic attack, and are more prone for ternalization (conversion into trivalent form). Nevertheless, they remain reasonably stable under acidic, neutral, or moderately basic conditions, and they can be kept safely in air without oxidation, although a slow hydrolysis caused by humidity may occur. In contrast to the monoesters, *H*-phosphonate diesters are hardly activated with condensing agents, and usually cannot be esterified into phosphite triesters.

By far the synthetically most useful *H*-phosphonate diesters are those bearing two different alcohol moieties, especially those derived from biologically important natural products. Since synthetic methods and goals in the area of simple alkyl/aryl *H*-phosphonate esters vs esters of biomolecules are often significantly different, this criterion was chosen to organize the material in this chapter.

2 Alkyl/Aryl *H*-Phosphonate Esters

2.1 Synthesis

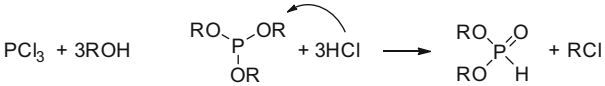
In industry, symmetrical *H*-phosphonate diesters are typically produced by esterification of phosphorus trichloride under base-promoted or base-free conditions. The latter version, known as McCombie's process [3] (Scheme 1), was recently applied as a first step in procedures leading to various phosphoramidate polydentate ligands [4], hydrazones [5], and phosphate-based ionic liquids [6]. The yields of *H*-phosphonates could be excellent (93–94%) [5], although in other cases they were 'moderate' [6] or variable (35–78%) [4].

For compounds resistant to dealkylation, e.g., those containing fluoroalkyl groups, an alternative approach developed by Timperley et al. in 2002 [7] can be used, as was shown in the preparation of bis(2,2,2-trifluoroethyl) *H*-phosphonate (not isolated) [8] (Scheme 2).

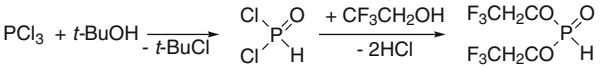
It is worth noting that the group of Montchamp has undertaken efforts to eliminate the dangerous and environmentally unfriendly PCl_3 from organophosphorus chemistry [9, 10]. One of their proposals is a new method for synthesis of *H*-phosphonate diesters based on oxidative coupling of hypophosphorous acid (H_3PO_2) with alcohols [11]. The two-stage process starts with esterification of H_3PO_2 with an alcohol [12, 13] towards a hypophosphite ester $(RO)P(O)H_2$, which in the presence of a nickel catalyst (5 mol%) undergoes oxidative coupling [14] with an excess of alcohol (3 equiv.) to yield the final *H*-phosphonate diester in high to excellent yields [11] (Scheme 3).

For the intermediate hypophosphite monoesters bearing electron-withdrawing groups, e.g., R = Ph or CH_2CH_2Cl, the final *H*-phosphonate diesters were formed readily without a catalyst. This could be attributed to a higher propensity to ternalization of such intermediate monoesters and, consequently, their facile oxidation by air [11].

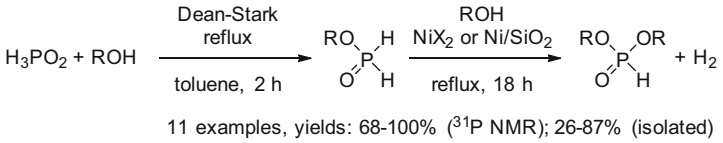
Since H_3PO_2 is also a substrate for the Ni-catalyzed oxidation, a reversed order of the reactions is possible (Scheme 4). This variant turned out to be very efficient for the preparation of *H*-phosphonate diesters with R=Bu or CH_2CH_2Cl (86% and



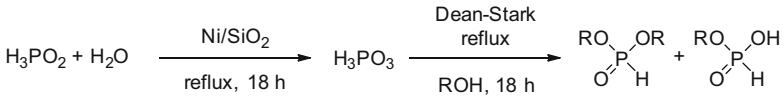
Scheme 1 McCombie's process for synthesis of *H*-phosphonate diesters



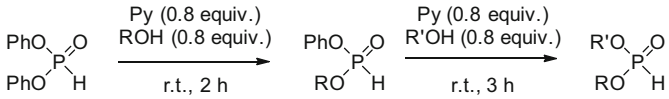
Scheme 2 Synthesis of *H*-phosphonate fluoroalkyl diesters



Scheme 3 Synthesis of *H*-phosphonate diesters starting from hypophosphorous acid



Scheme 4 Synthesis of *H*-phosphonate esters starting from hypophosphorous acid via H_3PO_3



Scheme 5 Synthesis of *H*-phosphonate diesters via stepwise transesterification of DPP

98%, respectively), while for the reaction with benzyl alcohol a quantitative formation of the monoesters was observed (^{31}P NMR) [11].

A convenient procedure for the preparation of alkyl phenyl and unsymmetrical dialkyl *H*-phosphonate diesters under solvent-free conditions was elaborated by Hoffmann et al. [15]. This approach consists of two consecutive pyridine-assisted transesterifications of diphenyl *H*-phosphonate (DPP) (Scheme 5).

In contrast to the previously developed DPP-based strategies [16, 17], selective formation of a monosubstituted product in the first stage was achieved by using a limited amount of pyridine (0.8 equiv.) and sub-stoichiometric amount of an alcohol. Apart from the desired products, the reaction mixture in both stages contained only pyridine and phenol, which could be evacuated by a simple reduced-pressure distillation. This is both an advantage and limitation, since the method is applicable to non-volatile esters only. The yields were in the range 70–90%.

Similarly, partial transesterification of DPP with MeOH in THF (−5°C/30 minute) was achieved by using only catalytic amount of TEA. In this case, however, the mixed *H*-phosphonate diester formed was used further without purification [18]. A different approach was chosen by Fraix et al. for the preparation of symmetrical *H*-phosphonate diesters of higher alcohols (C_{14} and C_{22}) containing disulfide bridges. To this end, DPP was heated at 120°C for 1 h with stoichiometric amount of an alcohol under vacuum, affording the products with a quantitative yield [19].

Keglevich et al. investigated transesterification of $(MeO)_2P(O)H$ (DMP) and $(EtO)_2P(O)H$ (DEP) with alcohols under microwave conditions which led to mono or bis ligand-exchanged products. From the resulting mixtures, (EtO)(RO)P(O)H

esters (R=Me, *i*-Pr, *n*-Bu, *n*-Pe, *n*-Oct, and *i*-Oct) were isolated chromatographically with 50–60% yields [20].

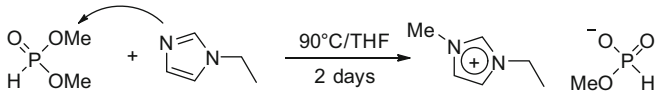
H-Phosphonate diesters can be transformed into the corresponding monoesters by selective monodealkylation. A novel approach to this reaction was proposed by Bryant et al. [21]. Thus, refluxing symmetrical dialkyl diesters in *t*-$BuNH_2$ yielded the desired monoesters as $(RO)(O^-)P(O)H{\cdot}t\text{-}BuNH_3^+$ salts (R=Me, Et, *i*-Pr, Bn, and *n*-Bu), which could be readily isolated in crystalline forms. The susceptibility of higher (R>Me) dialkyl *H*-phosphonates, $(RO)_2P(O)H$, to dealkylation contrasted with the known stability of analogous phosphate triesters $(RO)_3PO$ (R>Me) under the same conditions [22].

2.2 Selected Applications

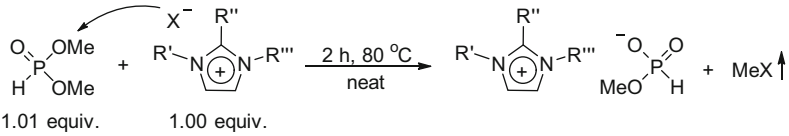
A unique feature of *H*-phosphonates is that their oxidation may be readily associated with introduction of an additional ligand yielding, e.g., phosphate triesters, phosphoramidates, phosphorothioates, etc. While the majority of applications of *H*-phosphonates described in this section involved their oxidative coupling or oxidation, *H*-phosphonate esters per se were also prepared as the end products for selected purposes.

A growing interest in ionic liquids as media for 'green chemistry' induced a renaissance of imidazolium *H*-phosphonate monoesters. Such salts, which are room temperature ionic liquids (ILs), were recently prepared [23] according to a known approach [24, 25], in which DMP acted as an alkylating agent and, after losing one ligand, served as an anion. Yield: 95% (Scheme 6).

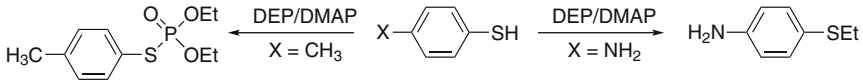
Such ILs drew attention because of their ability to dissolve cellulose [23] and milled wood [26], though there is still a challenge to achieve some advantageous physical properties of analogous imidazolium acetates [27]. In another study, *H*-phosphonate ILs were found to be superior in dissolving other types of carbohydrates [28]. Interestingly, while low-temperature dissolution of cellulose was not associated with its derivatization [23, 29], above 100°C the methyl *H*-phosphonate anion underwent transesterification by carbohydrates. After 3 h heating at 160 °C the degree of phosphonylation was 1.30 and the produced imidazolium salt of cellulose *H*-phosphonate was readily soluble in water (45 g/100 g H_2O) [29]. The popular synthetic procedure for imidazolium *H*-phosphonate shown in Scheme 6 had, however, an intrinsically limited range of products which can be formed. A more flexible approach for synthesis of a wider range of *H*-phosphonate-based ILs was developed by Froschauer et al. [30] (Scheme 7).



Scheme 6 Synthesis of imidazolium *H*-phosphonates monoesters using *N*-alkylimidazole



Scheme 7 Synthesis of imidazolium *H*-phosphonates monoesters using imidazolium halides



Scheme 8 Reactions of diethyl *H*-phosphonate with thiophenols

Here, the imidazolium halides of different structures served as a source of halide anions to dealkylate DMP, while the imidazolium cations bearing a variety of substituents remained intact.

Absorption of residual acetylene impurity from industrial ethylene is a relatively novel application of room temperature ionic liquid. Cheong, Kim et al. found that *H*-phosphonate-based IL was especially suitable for this purpose because of its outstandingly high acetylene binding capacity, which was attributed to its very high hydrogen bond basicity [31].

Phosphate-based ILs are typically prepared by dealkylation of trialkyl phosphates by appropriate imidazoles. However, this type of ILs can also be obtained by oxidation of dialkyl *H*-phosphonate, as was shown recently by Dehaen et al. [6]. The reaction proceeded in a DCM-perhydrol system in the presence of NaOH and imidazolium chloride (or other onium-type halides). The two-phase system prevented hydrolysis of the starting *H*-phosphonate. Since the procedure requires aqueous work-up, the scope of applications of this approach is limited to hydrophobic products.

In general, the above methods for synthesis of imidazolium salts of *H*-phosphonates rely on dealkylation of *H*-phosphonate diesters, which reflects their reasonably strong alkylating properties. Alkylation of amines by *H*-phosphonates was described in 1977 by Hayashi et al. [32] and in 1994 by Gancarz [33], albeit the yields were rather low and the reactions were not specific. Recent attempts to alkylate 3-mercapto-1,2,4-triazinone with DMP or $(i\text{-PrO})_2\text{P(O)H}$ (DIPP) were unsuccessful and led respectively to its dimerization or phosphonate formation [34]. In contrast, Quan et al. reported high yields of *S*-ethylated 1,3,4-thiadiazole-2-thiols when diethyl *H*-phosphonate (DEP) was used as an alkylating agent in the presence of a base, preferably DMAP (five examples, yields: 73–78%) [35]. Interestingly, ethylation of *p*-mercaptoaniline was fully chemoselective towards the SH group, while *p*-mercaptotoluene was not ethylated but instead converted into *O*,*O*-diethyl *S*-(*p*-tolyl) phosphorothioate, (Scheme 8).

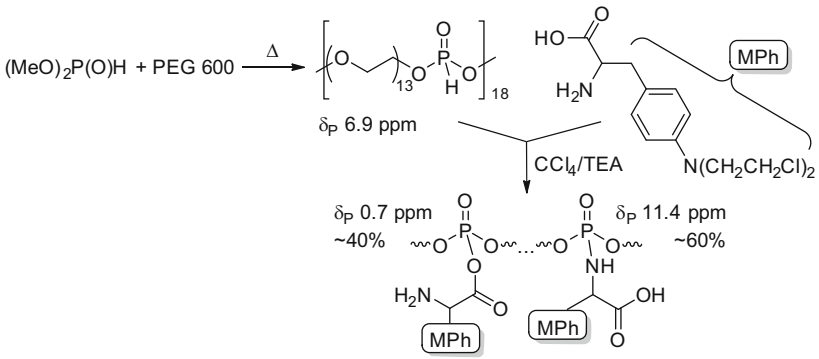
DMP, DEP, and even DIPP could, however, efficiently and selectively monoalkylate a range of anilines and cycloalkylamines in the presence of an indium

triflate catalyst under solvent-free conditions and MW irradiation (21 examples, yields: 61–91%). For *p*-aminophenol the reaction was fully chemoselective towards the NH_2 group, although for this compound *N*,*N*-dialkylated product was obtained and the yield was significantly lower (35%) [36].

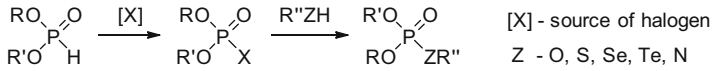
The above procedures for alkylation of amines and thiols required elevated temperatures exceeding 110°C. In another high-temperature process (160°C, 5 h), DMP was used as a reagent for degradation of polyurethane foam wastes (3:1 DMP: PU mass ratio) in the presence of catalytic amounts of *t*-BuOK (0.5–1% of PU mass), potassium (0.17–0.35%), or azobis(isobutyronitrile) (1%) [37]. ^{31}P NMR studies revealed that, under base catalysis, polyurethane was cleaved via cross-transesterification and methyl *H*-phosphonate residue was incorporated into the polymer as a terminal unit, while AIBN induced a radical mechanism, resulting in formation of terminal dimethyl *P*-acylphosphonate [37]. The topic of application of *H*-phosphonates for polymer degradation was reviewed recently by Troev, Rodriguez et al. [38].

Applications of *H*-phosphonates in polymer synthetic chemistry were summarized in a recent book by Troev [39]; however, several articles have been published since then. Thus, a new method of oxidation of poly(alkylene *H*-phosphonate)s with trichloroisocyanuric acid was developed. Depending on the degree of oxidation, the poly(phosphate – *H*-phosphonate)s obtained differed in solubility and susceptibility to hydrolysis [40]. In another study, poly(PEG *H*-phosphonate)s were derivatized with 9-anthrylidene-*p*-toluidine Schiff base yielding a polyphosphonate bearing multiple anthracene moieties, reaching in some cases 100% P–H → P–C conversion. The polymers were tested against human tumor cells and some of them showed promising activity and low toxicity. A distribution of the anthracene-containing polymers in cells could be observed using fluorescence microscopy [41]. The same type of PEG *H*-phosphonate polymer was derivatized with melphalan, an anticancer drug constructed with a nitrogen mustard linked to a phenylalanine residue [42]. The *H*-phosphonate residues of the polymer were either oxidized to a blend of phosphate di- or triesters and coupled with melphalan molecules by electrostatic interactions, or joined with the drug covalently via the Atherton–Todd reaction, yielding a product containing partly phosphoramidate and partly acylphosphate linkages (Scheme 9). Such conjugates showed significantly improved anti-tumor activity.

The Atherton–Todd reaction was similarly used to couple a dinuclear platinum complex, $[(NH_3)_2ClPtNH_2]_2$-spermidine, to *H*-phosphonates. The obtained phosphoramidate polymer had, however, slightly lower activity than the parent platinum compound [43]. Another drug conjugated to a PEG *H*-phosphonate polymer was an anti-HIV nucleoside derivative, AZT. NMR analysis showed a quantitative conversion of the P-H bonds into P-$O^{5'}$AZT triesters under the Atherton–Todd conditions using a 1:1 ratio of AZT per P-H bond. Cytotoxicity of the "polyAZT" obtained was reduced ca. threefold in comparison to the parent nucleoside; however, its antiviral potency has not been studied. The product was water soluble and hydrolyzed in acidic solution (pH 3.5) within 24 h to a putative $H(OC_2H_4O)_4$-PO_2H-$O^{5'}$AZT diester [44]. The papers cited above are part of



Scheme 9 Synthesis of drug-charged polymer via poly(alkylene *H*-phosphonate)s



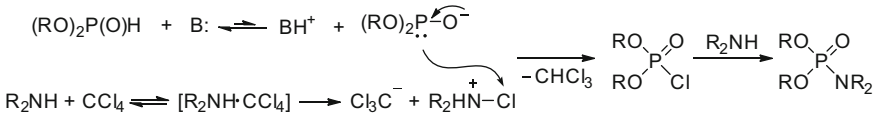
Scheme 10 Atherton–Todd reaction ([X]=CCl_4/base, $R''ZH = R^1R^2NH$) and its modifications

Troev's wider studies on introduction of drug molecules into PEG *H*-phosphonate polymers [39, 45].

A different strategy to the synthesis of phosphonate polymers was used by Liu et al. [46]. At first, DEP reacted with a functionalized Schiff base and the phosphonate formed was subjected to polycondensation with phenylphosphonic dichloride. The polymer obtained, bearing multiple phosphonate residues, showed improved flame-retardant properties because of formation of a cohesive and dense char layer at high temperatures [46]. Simple monomeric esters and amides derived from *H*-phosphonate diesters were also studied as flame retardants for PU foams [47, 48].

The Atherton–Todd reaction [49, 50], mentioned already several times, has great synthetic potential. According to the original publications, *H*-phosphonate diesters were reacted with CCl_4 or other halogenocarbons under basic conditions to form halogenophosphates, in which the halogen atom was substituted subsequently with an amine, yielding the final phosphoramidates. The range of halogen donors for the first step, and nucleophiles for the second, later appeared to be much broader, and a variety of P(V) derivatives can be obtained accordingly (Scheme 10).

The reaction was recently used as a convenient method for the preparation of phosphoramidate diesters, and phosphorothioate or phosphate triesters from *H*-phosphonates [4, 19, 35, 42, 47, 48, 51–62]. Some examples include conjugation of porphyrin [57, 61], hydroxylamine [58], propargyl [59, 60], or disulfide [19] functions via the P–N bond. Similar chemistry was applied to derivatize other compounds containing an active P–H bond (*H*-phosphinates, phosphine oxides, hydrospirophosphoranes, etc.) [53, 63–65].



Scheme 11 Participation of chloroammonium cation in the Atherton–Todd reaction

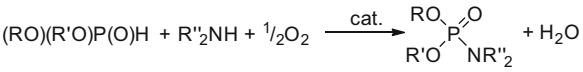
In contrast to a typically smooth Atherton–Todd amidation, a corresponding oxidative esterification is often less efficient and associated with formation of side-products, e.g., pyrophosphates. This problem was partly relieved by Wagner et al. [53] by applying a brominating agent, $CBrCl_3$ (introduced by Atherton and Todd in 1947 [50] but used rather scarcely since) instead of CCl_4. In consequence, some sterically demanding compounds could be obtained more rapidly and under milder conditions. The same brominating agent was also used recently by others [55, 56, 60]. For the Atherton–Todd synthesis of other challenging compounds (adamantanylalkylamides), application of microwave irradiation significantly increased the rate and yield of the reaction [51]. It is worth noting that, according to the studies by Krutikov et al., the actual donor of the chlorine atom is not CCl_4 but chloroammonium cation formed in situ from an amine and CCl_4 [66] (Scheme 11).

Apart from CCl_4 and other polyhalogenated hydrocarbons, there is a range of chlorinating agents that can be used for the first stage of the oxidative condensation. Recently, Dubey et al. developed *N*,*N*-dichloro poly(styrene-*co*-divinyl benzene) sulfonamide and found that it can be exploited as a reusable chlorinating agent for convenient P–H → P–Cl conversion in almost quantitative yields [67]. Han et al., in turn, found that $CuCl_2$ could be used for this purpose under unexpectedly mild conditions, i.e., 0.5 h at r.t., provided an appropriate solvent is used [68].

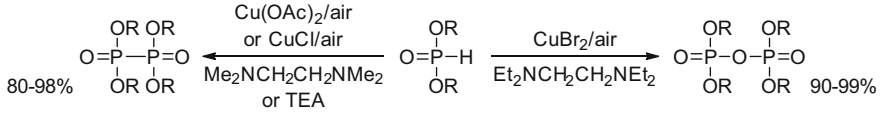
An interesting supplementation to the above approaches is elemental iodine-catalyzed oxidative coupling promoted by 50% aq. H_2O_2 [69] (it is worth noting that the use of I_2 in the Atherton–Todd-type reaction has been practically limited to nucleotide chemistry). With this protocol, despite the aqueous conditions, phosphoramidates and phosphate triesters were obtained in good to excellent yields, and the reaction did not require base catalysis. In a related approach, applying the elemental iodine as a catalyst, a range of *N*-arylphosphoramidates were formed in coupling of arylamines with DEP or DMP using air as the oxidant [70]. The reaction was a solvent-free, room-temperature process, and the yields were usually good (ca. 60–80%, reaction time, 30–60 min), although in some cases only traces of phosphoramidates were produced (e.g., for *p*-aminophenol or *o*-bromoaniline).

In 2013, several articles appeared on a copper-catalyzed amidation of *H*-phosphonate using air as the oxidant. The only side-product of the reaction is water [71–73] (Scheme 12).

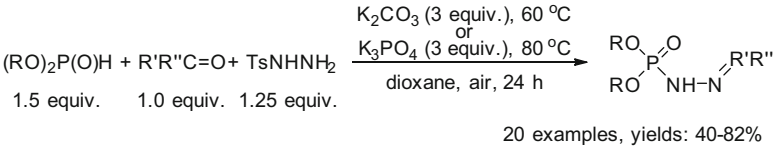
This type of reaction was studied previously by Okamoto et al. (1988) who used $CuCl_2$ as a catalyst for air-driven oxidative coupling of *H*-phosphonate diesters with alcohols [74]. In the most recent contributions, the catalysts of choice were



Scheme 12 Copper-catalyzed amidation of *H*-phosphonate diesters



Scheme 13 Copper-catalyzed oxidation of *H*-phosphonate diesters



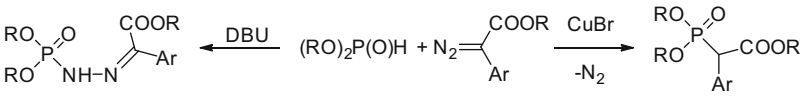
Scheme 14 Three component reaction of *H*-phosphonate diester, aldehyde and tosylhydrazide

identified as $Cu(OAc)_2$ for reactions with amides [71], and CuI in ACN [72] or CuBr in toluene [73] for reactions with amines. A proper choice of the catalyst and solvent was critical since Cu(I) catalysts were ineffective for amides, and, vice versa, $Cu(OAc)_2$ was ineffective in reactions with amines (because of their oxidation to aldehydes and imines, and dimerization of *H*-phosphonate to hypophosphate). A catalytic cycle involving Cu(I) → Cu(II) → Cu(III) → Cu (I) redox processes and participation of an intermediate H_2O_2 was proposed [72]. The aforementioned hypophosphate [72] may become an exclusive product of copper-catalyzed reactions if no amine is present in the reaction mixture [75]. Alternatively, such a reaction could be switched towards tetra(alkyl/aryl) phosphates simply by changing the catalyst or amine [75] (Scheme 13).

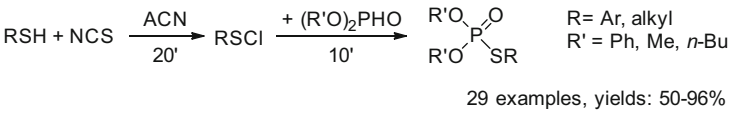
The Atherton–Todd reaction is one of the methods for synthesis of phosphorohydrazones. It was found that the use of external oxidant was not necessary for a related three-component reaction of *H*-phosphonate diester, aldehyde, and tosylhydrazide [76] (Scheme 14).

The same type of compounds was prepared in the reaction of DEP or DPP with α-diazoesters under strongly basic conditions. However, in the presence of CuBr, the reaction switched into an alternative pathway, leading to *C*-phosphonates instead [77] (Scheme 15).

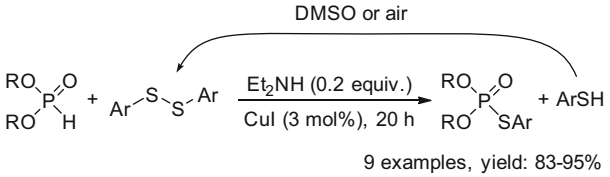
Oxidative thioesterification is a wide branch of derivatization of *H*-phosphonate diesters and in general, can be achieved via three methods: (1) sulfurization (e.g., S_8) followed by *S*-alkylation; (2) Atherton–Todd reaction with thiol derivatives; and (3) reactions with disulfides. The first approach is convenient when appropriate alkylating agents are readily available, and it was recently used for the preparation of several *S*-alkyl phosphorothioates [78]. For the Atherton–Todd procedure,



Scheme 15 Reactions of *H*-phosphonate diesters with α-diazoesters



Scheme 16 Reaction of *H*-phosphonate diesters with thiols pre-activated with *N*-chlorosuccinimide



Scheme 17 Reaction of *H*-phosphonate diesters with diaryl disulfides

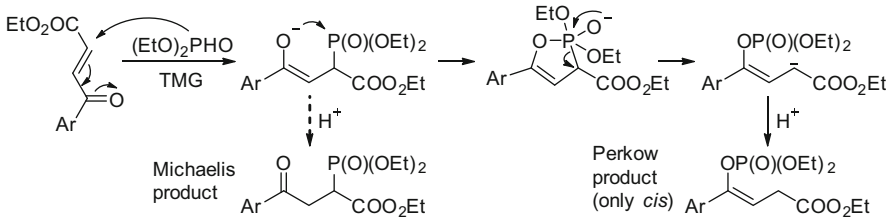
instead of the classical halogenation of the *H*-phosphonate followed by sulfhydrolysis, Lee et al. proposed initial chlorination of thiols to form sulfenyl chlorides, and subsequent reaction with *H*-phosphonates. A range of phosphorothioate triesters were obtained by this method, most with high yields of ca. 80–95% [62] (Scheme 16).

Similarly to the amidation, a CuI-catalyzed air-oxidized version of the Atherton–Todd reaction was recently developed for the synthesis of *O*,*O*-dialkyl *S*-aryl esters, which were obtained in ca. 90% isolated yields (DMF + TEA, r.t., 5 h) [79]. The same copper(I) salt [80] or CsOH [81] was used as catalyst for reactions of dialkyl *H*-phosphonates with a series of diaryl disulfides [80, 81] as well as diselenides and ditellurides [80]. Under optimized conditions (DMSO, r.t., 20 h), (S/Se/Te)-aryl phosphate triester derivatives were obtained in excellent yields (often ≥90%). In the absence of air, DMSO probably served as an oxidant, since 0.5 equiv. of ArSSAr was sufficient to esterify 1 equiv. of *H*-phosphonate [80] (Scheme 17).

Similar reactions proceeding via a free radical mechanism were reported as well, but these were only effective in the seleno series [82].

Another group of products of the Atherton–Todd-type reaction are phosphorofluoridates. Recently, KF was used as a fluoride donor in combination with trichloroacetonitrile [83], trichloroisocyanuric acid [84], or dichlorodimethylhydantoin [85] as chlorinating agents. Excellent yields of phosphorofluoridate products were reported in each case.

An *H*-phosphonate version of the Perkow reaction [86] allows preparation of enol phosphate triesters without an external oxidant. Recently, its conditions were optimized to reduce the competing Michaelis addition for a range of aryl



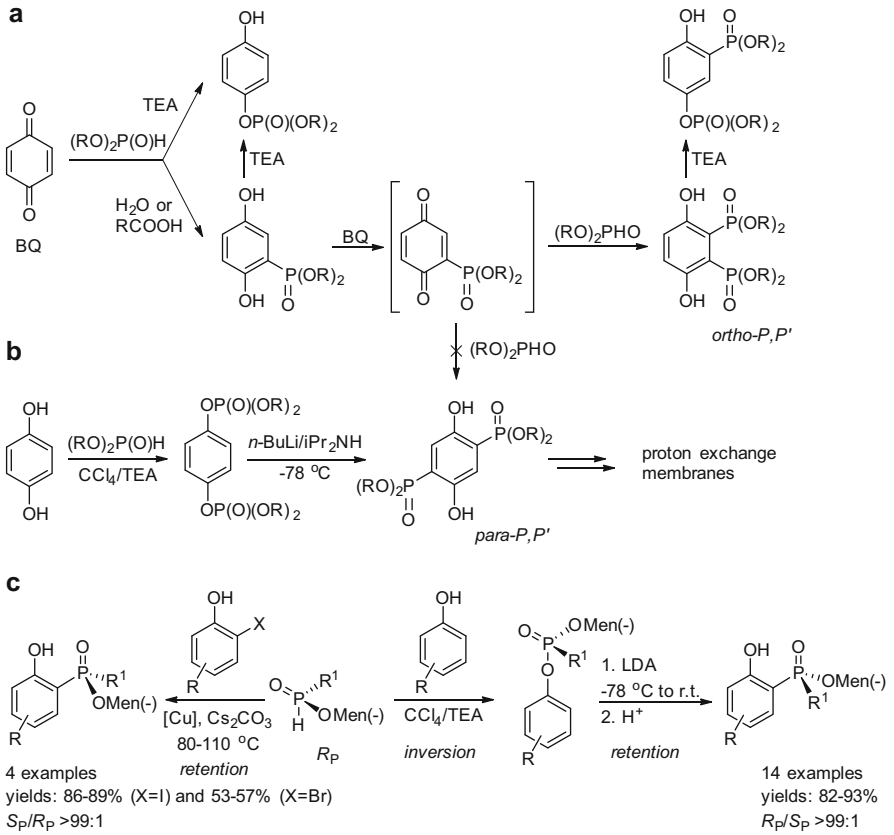
Scheme 18 Putative mechanism of the Perkow-type reaction of diethyl *H*-phosphonate

4-oxo-enoates. A mechanism involving a cyclic intermediate was assumed to be the most plausible one, since it explained the lack of *cis*/*trans* isomerization [87] (Scheme 18).

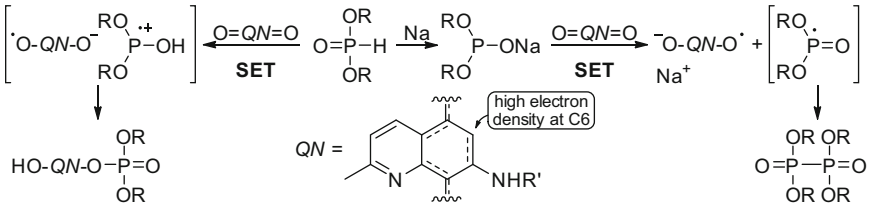
Also, 1,4-benzoquinones are known to react with *H*-phosphonate diesters toward either phosphate triesters or arylphosphonates, usually accompanied by bisphosphonates formation [88]. These reactions were studied recently by Yin, Han et al. [89] and Döring et al. [90]. Various phosphates were obtained under anhydrous basic conditions at r.t., while in the presence of water or acids at elevated temperature the phosphonates were formed (Scheme 19a), both in high yields [89]. The positions of the two phosphonate groups attached to the hydroquinone ring were assigned unambiguously as *ortho* by NMR spectroscopy and X-ray analysis [90] (thus, the postulated *para* assignment [89] was apparently mistaken). Interestingly, the phosphonate and diphosphonate products rearranged respectively into phosphates and phosphate-phosphonates upon prolonged heating in basic solution [90].

This phosphonate–phosphate rearrangement contrasts with the known phosphate–phosphonate transformation which proceeds cleanly under strongly basic conditions for 1,4-hydroquinone diphosphate tetraalkyl esters, yielding a product, in which the phosphonate groups are in a *para* arrangement (Scheme 19b) [91]. Such aryl diphosphonates were recently prepared and studied as reactants for the preparation of proton exchange membranes for fuel cells [92]. The process shown in Scheme 19b (Atherton–Todd oxidation followed by esterification and phosphate-phosphonate rearrangement) is also effective for phenols, for which the intramolecular course of the phosphate–phosphonate rearrangement was confirmed. Interestingly, in analogous reaction of P-chiral *H*-phosphinates, phosphinate products were formed fully stereospecifically with inversion of configuration on the phosphorus atom, in contrast to the direct phosphinylation of *o*-halogenophenols, which afforded arylphosphonites with retention of configuration (Scheme 19c) [93].

Despite the absence of an external base, phosphate triesters were formed as sole products in the reaction of quinolin-5,8-diones with *H*-phosphonates, while alkali salts of the same *H*-phosphonates yielded tetraalkyl hypophosphates. The absence of the P–C bond-containing products (see above) was attributed to high electron density at the C6 atom of the quinoline skeleton. In both instances, an SET mechanism, with different cation localization in the intermediates, was determined [94, 95] (Scheme 20).



Scheme 19 Synthesis and rearrangements of hydroquinone and phenyl phosphate and phosphonate derivatives



Scheme 20 Reactions of *H*-phosphonate diesters with quinolin-5,8-diones

As a final topic of this section, new data on properties of pyro-*H*-phosphonic acid (a monofunctional phosphonylating agent which can be used for the preparation of nucleoside *H*-phosphonates [96]) are presented. Its pK_{a2} was determined as 0.44 ± 0.1, so, apart from very acidic media, this compound exists as a dianion.

Its rate of hydrolysis has a minimum at pH ~6 and is higher than that of pyrophosphate over the whole pH range. Interestingly, but not surprisingly, while the hydrolysis rate of pyrophosphate decreases under basic conditions, for pyro-*H*-phosphonate it always increases with pH, reaching a 10^{10}-fold difference at pH 14 compared to pyrophosphate. Similarly, diethyl pyro-*H*-phosphonate was found to hydrolyze orders of magnitude faster than tetraethyl pyrophosphate [97].

3 *H*-Phosphonate Esters of Biomolecules

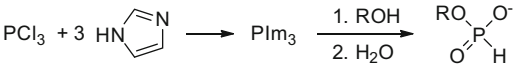
Application of *H*-phosphonates in the chemistry of natural products dates back to 1952–1957 and the works of Lord Todd's team, which described the first synthesis of dinucleoside phosphate diesters [98–100]. After that, *H*-phosphonates were practically abandoned in nucleic acids chemistry for almost 20 years, until Stawinski's group [101–103] and, independently, Froehler and Matteucci [104, 105] re-introduced this chemistry as a comprehensive approach to the synthesis of oligonucleotides. *H*-Phosphonates also emerged as invaluable tools for solving problems encountered in transformations requiring robust and flexible chemistry.

Nucleoside *H*-phosphonate chemistry has been reviewed in several papers in the past, and the last summaries were published in 2002–2007 [2, 106–108]. The topic of *H*-phosphonates was also comprised in two accounts on oligonucleotide synthesis published by Reese [109] and Caruthers [110], as well as in a review by Virta on the base-sensitive nucleotide analogues (2009) [111], and in an account on nucleoside triphosphates by Kore and Srinivasan [112]. The state of art for medical applications of AZT *H*-phosphonate was summarized by Khandazhinskaya [113].

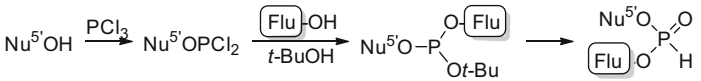
3.1 Phosphonylation of Biomolecules

There are several well-established methods for phosphonylation of nucleosides/biomolecules, and most have been used for different purposes in the last few years. Thus, the tris(imidazolyl)phosphite approach [103] was applied successfully for phosphonylation of nucleoside 3′-OH group [114, 115], cholesterol [116], and lipid derivatives [117] (Scheme 21), but this method failed for phenylselenyl nucleoside derivatives [118].

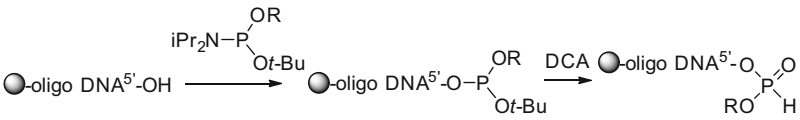
Although there are milder phosphonylating agents known, in some cases phosphorus trichloride is used for phosphonylation of nucleosides, particularly when mixed diesters or *H*-phosphonamidates are desired. For example, Sun et al. reacted PCl_3 successively with nucleosides, NH_2 groups of esterified amino acids, and finally water, to obtain *N*-[AA] *H*-phosphonamidate esters of AZT and d4T in good yields [119]. Zhao's group in turn adapted their earlier PCl_3 method [120] for a one-pot synthesis of fluorescently labeled 5′-nucleoside *H*-phosphonate diesters [121]. In this instance, PCl_3 was treated consecutively with a nucleoside, a



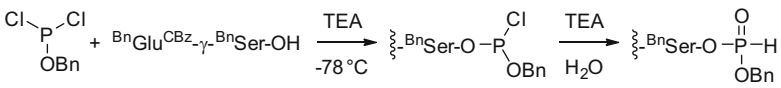
Scheme 21 Tris(imidazolyl)phosphite approach to phosphonylation of biomolecules



Scheme 22 Synthesis of fluorescently labeled 5′-nucleoside *H*-phosphonate diesters using PCl_3



Scheme 23 Phosphonylation of solid-supported oligonucleotides via phosphite triesters



Scheme 24 Phosphonylation of peptides using $BnOPCl_2$

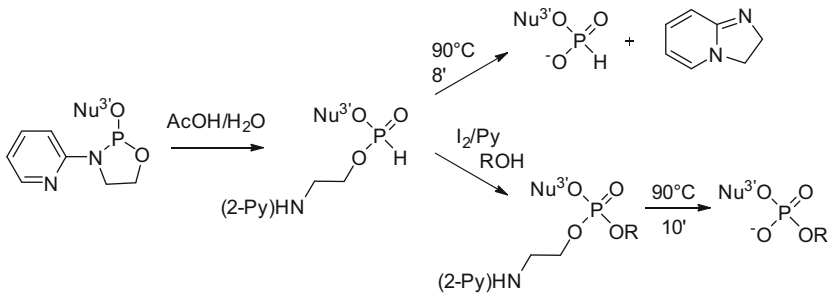
primary alcohol bearing a fluorescent group, and *tert*-butanol. The obtained triesters underwent the Arbuzov-type of the reaction of selective dealkylation of the *tert*-butyl group, yielding the desired *H*-phosphonate diesters (50–70%) (Scheme 22).

The possibility of a selective cleavage of the *tert*-butyl group from a phosphite triester was also exploited by Morvan et al., although their route to the transient phosphite was different [122] (Scheme 23).

Berkman et al. [123] used $BnOPCl_2$ for phosphonylation of protected Glu-γ-Ser dipeptide (Scheme 24) as a superior alternative to the previously used phosphoramidite chemistry [124], and achieved ca. a twofold increase in the yield of products.

The transiently protected *H*-phosphonate was subsequently amidated and deprotected by hydrogenation, which cleaved simultaneously all other protecting groups. The product was further derivatized, yielding fluorescent compounds having inhibitory activity against prostate-specific membrane antigen [123, 124].

Monochloro P(III) phosphitylating agents (salicyl chlorophosphite and bis(*N*, *N*-diethylamino)chlorophosphine [125]) were used for the preparation of *H*-phosphonates of nucleosides [126], saccharide derivatives [127, 128], and peptides [129], while *H*-phosphonates of flavin [130], hydroxymethylcoumarines [131], and hydroxyalkyl derivative of thioctic acid [132] were obtained by another classical approach – monoesterification of H_3PO_3 promoted by a condensing agent [96]. A well known acid-catalyzed hydrolysis of 2-cyanoethyl nucleoside



Scheme 25 Synthesis and transformations of nucleoside 2-(2-pyridyl)aminoethyl *H*-phosphonate

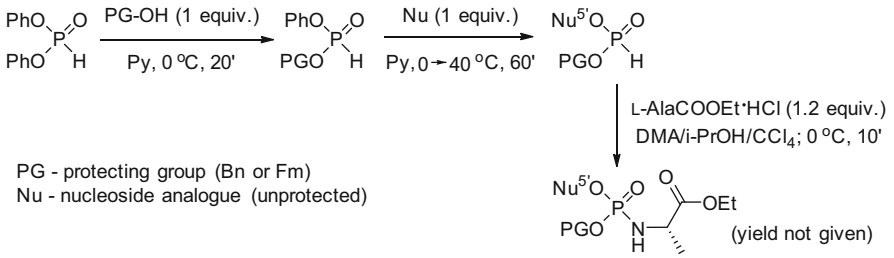
3′-*O*-phosphoramidites followed by β-elimination of the CE group [101] was also used recently as a route to *H*-phosphonates [133, 134], apparently because of better commercial availability of the appropriate phosphoramidites. A different type of phosphoramidite was developed by Chmielewski, namely 2-(nucleosid-3′-yl)-3-phenyl-1,3,2-oxazaphosphorlidine, which contained a masked thermolabile protecting group. In the *H*-phosphonate diester obtained by acid hydrolysis, the protecting group was in a form which could be cleaved thermolytically into *H*-phosphonate monoester, or via a preceding oxidative coupling, to a phosphate diester [135] (Scheme 25).

A new method for the preparation of fluorenylmethyl *H*-phosphonate [136] was described, in which, instead of PCl_3, pyridinium pyro-*H*-phosphonate [137] was used to introduce the *H*-phosphonate group into fluoromethanol [138]. Fluorenylmethyl *H*-phosphonate is a phosphonylating reagent that yields temporary lipophilic *H*-phosphonate diesters, which after flash chromatographic purification can be rapidly deblocked by mild β-elimination. In the last few years it has been successfully used for 5′-phosphonylation of fragile phenylselenyl [118], acetyl [139], azidoalkyl [140], azido, and dideoxy nucleosides [141].

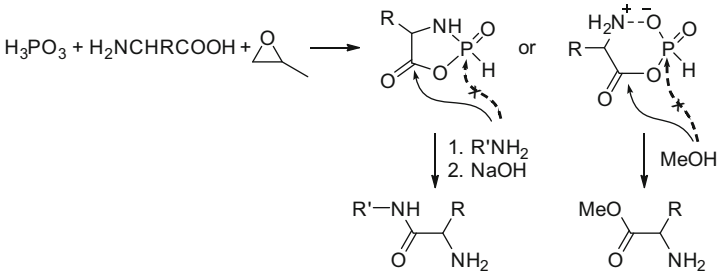
Currently, the most commonly used method for phosphonylation of biomolecules is a pyridine-catalyzed transesterification of DPP [16, 17], which was recently used for the preparation of nucleoside 5′- [18, 142–151] and 3′-*H*-phosphonates [152–155], acyclovir [156], amino acids [18, 150, 151], and cholic acid derivatives [157, 158]. In a variant of this procedure, Gardelli et al. prepared alkyl phenyl *H*-phosphonates (benzyl and 9-fluorenemethyl) by reacting DPP with BnOH or FmOH, respectively (1 equiv., 0°C/20 min) in pyridine, and used the crude products for esterification of a nucleoside [159] (Scheme 26).

A stepwise one-pot transesterification of DPP with FmOH (0.83 equiv., −5°C/30 min) followed by *N*-Boc-ethanolamine (1.17 equiv., 40°C/60 min) was also reported. The crude diester obtained was subsequently oxidatively coupled under the Atherton–Todd conditions with amino acid derivatives, yielding the respective phosphoramidates (yields not given) [160].

The choice of an appropriate phosphonylation strategy may have a dramatic impact on the yield, usually caused by work-up and purification problems. For example, phosphonylation of 2-*N*-propionyl-2′,3′-*O*-isopropylideneguanosine



Scheme 26 Phosphonylation of nucleoside with (FmO)(PhO)P(O)H or (BnO)(PhO)P(O)H pre-formed in situ from DPP and an appropriate alcohol

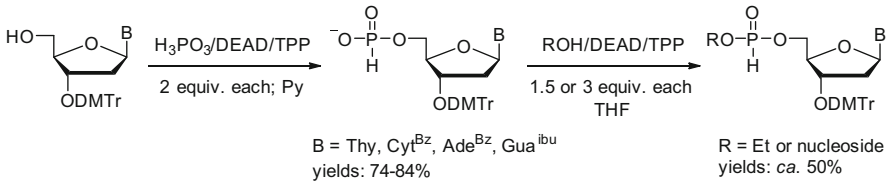


Scheme 27 Cyclic and quasi-cyclic *H*-phosphonates as postulated intermediates for derivatization of amino acids

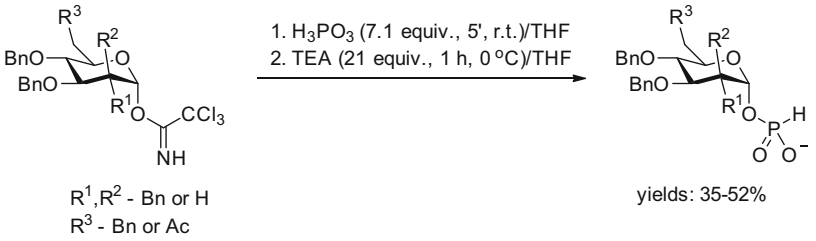
with DPP or PIm_3 yielded 5′-*H*-phosphonate in 9% and 18% isolated yield, respectively, while in the H_3PO_3/PvCl approach the product was isolated in 97% yield [131]. Similarly, an attempt to prepare deoxynucleoside 3′,5′-cyclic *H*-phosphonate using DPP failed, while upon adding a condensing agent (PvCl) to 3′-*H*-phosphonate the desired product was formed quantitatively (^{31}P NMR). Such cyclic *H*-phosphonate was particularly susceptible for hydrolysis or transesterification and was oxidized or sulfurized in situ without isolation [161].

A known method for esterification of H_3PO_3 is its reaction with oxiranes towards reactive β-hydroxyethyl *H*-phosphonate esters, which readily undergo mono- or bis-substitution with nucleophiles. In such H_3PO_3–oxirane–amino acids system, cyclic or quasi-cyclic mixed anhydrides were postulated to form and react further with the added nucleophiles, yielding derivatized amino acids, e.g., methyl esters [162] or dipeptides [163] (Scheme 27).

A similar cyclic mixed anhydride was identified as an intermediate in the reaction of PCl_3 with amino acids [164]. The reported stability of the putative mixed anhydrides (stable solutions in TFA or water) and their reactivity towards the carbonyl carbon are both in sharp contrast with the properties of pivalic *H*-phosphonic mixed anhydrides, which are extremely reactive phosphonylating compounds.



Scheme 28 Phosphonylation of nucleosides under the Mitsunobu conditions



Scheme 29 Phosphonylation of trichloroacetimidate derivatives of carbohydrates with H_3PO_3

In the methods presented so far, the esterification proceeded via an attack of ROH hydroxyl group at an electrophilic phosphorus center. A mechanistic different course of the reaction was exploited in a novel approach to the synthesis of nucleoside 5′-*H*-phosphonates under the Mitsunobu conditions (Scheme 28).

The *H*-phosphonate monoesters were obtained in ca. 80% isolated yields, while the attempts to esterify them further under the same conditions were moderately successful (yields of ca. 50%) [165]. Ito et al., in turn, adapted a method originally developed for the introduction of dibenzylphosphoric acid [166] to phosphonylation of carbohydrates. Thus, the anomeric hydroxyl groups of suitably protected hexoses were converted into trichloroacetimidate derivatives and subjected to the reaction with H_3PO_3. The yields of *H*-phosphonate monoesters were not very high but a higher resistance to anomerization in comparison to the former phosphorylation with $(BnO)_2PO_2H$ was achieved [167] (Scheme 29).

3.2 H-*Phosphonate vs Phosphoramidite Approach*

The choice of *H*-phosphonate vs phosphoramidite chemistry for derivatization of nucleosides and other biomolecules is usually dictated by chemical and experimental reasons. In general, *H*-phosphonates are much more stable than phosphoramidites and significantly more reactive than phosphates, and can be readily converted into various derivatives.

A group of compounds which are often incompatible with phosphoramidite chemistry are those containing a redox-active moiety. *H*-Phosphonates are significantly more robust in such an environment and were successfully applied for the

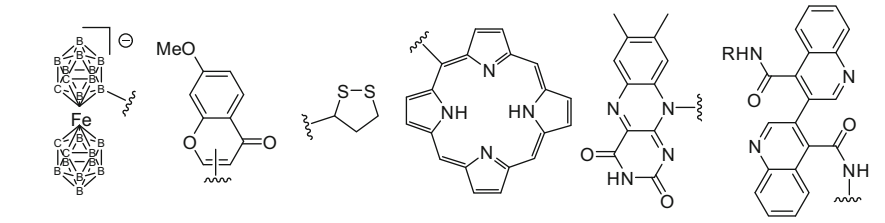
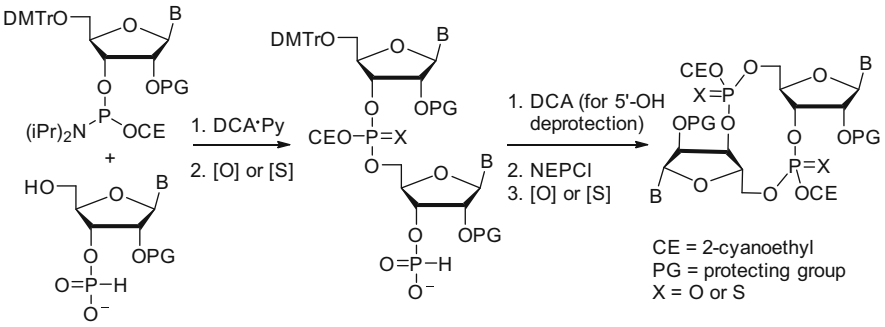


Fig. 2 Structural motifs incompatible with phosphoramidite chemistry



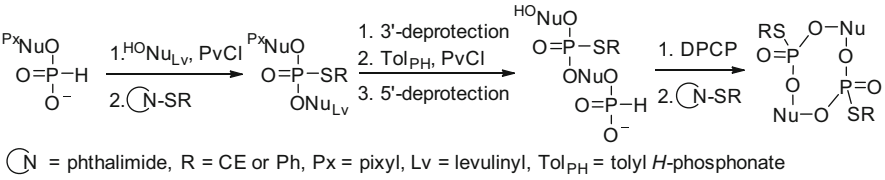
Scheme 30 Combining phosphoramidite and *H*-phosphonate chemistries in the synthesis of cyclic dinucleotides

synthesis of metallacarborane [114], chromenone [131], thioctic acid [132], porphyrin [152], and flavin [130] phosphorus esters (Fig. 2).

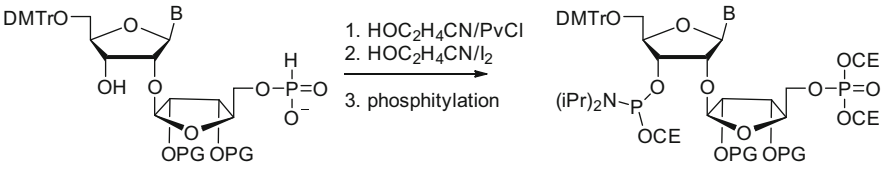
A phosphoramidite-containing bicinchoninic acid diamide was found to be unstable during chromatography [168], while the one with an azido group underwent undesired Staudinger reaction [153]; in both cases the *H*-phosphonate approach was successful. *H*-Phosphonate chemistry was also the method of choice in the synthesis of polyols [169] and azidosugar [127] phosphates, as well as nucleotide–peptide [129], nucleotide–lipid [117], and carbohydrate–glycerol [128] conjugates, for which the phosphoramidite approach failed.

Some nucleotide analogues containing two phosphorus centers have been prepared by combining the *H*-phosphonate and phosphoramidite chemistries. Thus, nucleoside 3′-*H*-phosphonates with a free 5′-OH group reacted cleanly with standard nucleoside 3′-phosphoramidites, yielding *H*-phosphonate building blocks for the synthesis of branched DNA [134] or intermediates for cyclic dinucleotides [133, 170] (Scheme 30). When nucleoside *H*-phosphonothioate (instead of *H*-phosphonate) was used in an analogous procedure, a cyclic product containing one phosphorodithioate linkage could be obtained, although with a very low yield (4% R_P + 1% S_P) [170].

The best results for cyclization were achieved using neopentylene chlorophosphate (NEPCl) [171] as a mild condensing agent. Similar cyclic



Scheme 31 *H*-phosphonate approach to the synthesis of cyclic dinucleotides



Scheme 32 *H*-Phosphonates as precursors for fully protected phosphate monoesters

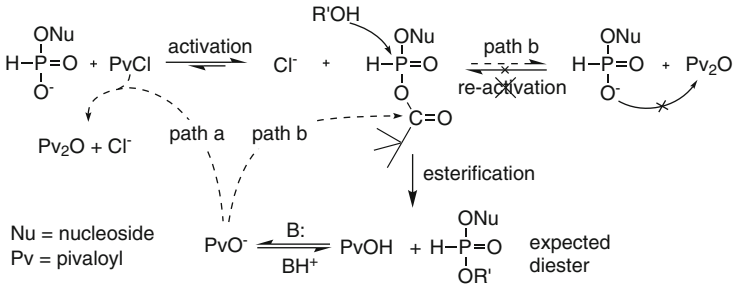
dinucleotides were also obtained by the *H*-phosphonate approach exclusively, using diphenyl chlorophosphate (DPCP) and low concentration of reagents in the cyclization step [172] (Scheme 31).

Chmielewski and Markiewicz in turn used the *H*-phosphonate group to convert it into bis(2-cyanoethyl) phosphate by consecutive esterification and oxidative esterification with cyanoethanol. The product could subsequently either be deprotected to 5″-phosphates of 2′-*O*-ribosylribonucleotides or be phosphitylated to obtain the designed phosphoramidite synthon as shown in Scheme 32 [149].

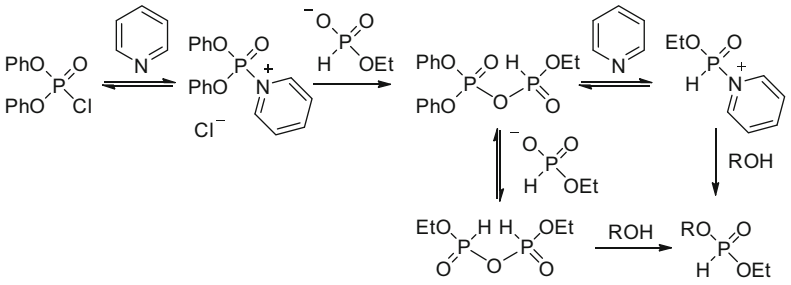
One should note that *H*-phosphonate monoesters, unlike phosphoramidites, are achiral at phosphorus. This appeared to be a significant advantage in separation of α and β epimers of 1,4-dioxane-based nucleotide analogues. Their 3′-phosphoramidites formed a difficult to separate mixture of four diastereomers, while two diastereomers of 3′-*H*-phosphonates were readily isolated and their absolute configuration determined. Afterwards, each isomer was incorporated into oligodeoxynucleotides designed for studies on duplex stability [173].

3.3 Condensation of Nucleoside H-*Phosphonates*

H-Phosphonate monoesters of biomolecules are usually used as substrates for further esterification, e.g., for internucleotide bond formation [101–105]. Typically, the monoester is activated by pivaloyl chloride in the presence of pyridine, and the mixed anhydride formed reacts with a nucleophile. Other bases can be used instead of pyridine, although some minimal nucleophilic catalysis and the resulting intermediacy of P–N$^+$ species are advantageous [174–176]. Both powerful nucleophilic catalysts (e.g., DMAP) and non-nucleophilic amines (e.g., TEA) were found to require larger excesses of PvCl for efficient coupling, although in neither case were



Scheme 33 Two putative pathways for capture of the reactive pivaloyl group (*dashed arrows*)



Scheme 34 Intermediates in condensation of *H*-phosphonate monoesters with alcohols

significant amounts of phosphorus-containing by-products detected, presumably because of low concentration of the amines used (3 equiv.). This demand for using excess condensing agent was attributed to the formation of pivalic anhydride via two possible pathways and two different condensation kinetics [174–176] (Scheme 33).

The main side reaction was found to be that of pivalate with a condensing agent (path "a"), while deacylation of the mixed anhydride (path "b") was less important. Strong nucleophilic catalysts can invoke additional side reactions because of formation of very reactive and not necessarily selective acyl onium species, which can, by acylation, eliminate a considerable part of the hydroxylic component of the condensation [174–176]. These results complement the former mechanistic studies by Sigurdsson and Stromberg [177, 178].

Page et al. studied a mechanism of internucleotide *H*-phosphonate bond formation promoted by diphenyl chlorophosphate (DPCP) [179]. Using ethyl *H*-phosphonate and tetrahydrofurfuryl alcohol as model reactants, it was found that pyridine acted as nucleophilic catalyst both on DPCP and the intermediate mixed anhydride (Scheme 34). Diethyl pyro-*H*-phosphonate was identified in the ^{31}P NMR spectra at δ_P −3 ppm, and ethyl pyridinium *H*-phosphonate at −2 ppm (tentatively) [179]. In contrast to clear-cut signals of acyl *H*-phosphonates in reactions promoted by PvCl [180], ^{31}P NMR signals of the hypothetical phosphoric – *H*-phosphonic mixed anhydride were not detected, presumably because of its very low

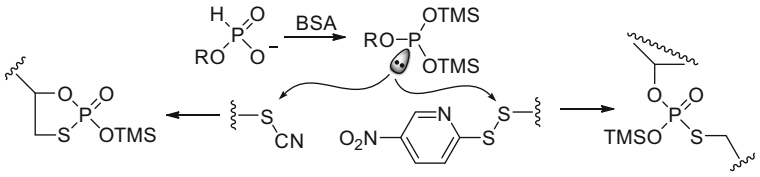
concentration. Nevertheless, under low pyridine contents (1.4 equiv.), kinetic studies revealed that esterification of this putative intermediate via diethyl pyro-*H*-phosphonate may compete with a route via ethyl pyridinium *H*-phosphonate [179] (a commonly assumed reactive intermediate in standard pyridine-catalyzed condensations of *H*-phosphonates [2, 177]).

Condensation of *H*-phosphonates with amines is more challenging than with alcohols because of high susceptibility of amines to acylation by condensing agents and their incomplete chemoselectivity in the reactions with mixed anhydrides [181]. Recently, however, Kraszewski et al. found that condensations of nucleoside 5′-*H*-phosphonates with a number of aryl amines promoted by DPCP proceeded smoothly [141]. The exception was more basic and strongly nucleophilic *p*-aminopyridine, for which attempts to prepare *N*-aryl nucleoside *H*-phosphonamidate failed (in this case, the desired phosphoramidates were obtained using other new P(V) amidophosphorylating reagents). Unlike *N*-alkyl nucleoside *H*-phosphonamidates, the *N*-aryl analogues were unstable and had to be oxidized without isolation.

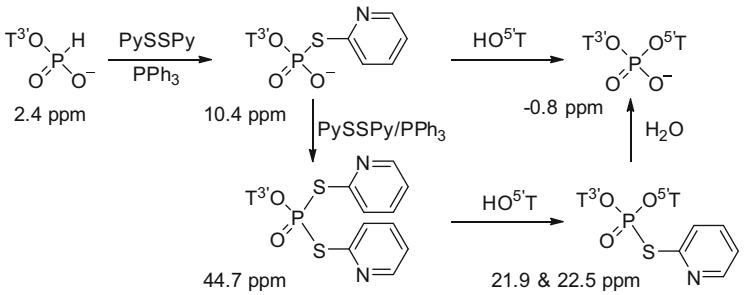
3.4 P–H to P–XR Transformations

The *H*-phosphonate group is introduced into biomolecules usually for the purpose of its subsequent oxidation, sulfurization, or oxidative coupling. The last transformation, which is usually carried out with halogens or according to the Atherton–Todd protocol [49, 50], was recently exploited for the preparation of diester [18, 122, 142, 146, 150, 151, 182] and monoester phosphoramidates [145], and phosphate triesters [44], under typical conditions. Another type of oxidative coupling was the Arbuzov-type reaction of ternalized *H*-phosphonates with active S(I) species to form internucleotide phosphorothiolates [154, 155, 183] or thioglycerol oxathiaphospholane derivatives [184, 185] (Scheme 35).

It is worth noting that attempts to prepare this type of compound failed using phosphoramidite or phosphite triester intermediates [154, 185]. When symmetrical 2,2′-dipyridyldisulfide (PySSPy) was used as a mercaptyl donor in such reactions, the *S*-(2-pirydyl) phosphorothiolate formed reacted readily with water or methanol, yielding phosphate mono- or diesters, respectively [186]. The same disulfide in tandem with PPh_3 is a well known redox condensation system [187]. In contrast, the



Scheme 35 Arbuzov-type reaction of ternalized *H*-phosphonates with active S(I) species



Scheme 36 Oxidative coupling of an *H*-phosphonate monoester to form *S*-(2-pirydyl) phosphorothiolate and the subsequent two alternative routes to the final dinucleotide derivative

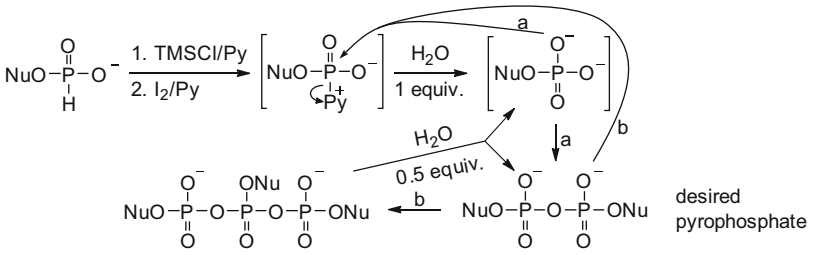
attempted use of these reagents for the synthesis of *H*-phosphonate diesters yielded phosphate diesters instead. Mechanistic studies revealed that the PySSPy/PPh_3 reactant system is able to oxidize an *H*-phosphonate monoester in pyridine without pre-silylation [188] (Scheme 36).

Nucleoside alkyl *H*-phosphonate diesters react with diaryl disulfides or diselenides (0.5 equiv.) in the presence of CuI, also without pre-silylation, and afford *S*-aryl or *Se*-aryl (thio/seleno)phosphate triesters [80]. The same catalyst was used for an air-oxidized amidation of alkyl nucleoside *H*-phosphonate, although the yields were moderate (<60%) [72].

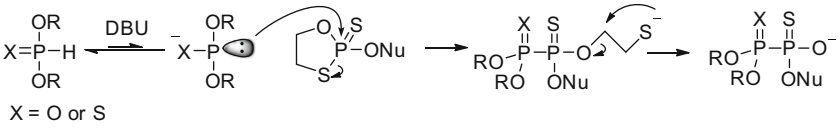
Elemental sulfur is a convenient reactant for transformation of *H*-phosphonate diesters into phosphorothioates. In a recent contribution, Stawinski et al. [189] found that the rate of this reaction was proportional to polarity of solvents and basicity of amines, apparently not only because of promotion of ternalization of *H*-phosphonates but also because of activation of sulfur. Interestingly, ternalization effected by silylation significantly enhanced the rate of sulfurization of $(EtO)_2P(O)H$ (16 h → <2 min), while for $(T^{3'}O)(T^{5'}O)P(O)H$ and $(PhO)_2P(O)H$ the results were opposite (10 min → 40 min and <2 min → 21 h, respectively). This was rationalized in terms of reactivity and concentration of tervalent species in the reaction mixtures.

Nucleoside *H*-phosphonate monoesters can be converted into symmetrical dinucleoside diphosphates by oxidation in the presence of limited amounts of water. Strict conditions securing high yields (70–90%) in this approach were developed by Sun et al. [148]. The process started with silylation of *H*-phosphonate followed by addition of I_2 in pyridine to obtain an intermediate pyridinium adduct of metaphosphate. Then, 1.5 equiv. of water was added in two portions. Such a stepwise procedure was necessary to hydrolyze – in a controlled manner – a putative trinucleoside triphosphate, a side-product observed in the reaction mixture by ^{31}P NMR spectroscopy (Scheme 37).

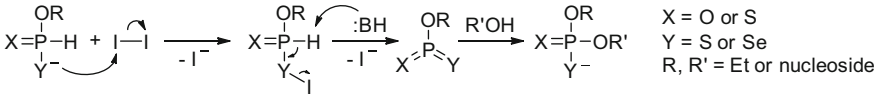
Dialkyl dinucleoside symmetrical pyrophosphates were, in turn, obtained during air-oxidation of alkyl nucleoside *H*-phosphonates catalyzed by $CuBr_2$/tetramethylethylenediamine. As described for simple dialkyl *H*-phosphonates (see above), by a slight change of the catalytic system, dialkyl dinucleoside symmetrical



Scheme 37 Mechanism of dinucleoside pyrophosphate formation



Scheme 38 Formation of nucleoside hypophosphate derivatives



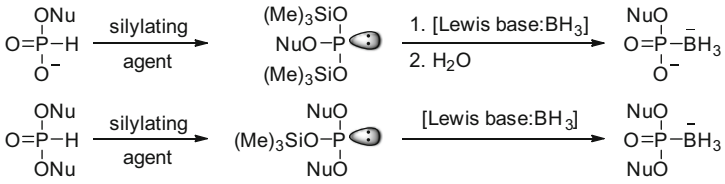
Scheme 39 Mechanism of oxidation of *H*-phosphono(thio/seleno)ate monoesters via metaphosphate intermediates

hypophosphates were obtained with high yields [75]. Formation of a P–P bond was also observed in a rather unusual reaction of $(MeO)_2P(O)H$ and $(MeO)_2P(S)H$ with nucleoside 5′-(1,3,2-oxathiaphospholane)s [190] (Scheme 38).

Subsequent studies revealed that the reaction is highly stereospecific and proceeds with retention of configuration. The obtained hypothio- and hypo(P(I),P(II)-dithio)phosphates could be converted into various other P–P derivatives, including hypo- and hypothiophosphate analogues of NTPs [191]. Application of *H*-phosphonates in the preparation of nucleoside triphosphates was included in a recent review by Kore and Srinivasan [112].

In contrast to *H*-phosphonate monoesters, their thio or seleno analogues are readily oxidized by iodine. Detailed studies on this topic revealed elimination-addition mechanism with an intermediate formation of (thio/seleno)metaphosphate monoesters [192, 193] (Scheme 39). Nucleotide derivatives were obtained via this method preparatively in high isolated yields of ca. 80–90% [193].

The exchange of the oxygen in *H*-phosphonate by a nitrogen atom has the opposite effect and oxidation of *N*-alkyl *H*-phosphonamidate esters proceeds reluctantly over hours [194]. It was found, however, that *N*-aryl nucleoside *H*-phosphonamidates can be oxidized rapidly and efficiently, presumably because of their easier tautomerization to trivalent species. The *N*-aryl AZT phosphoramidates obtained appeared to be non-toxic and highly active anti-HIV



Scheme 40 Boronation of *H*-phosphate mono- and diesters

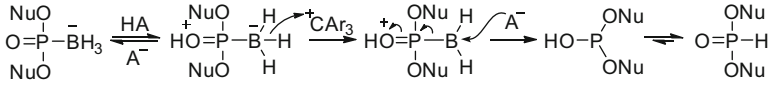
pro-nucleotides [141]. Nucleoside *H*-phosphonamidates of α-amino acids (of AA-NH-P_H-AZT type) could also be oxidized (I_2/H_2O/Py/TEA, 1 h) or sulfurized (S_8/Py/TEA, 4 h) efficiently (80–90% isolated yields) [119].

Kinetic [195] and stereochemical [196] evidence indicated that 2-pyridyl or 2-pyridyl *N*-oxide anchored to the (thio)phosphate group act as intramolecular nucleophilic catalysts. Recently, oxidation of *H*-phosphonates with 2-Py groups attached via linkers of different length and structure was studied and did not give such conclusive results. For example, the rates of oxidation of *H*-phosphonates containing 2-Py groups bound by linkers containing 1, 2, and 3 methylene groups were of a ratio of ca. 3:2:1, which did not fit the expected switching of an intermolecular mechanism assumed for the longest linker into an intramolecular one, anticipated for the shortest linker. The rate of oxidation for the (2-Py) $NHCH_2CH_2$– group was in turn ca. ten times higher than that for the $PhNHCH_2CH_2$– group, supporting the concept of nucleophilic catalysis but not necessarily its intramolecular character [139].

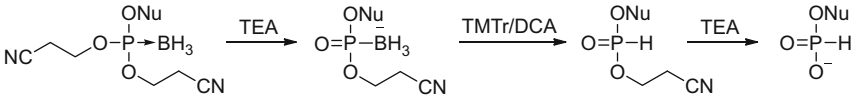
Boranephosphonates (also known as boranophosphates) contain a borane group in place of one non-bridging oxygen atom of a phosphate ester, and can be considered as adducts of phosphites (Lewis bases) and BH_3 (Lewis acid). These compounds can be readily formed from presilylated *H*-phosphonate mono- or diesters, and borane complexes [197] (Scheme 40).

A similar approach was applied recently to nucleoside 5′-*H*-phosphinates, although the yields of the corresponding boranephosphinates were rather low (~20%) because of concomitant partial oxidation of *H*-phosphinates to *H*-phosphonates [198]. Boronation of *H*-phosphonate diesters is a stereospecific reaction and was exploited in a stereocontrolled synthesis of boranophosphonate derivatives of oligonucleotides and oligo(glycosyl phosphate)s [199–201].

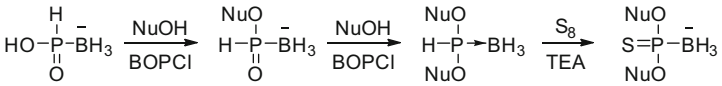
Boranephosphonate diesters in contact with a trityl cation collapse to the appropriate *H*-phosphonates and, consequently, deprotection of DMTr-protected hydroxyl groups requires the presence of a DMTr cation scavenger, e.g., Et_3SiH [202] or Py:BH_3 [203]. On the other hand, this feature allows the use of borane as a protecting group for the P–H bond. Recently, this application was studied systematically by Wada et al. [204], who found that the best results (and quantitative yields) were obtained when trimethoxytritanol (TMTrOH) in conjunction with TFA was used as a source of particularly stable trityl cations. A proposed mechanism involves protonation of the phosphoryl oxygen in the boranephosphonate group



Scheme 41 Mechanism of deboronation of dinucleoside boranephosphonates with trityl cations



Scheme 42 Deboronation of protected boranephosphonates toward *H*-phosphonate monoesters



Scheme 43 Synthesis of dinucleoside boranephosphonothioate via *H*-boranephosphinates

followed by abstraction of proton from the BH_3 group and its subsequent elimination by carboxylate anion (Scheme 41).

As an extension of these studies, it was shown that bis(cyanoethyl) boranephosphonate esters of nucleosides can be deprotected to afford nucleoside *H*-phosphonate monoesters [203] (Scheme 42).

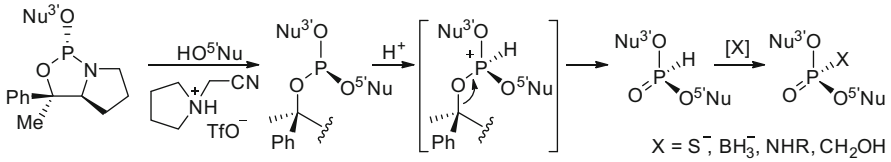
The strategy of BH_3-protection of *H*-phosphonates was exploited successfully in a stereoselective synthesis of 1,2-*trans*-disaccharide phosphodiesters [205].

A new class of *H*-phosphonate–borane compounds emerging recently are *H*-boranephosphinates (or *H*-boranophosphonates or borane complexes of phosphinates). Although these P(I) species are beyond the scope of this account, their applications in organophosphorus [206] and nucleic acid [207–209] chemistries are worth noting, e.g., in the synthesis of dinucleoside boranephosphonothioates (Scheme 43).

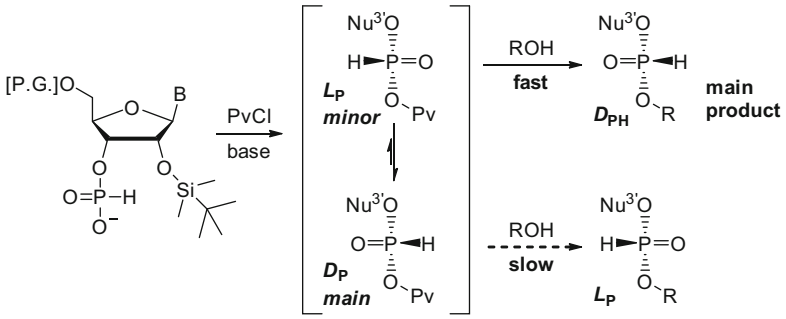
A comprehensive review on nucleotide boranephosphonates was published in 2007 by Shaw and coworkers [197], while the stereochemical topics were reviewed by Oka and Wada in 2011 [210].

3.5 Stereochemical Aspects

H-Phosphonate diesters with different ligands at the phosphorus center are chiral molecules, which are configurationally stable under conditions used in the chemistry of natural products. They can be readily converted in a stereospecific manner into a range of chiral products of various applications. The main problem in stereochemistry of *H*-phosphonates of biomolecules is probably generation of stereochemically pure compounds or isolation of individual diastereomers from



Scheme 44 Stereocontrolled synthesis of P-chiral internucleotide bond via *H*-phosphonates

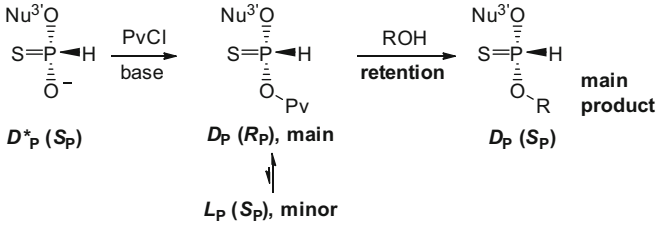


Scheme 45 Dynamic kinetic asymmetric transformation as a mechanism of diastereoselective esterification of ribonucleotide 3′-*H*-phosphonates. The D_P/L_P notation used in the scheme reflects the position of a single-bonded ligand in P-chiral internucleotide bonds; it was designed for convenient presentation of the actual stereochemistry of reaction [216–218]

their mixtures. The last topic was studied recently by Gao et al. for d4T benzyl- and isopropyl *H*-phosphonates (anti-HIV pro-nucleotides). A rapid (<5 min) and reproducible baseline resolution of their *P*-diastereomers by RP-HPLC was achieved under isocratic elution conditions [211].

In 2006, Oka and Wada applied their oxazaphospholidine approach to stereocontrolled formation of P-chiral internucleotide bonds for obtaining diastereochemically pure *H*-phosphonates [212], which led subsequently to stereospecific synthesis of the backbone-modified (P–S, P–N, P–B, P–C diesters, phosphate triesters) oligonucleotides [199, 200, 213] and glycosyl [201, 214] derivatives (Scheme 44). The reaction proceeds with an overall inversion of configuration and high stereospecificity (96% to >98% *de*). Both P-epimers are available by this approach.

Ribonucleoside 3′-*H*-phosphonates bearing a bulky 2′-O-protecting group are known to react with nucleosides with significant diastereoselectivity [215]. Sobkowski et al. recently identified the underlying mechanism of this phenomenon and assigned it to spatial and electrostatic demands of a rapidly epimerizing pivalic–*H*-phosphonic mixed anhydride, a reactive intermediate during the esterification. Its minor P-epimer was found to be much more reactive than the major one and the whole process was found to be a dynamic kinetic asymmetric transformation [176, 180] (Scheme 45).



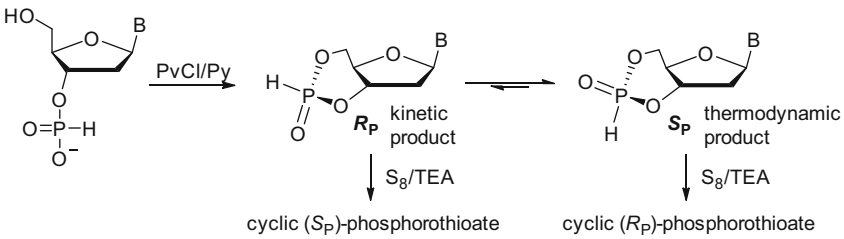
Scheme 46 Retention of configuration in condensations of ribonucleotide 3′-*H*-phosphonothioates with alcohols

Additional mechanistic studies revealed the influence of base, acid, and nucleophilic catalysis on stereochemistry as well as its correlation with pK_a and *H*-bonding basicity of amines used [174, 175]. Under optimized conditions, the diastereoselectivity reached ca. 85% *de* for A_{PH}, G_{PH} and U_{PH}, and 74% *de* for C_{PH} [219].

As already indicated in Scheme 30, the formation of cyclic dinucleotides via intramolecular condensation of 3′-*H*-phosphonate of a dinucleotide bearing 2′-*O*-*tert*-butyldimethylsilyl groups was fully diastereoselective towards the R_P configuration [133, 170], confirming earlier observations by Battistini et al. [220]

In contrast to *H*-phosphonates, *H*-phosphonothioate monoesters are P-chiral compounds. Recently, three methods for diastereoselective preparation of individual diastereomers of ribonucleoside *H*-phosphonothioates were developed, and their absolute configurations were tentatively assigned via a stereochemical correlation analysis of ^{31}P NMR spectra [221]. Condensation of these monoesters with alcohols appeared to be diastereoselective, similar to the oxo series. Intriguingly, though, the reaction seemed to proceed with an unusual retention of configuration (Scheme 46), probably caused by an apical-equatorial geometry of the entry of a nucleophile and departure of a leaving group during the substitution, or pseudorotation of an intermediate phosphorane [222].

As already mentioned, *H*-phosphonate diesters are usually considered as configurationally stable [223]. This, however, was not the case for deoxynucleoside 3′,5′-cyclic *H*-phosphonates. These compounds, formed by cyclization of 3′-*H*-phosphonate monoesters in a highly diastereoselective manner (R_P/S_P ratio 9:1), epimerized upon standing, affording the S_P diastereomer as a main thermodynamic product (R_P/S_P ratio 1:9). Upon stereospecific sulfurization, performed immediately after cyclization or after 5 h, both diastereomers of 2′,3′-cyclic phosphorothioates were obtained in similar diastereomeric excess [161] (Scheme 47).



Scheme 47 Kinetic and thermodynamic products of cyclization of nucleotide 3′-*H*-phosphonates

4 Final Remarks

Recent developments in *H*-phosphonate chemistry, as reviewed in this chapter, support the view that these four-coordinate pentavalent P(III) derivatives have become established synthetic intermediates for the preparation of biologically and industrially important phosphorus compounds. Because of the existence of phosphonate–phosphite equilibria, and the presence of the P–H bond, these compounds provide unparalleled versatility and convenience in organic synthesis for creation of complex molecular structures, by acting as electrophiles, nucleophiles, or free radicals.

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Recent Advances in *H*-Phosphonate Chemistry. Part 2. Synthesis of C-Phosphonate Derivatives

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Abstract This chapter provides an overview of recent advances in the development of new methods and protocols for the formation of the P–C bond using *H*-phosphonate diesters as starting materials. Various chemical and stereochemical aspects of the transition metal-catalyzed cross-coupling and organocatalyst-promoted reactions which are relevant to the synthesis of structurally diverse C-phosphonate derivatives are surveyed.

Keywords Aminophosphonates · C-phosphonates · *H*-Phosphonates · Hydroxyphosphonates · Organic catalysis · Transition metal catalysis

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Abbreviations

Al-salalen	1,2-Diaminocyclohexane-based Al-complexes
BHT	Butylated hydroxytoluene
BINOL-Al	Binaphthyl Al-complex; for the structure
BINOL-Ti	Binaphthyl Ti-complex
bipy	2,2′-Bipyridine
Cp_2ZrHCl	Bis(cyclopentadienyl)zirconium hydrogen chloride
Cpf	Cyclopalladated ferrocenylimines
DBN	1,5-Diazabicyclo(4.3.0)non-5-ene
DIPEA	*N,N*-Diisopropylethylamine
DMA	*N,N*-Dimethylacetamide
dmphen	2,9-Dimethyl-1,10-phenanthroline
DPAP	2,2-Dimethoxy-2-phenylacetophenone
dpephos	Bis-[2-(diphenylphosphino)phenyl]ether
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	Dichloro[1,3-bis(diphenylphosphino)propane
KHMDS	Potassium bis(trimethylsilyl)amide
$Pd_2(dba)_3(CHCl_3)$	Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct
PEG-600	Polyethylene glycol, MW 600 Da
Pht-M	Tetra-*tert*-butylphthalocyanine complexes
Pro	Proline
(*R*)-BINAP	(*R*)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Schiff-Al	Tridentate Schiff base Al(III) complexes
SDS	Sodium dodecylsulfate
(*S*)-TRIP	Binaphthyl-derived phosphoric acid
TAP	Tetraaminophosphonium salt
TBO-Al	Bis(8-quinolinato) dinaphthyl
TPP	Triphenylphosphine
TPPA	Phthalocyanine analogues
Tween-20	Polyoxyethylene sorbitan monolaurate
Xantphos	(9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis-(diphenylphosphine)

1 Introduction

Four-coordinated phosphorus compounds containing P–C bonds (C-phosphonates and C-phosphinates) are stable, usually non-hydrolyzable by enzymes, and serve as isosteric analogues of phosphate esters [1–3]. Thus, they are ideal for use as target-specific modulators of a variety of biological processes, e.g., pesticides and therapeutics [4]. Compounds with single or multiple P–C bonds are also important synthetic intermediates [5] and find broad agricultural [6, 7] and industrial applications [8].

For the formation of the P–C(sp^3) bond, the most common approaches are still those involving the Michaelis–Arbuzov [9, 10] and the Michaelis–Becker reactions [11, 12], or the addition to a carbonyl group [13, 14]. However, in recent decades, the transition metal mediated P–C bond formation strategy has started to become widely used, especially in the synthesis of P–C(sp^2) derivatives [5, 15–18]. In the context of using *H*-phosphonate diesters as phosphorus partners for P–C bond formation, we discuss recent progress in the addition of these compounds to carbonyl derivatives (aldehydes, ketones, imines) and in the transition metal catalyzed cross-coupling reactions which afford products with P–C(sp), P–C(sp^2), and P–C(sp^3) bonds [17].

This review covers selected, important contributions to *H*-phosphonate chemistry in the last 5 years (2009–2013) towards C-phosphonate synthesis. Different aspects of *H*-phosphinate and *H*-phosphine oxide chemistry have recently been reviewed [17, 19–22].

2 Synthesis of α-Aminophosphonates and Related Compounds

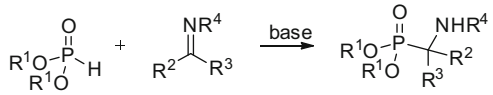
Addition of *H*-phosphonate diesters to a carbonyl group and its derivatives has been known for years as a convenient way to prepare α-functionalized C-phosphonates, especially α-aminophosphonates and α-hydroxyphosphonates [13, 14]. Because of a wide range of practical applications [5–8], recent research in this area has been focused on finding new catalysts and developing stereoselective approaches [23].

α-Aminophosphonates are typically formed in base catalyzed reactions of imines with *H*-phosphonate diesters (the Pudovik reaction [24]) or in a three-component one-pot reaction involving a carbonyl compound, an amine, and an *H*-phosphonate diester (the Kabachnik–Fields reaction [14, 25]). General forms for these reactions are shown in Scheme 1.

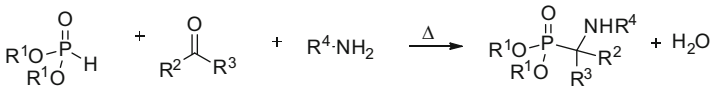
The Kabachnik–Fields reaction, because of its wide scope and experimental simplicity, has, in recent years, dominated the synthetic procedures for the preparation of aminophosphonates. This reaction is usually carried out with equimolar amounts of reactants with or without removal of water (e.g., molecular sieves, azeotropic distillation), and with or without a catalyst. The most significant modifications recently introduced consist of using microwave irradiation as an energy source [26, 27], ionic liquids as a reaction medium [13], and different types of catalysts [28]. Some mechanistic aspects of this reaction have also been investigated [14, 28].

A typical example is the preparation of α-aminophosphonates containing an adamantyl moiety (70–80% yield), using microwave heating in the presence of cadmium(II) iodide as a catalyst and molecular sieves (4 Å) as a dehydrating agent [27]. As substrates, various primary amines containing adamantyl fragments, 2-methylpropanal, and diethyl *H*-phosphonates were used. Since the reaction

The Pudovik reaction



The Kabatchnik-Fields reaction



R^1 = alkyl; R^2, R^3 = alkyl or aryl; R^4 = alkyl, aryl or H

Scheme 1 The Pudovik and the Kabachnik–Fields reactions

system in the Kabachnik–Fields reaction is rather complex, various bimolecular processes between the reactants may cause the formation of unexpected products, especially under microwave heating conditions [26].

The addition of phosphorus nucleophiles to imines (substrates in the Pudovik reaction and the putative intermediates in the Kabachnik–Fields reaction) is catalyzed by Lewis acids (e.g., $SnCl_2$, $SnCl_4$). However, because of the generation of water during the course of the Kabachnik–Fields reaction, these Lewis acids are often deactivated. To overcome this problem, micellar solutions of surfactants were used as catalysts. Sobhani and Vafaee [29] reported on the efficient formation of α-aminophosphonates (yields >90%) from aldehydes, amines, and diethyl *H*-phosphonate in the presence of sodium dodecylsulfate (SDS, Fig. 1) in aqueous solution. The nonionic surfactant Tween-20 (polyoxyethylene derivative of sorbitan monolaurate; Sorbitan-20; Fig. 1) was also used under environmentally friendly conditions for the one-pot, three-component synthesis of aminophosphonates [30]. The major advantages were claimed to be the wide scope of substrates, simple work-up, short reaction time (ca 30 min), and high yields.

Metallophthalocyanines, structurally related to metal porphyrins, are used as efficient catalysts in organic synthesis [31]. In 2003, Matveeva et al. [32] reported on the application of tetra-*tert*-butylphthalocyanine–metal complexes (Pht-M, Fig. 1) to the Kabachnik–Fields reaction. Various α-aminophosphonates derived from sterically hindered ketones were obtained in acceptable yields. These conditions were extended to reactions involving aminopyridines as amino components [33]. In toluene (110°C, 24–78 h), in the presence of molecular sieves (4 Å), 3-aminopyridine and diethyl *H*-phosphonate afforded the corresponding α-aminophosphonates, both with aldehydes and ketones, while 2- and 4-aminopyridines reacted only with aldehydes (yields ca. 70%). An eco-friendly version of this reaction was also developed using a water-soluble Cu(II) complex of a phthalocyanine analogue (TPPA, Fig. 1), in which the benzene rings were replaced by quaternary pyridine moieties [34]. Under aqueous conditions, in the

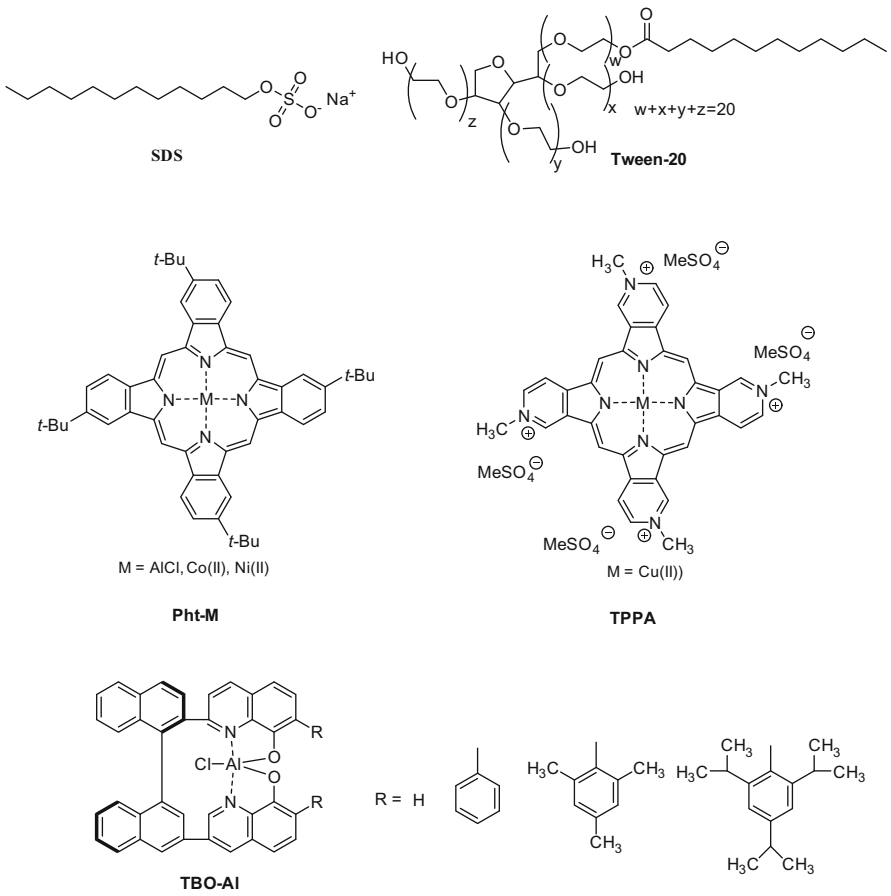
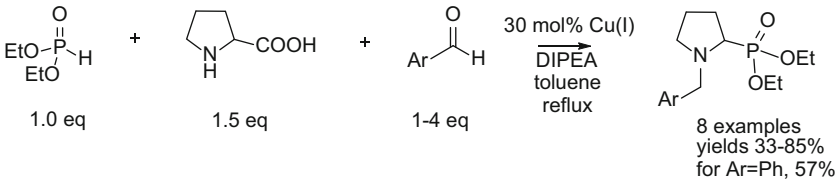


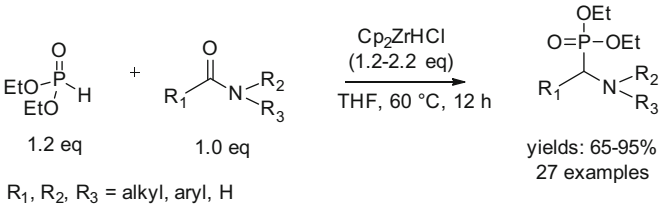
Fig. 1 Some surfactants and catalysts used in the synthesis of α-aminophosphonates

presence of a small amount of catalyst (0.16%), aminophosphonates derived from aromatic amines and diverse aldehydes (alkyl, aryl, allyl, heteroaryl) were formed in >90% yields in a short time (0.5–2 h).

A new, general protocol for the Kabachnik–Fields reaction, based on heterogeneous catalysis by H-beta zeolite, was developed by Choudhary et al. [35]; it was found to be applicable to aldehydes and ketones, as well as aliphatic and aromatic amines. Apart from high efficiency (yields ca. 90%), the major advantages of this method are operational simplicity, reusability of the catalyst, short reaction time, and tolerance to sensitive functional groups. Heterogeneous catalysts based on iron-doped single walled carbon nanotubes showed similar efficiency and usability [36]. Simple inorganic salts ($CaCl_2$ [37] and $KHSO_4$ [38]), phosphorofluoridic acid [39], and phenylboronic acid [40] have been advocated as superior, cheap catalysts for the Kabachnik–Fields reaction under solvent-free conditions. Tosyl



Scheme 2 Decarboxylative three-component coupling reaction for α-aminophosphonates



Scheme 3 Reductive phosphonylation of amides

chloride was also proposed as a catalyst for this reaction because of its ability to stabilize more nucleophilic, tervalent phosphite forms of *H*-phosphonates [41].

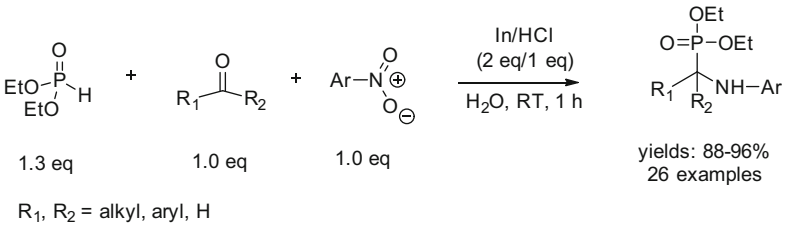
Despite the obvious advantages of using catalysts, for certain applications (e.g., synthesis of α-aminophosphonates containing rigid β-amino acids with the amino function at bridgehead positions) the uncatalyzed, thermal version of the Kabachnik–Fields reaction remains a viable option [42].

Apart from various modifications of the classical Kabachnik–Fields reaction, a handful of new methods for the preparation of α-aminophosphonates were recently developed. A copper/DIPEA-catalyzed reaction involving an aldehyde-induced decarboxylative coupling of proline with *H*-phosphonate diesters [43] is shown in Scheme 2. This reaction worked well with a variety of amino acids and turned out to be useful for the preparation of potential ligands for the organic synthesis of biologically important amino acid analogues. An uncatalyzed version of this reaction (absence of base and catalyst) was also developed [44].

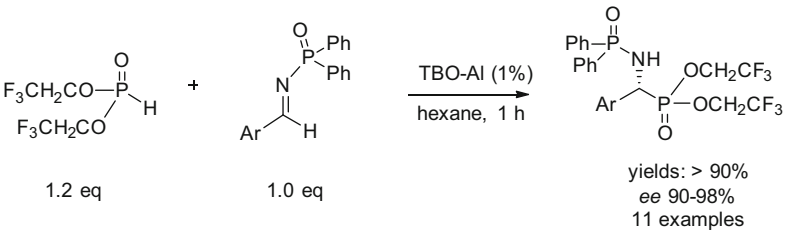
An interesting approach to α-aminophosphonate synthesis, based on in situ reduction of amides with bis(cyclopentadienyl)zirconium hydrogen chloride (Cp_2ZrHCl, the Schwartz's reagent) in the presence of dialkyl *H*-phosphonates, is presented in Scheme 3 [45]. The main advantages of this direct transformation of amides into aminophosphonates are a broad scope of substrates, mild reaction conditions, and good yields.

A distinct approach to α-aminophosphonates was developed using aromatic nitro compounds as the source of an amino component [46] (Scheme 4). This is a three-step, one-pot reaction which involves initial reduction of the nitro compound to an amine with In/HCl, followed by in situ reaction of the formed imine with *H*-phosphonate diester to afford the corresponding α-aminophosphonate derivative.

Since the synthesis of α-aminophosphonates produces a new chiral center on the α-carbon atom, these compounds are obtained in an enantioselective manner with



Scheme 4 Synthesis of aminophosphonates starting from nitro compounds



Scheme 5 Enantioselective synthesis of aminophosphonates using chiral catalyst

chiral auxiliaries. Because of the mechanistic complexity of the Kabachnik–Fields reaction, a Pudovik type of reaction with the preformed imine derivatives (see below) is normally used instead.

Scheme 5 depicts an enantioselective version of the Pudovik reaction using aldimines, an *H*-phosphonate diester, and a chiral catalyst TBO-Al (containing a chiral tethered bis(8-quinolinato) ligand) (Fig. 1) [47].

This catalytic system is very efficient both in yields of the formed α-aminophosphonates and degree of enantioselectivity ($ee > 90\%$) for various aromatic and heteroaromatic aldimines. With the growing interest in organocatalysis, new protocols were developed for enantioselective transformations of imines and related compounds into α-aminophosphonates. These transformations used quinine-squaramide [48] or chiral Brønsted acids [45] as catalysts [49, 50].

Regarding asymmetric synthesis employing the Kabachnik–Fields reaction, List et al. [51] described an impressive enantio- and diastereoselective protocol for the formation of β-branched α-aminophosphonates. The reactants consisted of racemic aldehydes, *p*-anisidine, and an *H*-phosphonate diester in the presence of chiral BINOL-derived phosphoric acid [(*S*)-TRIP, Fig. 2] (Scheme 6). This reaction was particularly challenging because it combined a dynamic kinetic resolution (at the level of imine formation) with the parallel creation of an additional stereogenic center on the α-carbon to the phosphorus center.

Another example of asymmetric synthesis of α-aminophosphonates is the addition of dialkyl *H*-phosphonates to *tert*-butylsulfinyl imines, where chirality is

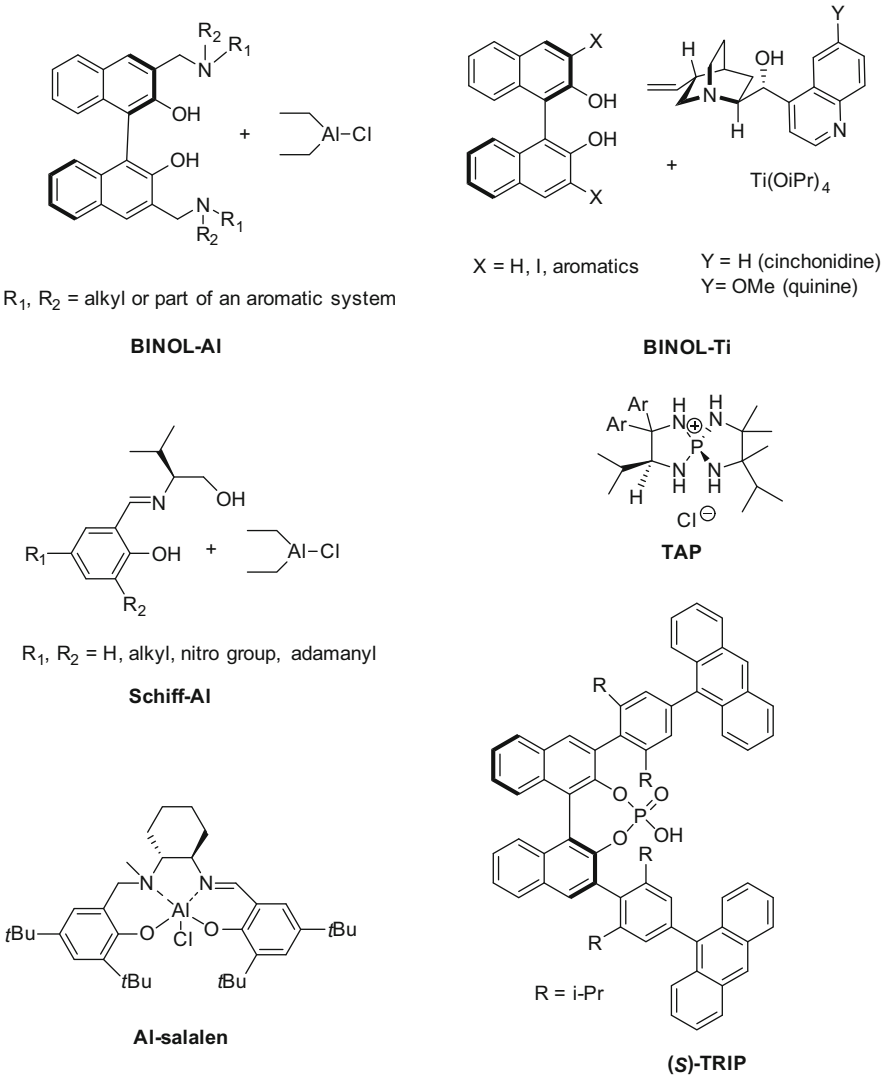
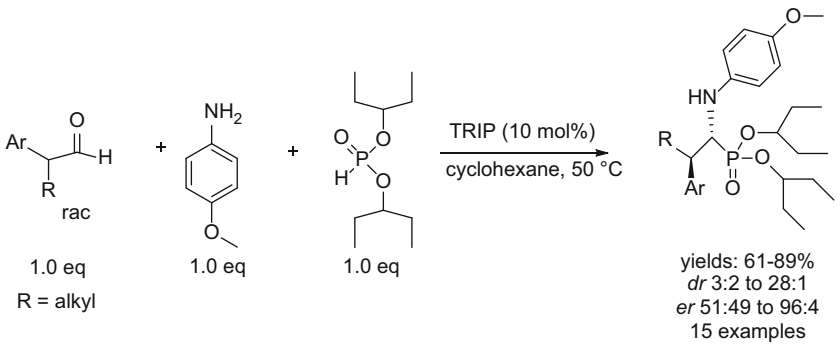
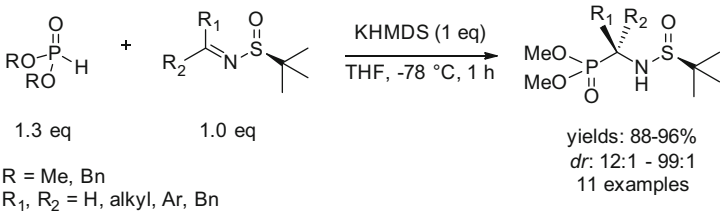


Fig. 2 Some catalysts used in the synthesis of α-amino- and α-hydroxyphosphonates

imparted by a chiral sulfinyl group [52] (Scheme 7). The reaction was carried out in the presence of potassium bis(trimethylsilyl)amide (KHMDS) as a base catalyst. The diastereoselectivity observed was usually high. Even a sterically hindered substrate (e.g., ketimine, derived from pinacolone) provided the α-aminophosphonates in high yield (94%) with a high diastereoselective selection (*dr* 99:1).



Scheme 6 Enantio- and diastereoselective Kabachnik–Field reaction



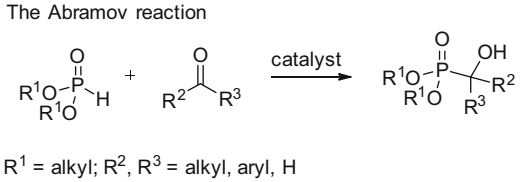
Scheme 7 Asymmetric synthesis of aminophosphonates

3 Synthesis of α-Hydroxyphosphonates and Related Compounds

α-Hydroxyphosphonates can be treated as analogs of natural phosphates and hydroxy carboxylic acids. As such, they attracted considerable interest as biologically active molecules, complexing agents, and important chemical intermediates [53, 54]. Preparative methods for α-hydroxyphosphonates are usually based on the addition of dialkyl *H*-phosphonates to aldehydes and ketones in an Abramov reaction [55] (Scheme 8). This experimentally simple reaction is further facilitated with catalyst addition [13, 53, 54].

Recently, basic alumina (chromatographic grade) was found to catalyze efficiently the addition of dimethyl *H*-phosphonates to a variety of carbonyl compounds (aldehydes and ketones) at room temperature under solvent-free conditions (reaction time ca. 72 h) [56]. To speed-up the reaction, microwave irradiation (in combination with a strong base, DBN) [57] and ultrasound excitation [58] (in the presence K_2HPO_4 as catalyst) were also used. In both cases, improved yields and shortened reaction times (5–45 min) were observed. To facilitate separation and recovery of the catalyst from the reaction mixtures, magnetic nanoparticles Fe_3O_4 with immobilized strong bases (guanidine) were proposed as novel, magnetic interphase nanocatalysts [59] (80°C, solvent-free conditions, aromatic and heteroaromatic aldehydes; yields 70–98%).

Scheme 8 Synthesis of α-hydroxyphosphonates using the Abramov reaction

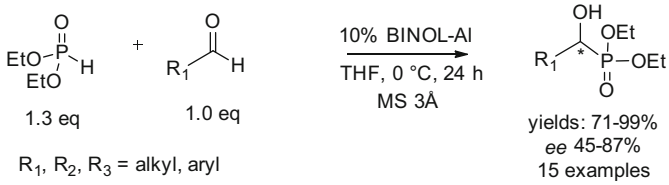


A highly efficient catalyst based on tetracoordinate lanthanide amides, $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$, was proposed by Xu and Shen [60]. A key factor affecting catalytic activity was the presence of LiCl. The reaction time was very short (5 min) and α-hydroxyphosphonates derived from aromatic aldehydes were obtained in high yields (>90%) using very little catalyst (0.1 mol%). This catalytic system was developed further by combining it with calix[4]pyrrole [61] to form dinuclear trivalent lanthanide amido complexes bearing tetra-anion calix[4]pyrrolyl ligands. Alternatively, the lanthanide catalyst could be combined with methylene-linked pyrrolyl-amino ligands [62] to form dinuclear lanthanide complexes. Both groups of catalysts turned out to be highly efficient for the hydrophosphonylation of aldehydes and inactivated ketones. Some mechanistic aspects of these lanthanide amide-catalyzed reactions have been investigated [60] as well. A high-valent oxo-molybdenum complex (MoO_2Cl_2) has also been suggested as a superior catalyst for the hydrophosphonylation of aldehydes [63]. Computational studies revealed that activation of the *H*-phosphonate diester started with coordination of the P=O group to molybdenum, followed by hydrogen transfer from the P–H bond to the Mo=O functionality [63].

In the last decade, the coordination chemistry of alkaline earth metals (Ca, Sr, Ba) became a major research area [64]. As a result, highly effective alkaline earth catalysts were developed for the sterically demanded hydrophosphonylation of aldehydes and inactivated ketones [65]. These heteroleptic complexes of type $[(Me_3Si)_2N]_2Ae(THF)_2$ (Ae=Ca, Sr, Ba), with or without multidentate ancillary ligands, exhibited exceptionally high reactivity in the Abramov reaction using as little catalyst as 0.02 mol% [65]. In most cases the reaction time under solvent-free conditions at room temperature was very short (1–10 min). Furthermore, for a given type of complex and for all carbonyl substrates investigated, the activity of the catalytic system always increased with the size of the metal atom (Ca < Sr < Ba) [53, 54].

For ketones known to be much less reactive than aldehydes in the Abramov reaction, the Lewis acid Ti(O*i*-Pr)$_4$ permitted efficient synthesis of quaternary α-hydroxyphosphonates [66]. Aromatic ketones, regardless of the electronic nature of an aryl moiety, showed high reactivity (yields >90%), while aliphatic ketones gave slightly lower yields (ca. 80%).

A new approach to α-hydroxyphosphonates was recently reported [67]. It makes use of alcohols or ethers as starting materials which are oxidized with $CuCl_2$/*tert*-butyl hydroperoxide to form in situ the corresponding carbonyl compounds. These are added to *H*-phosphonate diesters, affording α-hydroxyphosphonates in



Scheme 9 Enantioselective synthesis of α-hydroxyphosphonates using BINOL-Al catalyst

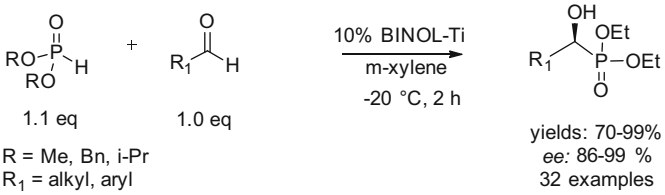
moderate to good yields [56]. This method can be convenient when the corresponding aldehyde is unavailable. The scope of this reaction remains to be established.

Since the biological activity of phosphonic acid derivatives is primarily determined by the absolute configuration of the α-carbon [68, 69], enantio/diastereoselective synthesis of α-hydroxyphosphonates has became a focus of synthetic endeavors in recent years [53, 54].

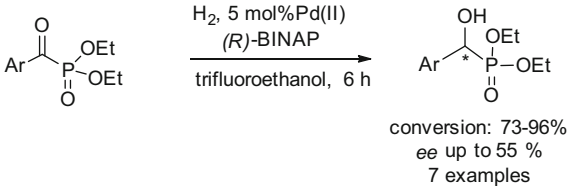
Feng et al. [70] developed a bifunctional chiral Al(III) complex of various BINOL derivatives (BINOL-Al, Fig. 2) for asymmetric hydrophosphonylation of aldehydes with *H*-phosphonate diesters (Scheme 9). This type of chiral catalyst binds both the electrophilic carbonyl substrate (via a metal center acting as a Lewis acid) and a nucleophilic phosphorus reagent (with the amine moiety acting as a Lewis base) in the transition state. This furnishes a strong stereoselection, affording α-hydroxyphosphonate derivatives with high enantioselectivity. The yields and the enantioselectivity may be improved by the presence of molecular sieves 3 Å [70]. A catalytic system as used for the enantioselective synthesis of α-aminophosphonates (TBO-Al) also worked well for the preparation of α-hydroxyphosphonates [47].

In addition, other Al(III) complexes containing chiral ligands were proposed for the enantioselective hydrophosphonylation of aldehydes. These are shown in Fig. 2 and include tridentate Schiff base Al(III) complexes (Schiff–Al) [71] and Al(III)-salalen complexes (Al–salalen) [72]. All these complexes were sterically and electronically adjusted to provide high enantioselective yields ($ee > 90\%$) in the addition process of *H*-phosphonate diesters to aldehydes (THF, −15°C, 24–60 h). A hydrogenated version of the chiral Schiff base in Fig. 2 was used for the enantioselective hydrophosphonylation of trifluoromethyl aromatic/heteroaromatic ketones (*ee* up to 90%) [73]. Computational studies on Schiff-Al [74] and Al-salalen [75] (Fig. 2) catalyzed hydrophosphonylation of benzaldehyde revealed some mechanistic aspects of these reactions. For the latter, calculations showed that the catalytic cycle involves formation of Al–phosphite (via P–H activation) as the catalytically active species, followed by coordination of benzaldehyde, nucleophilic addition, and deprotonation of *H*-phosphonate as the rate-determining step [66]. For the Schiff–Al-catalyzed reaction, the computations pointed to a dimer as a catalytically active species and to C–P bond formation as rate determining [65].

A self-assembled bifunctional catalyst based on BINOL derivatives and cinchona alkaloids (cinchonidine and quinine) coordinated by Ti(IV) cation was proposed by You et al. [76] (BINOL-Ti in Fig. 2 and Scheme 10). A modular



Scheme 10 Enantioselective synthesis of α-hydroxyphosphonates using BINOL-Ti catalyst



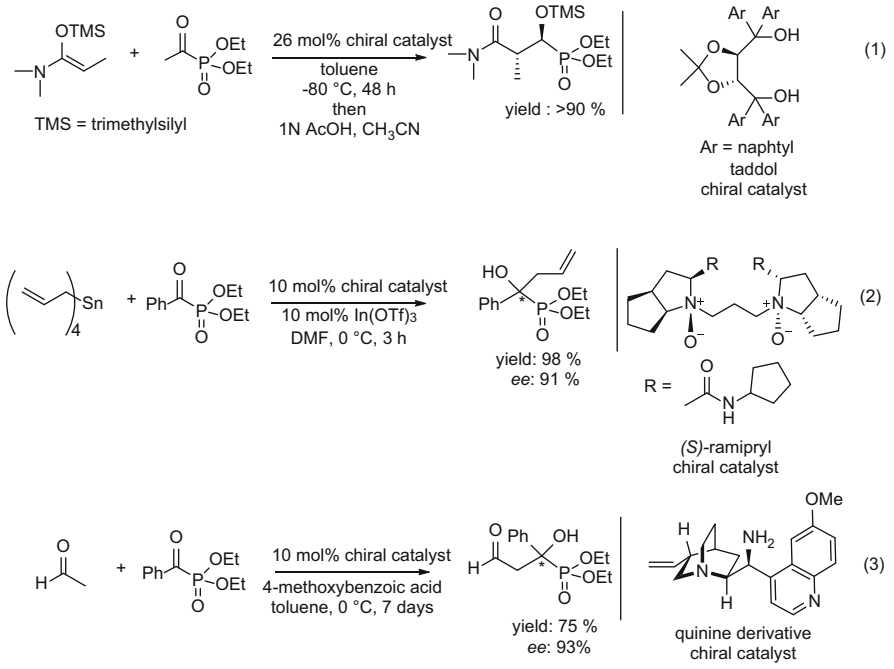
Scheme 11 Asymmetric hydrogenation of α-ketophosphonates

form of this catalyst is constructed from commercially available components which enable its steric and electronic properties to be tuned. This catalyst system seems to be more efficient in terms of yield and enantioselection compared to the one based on BINOL-Al.

The protocol developed by Ooi et al. [77] approaches the enantioselective synthesis of α-hydroxyphosphonate in a different way. This involves in situ formation of chiral dialkyl phosphite salt, a putative nucleophile in the Abramov reaction, from dialkyl *H*-phosphonate and a triaminoiminophosphorane [78], generated upon reaction of chiral tetraaminophosphonium salt TAP (Fig. 2) with KO*t*Bu. In THF, at −98°C, this chiral *P*-nucleophile adds to aromatic aldehydes in an enantioselective manner (*ee* 91–99%) to afford the corresponding α-hydroxyphosphonates in high yields (>90%) [77].

Apart from these protocols for P–C bond formation, enantioselective synthesis of α-hydroxyphosphonates can be realized via asymmetric hydrogenation or asymmetric addition to the carbonyl group of α-acylphosphonates. Although mechanistically different (formation of the P–C bond occurs via reaction of *H*-phosphonate diesters with acyl chlorides), we discuss these reactions here.

As shown in Scheme 11, asymmetric hydrogenation of α-ketophosphonates using chiral palladium catalysts [79] afforded various α-hydroxyphosphonates in excellent yields and with moderate enantioselectivity. Typical chiral ligands used for asymmetric hydrogenation [e.g., (*R*)-BINAP] can also be used for this purpose. Within the series of dialkyl benzoylphosphonates, the diisopropyl esters gave the highest *ee*. The reaction was strongly solvent-dependent and did not occur in nonfluorinated solvents (e.g., methanol, chloroform). In a ligand-free system (palladium on carbon), quantitative conversion into racemic hydroxyphosphonates occurred [79].



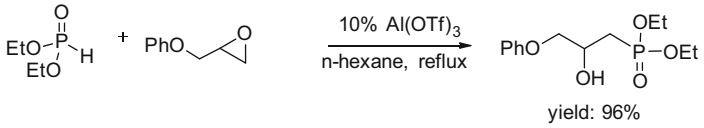
Scheme 12 Asymmetric addition to α-ketophosphonates to produce α-hydroxyphosphonates

Three additional examples of enantioselective synthesis of α-hydroxyphosphonates via addition to the carbonyl functionality of ketophosphonates are shown in Scheme 12. Reaction (1) represents the diastereoselective and enantioselective Mukaiyama aldol reaction catalyzed by various hydrogen-bond donors [80]. For the example shown, in the presence of a chiral taddol catalyst, the conversion was better than 90%, *dr* (anti/syn) 1:30, and *ee* 90%. This mild and general method provides access to α-hydroxyphosphonate derivatives with two chiral centers, using a commercially available chiral catalyst.

Reaction (2) shows a highly enantioselective allylation of aromatic α-ketophosphonates (conversion up to 98%, *ee* 91%) [81]. The bifunctional catalyst system, C_2-symmetric (*S*)-ramipryl and $In(OTf)_3$, provided Lewis base activation of tetraallyltin by the *N*-oxide functionalities, and indium(III) as Lewis acid, to activate aromatic α-ketophosphonate.

Reaction (3) is an example of a cross-aldol reaction between enolizable aldehyde (acetaldehyde) and an α-ketophosphonate. In the presence of an organocatalyst (9-amino-9-deoxy-*epi*-quinine), an enantioselective aldol coupling yielded β-formyl-α-hydroxyphosphonates (potential anticancer agents) [82] with high enantioselection (*ee* up to 93%).

In contrast to α-hydroxyphosphonates, the β-hydroxy derivatives received less attention as their preparations can be more complex [1]. However, a simple and



Scheme 13 Regioselective opening of epoxides by P-nucleophiles to produce β-hydroxyphosphonates

efficient synthesis of β-hydroxyphosphonate via opening of epoxides with phosphorus nucleophiles (phosphite triesters or *H*-phosphonate diesters) [83] was recently reported (Scheme 13). This reaction was recently extended to the synthesis of ribonucleoside 5′-β-hydroxyphosphonates by stereoselective opening of a chiral oxirane system in nucleoside derivatives with *H*-phosphonate diesters, in the presence of a silylating agent and BF_3 as a Lewis acid catalyst [84].

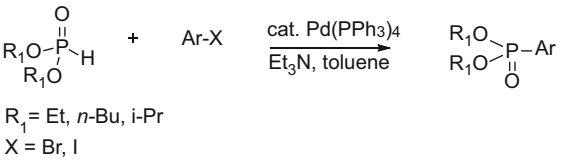
Other studies on biologically active hydroxyphosphonates involved determination of absolute configurations at the α-carbon of fosfazinomycins A and B from *Streptomyces lavendofoliae* containing an α-hydroxyphosphonate motif [85], delineation of decomposition pathways of aryl nucleoside α-hydroxyphosphonates [86] (potential anti-HIV agents), and development of an efficient method for the synthesis of nucleoside α-hydroxyphosphonate monoesters via iodine-promoted hydrolysis of the corresponding nucleoside aryl diesters [86].

4 Pd-Catalyzed Reactions

Transition metal-catalyzed formation of the P–C bond is an important method for preparing organophosphorus compounds [16, 19, 87], thus enabling the synthesis of C(sp^2)–P derivatives which are not accessible by the Michaelis–Arbuzov [9, 10] or Michaelis–Becker [11, 12] reactions. Cross couplings promoted by palladium are stereospecific and occur with retention of configuration at the stereogenic phosphorus center [88–90].

The first palladium(0)-catalyzed cross-coupling reaction between aryl and vinyl bromides and *H*-phosphonate diesters was reported by Hirao et al. [91, 92] (Scheme 14). This classic method has been significantly modified and improved in terms of type of catalyst, palladium source, and reaction conditions to meet the requirements of contemporary synthetic organic demands [16, 17].

By using $Pd(OAc)_2$ as a palladium source and dppf (see Fig. 3) as ligands, Montchamp et al. [93] expanded the scope of the Hirao reaction by including, among other things, activated aryl chlorides as substrates. Stockland et al. [94] developed a room temperature version of the Hirao reaction by using aryl iodides as substrates, $Pd(OAc)_2$ and dpephos (Fig. 3) as a catalytic system, and replacing *H*-phosphonate diesters with more powerful nucleophiles, i.e., their silver salts.



Scheme 14 The Hirao cross-coupling reaction of dialkyl *H*-phosphonates with C(sp^2)-X partners

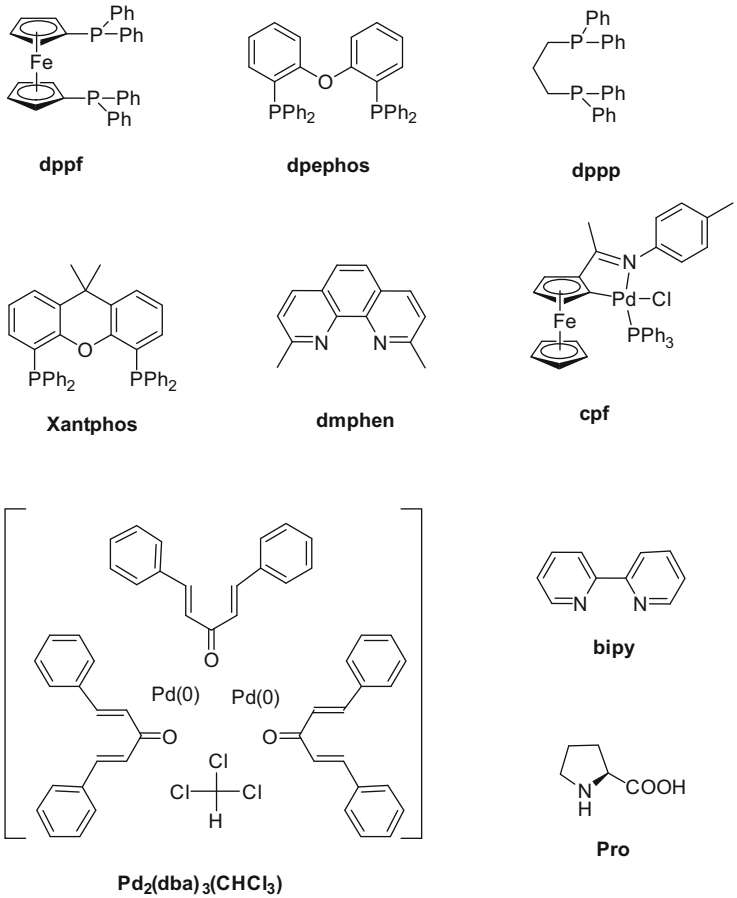


Fig. 3 Some ligands and catalysts/precatalysts used in a palladium-catalyzed cross-coupling reactions

Aminopyridines are poor substrates for the cross-coupling reactions because of the enhanced complexation of palladium. Thus, 2- and 4-aminopyridine derivatives (bromides) under original Hirao's conditions usually give low yields of the

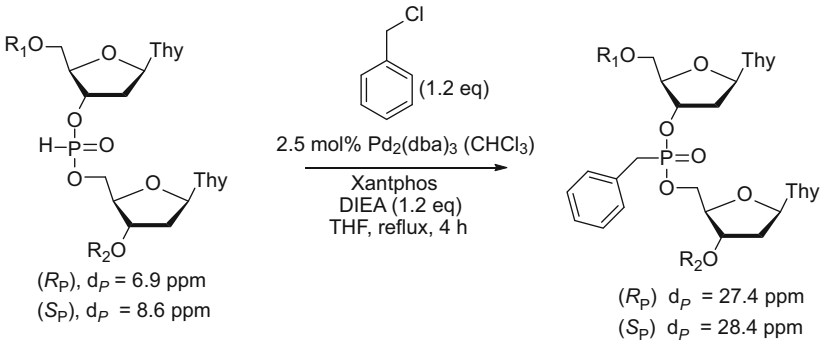
corresponding aminopyridylphosphonates. However, by using ethanol as the solvent and $Pd(OAc)_2$–triphenylphosphine (TPP) as the catalyst system, the yields can be significantly improved [95]. Efficient synthesis of arylphosphonates by the cross coupling of aryl imidazoylsulfonates with *H*-phosphonates, catalyzed by $Pd(OAc)_2$–dppp (Fig. 3) (iPr$_2$NEt as a base), was also reported [96]. The reaction showed good substrate generality and the best results (yields 85–97%) were obtained with dioxane as the solvent. Using $Pd(OAc)_2$ in combination with Xantphos (Fig. 3), an efficient cross coupling of 3-, 4-, and 5-halopyrazoles with *H*-phosphonate diesters, *H*-phosphinates, and secondary phosphine oxides was achieved (THF, 70°C, Et_3N) [97]. Finally, a general and environmentally friendly protocol was developed for the synthesis of arylphosphonates from the corresponding aryl halides (I, Br, Cl) and *H*-phosphonate diesters using standard Hirao catalyst, $Pd(PPh_3)_4$, in polyethylene glycol (PEG-600) (reaction times 15–25 h, yields 80–95%) [98].

Stereoselective synthesis of highly functionalized P-stereogenic nucleosides via a palladium-catalyzed P–C cross-coupling reaction was reported by Hayes et al. [99]. By using the $Pd(OAc)_2$–TPP catalyst system in THF with propylene oxide as a base, completely stereospecific coupling of nucleoside *H*-phosphonate diesters with nucleoside vinyl bromide was achieved. A general and efficient method for the microwave-assisted formation of the P–C bond was also developed. This method is applicable to complex, biologically relevant compounds such as cholesteryl and dinucleotide derivatives [100]. Using a prevalent palladium catalyst, $Pd(PPh_3)_4$, and Cs_2CO_3 as a base in THF, various aryl-, heteroaryl-, and vinylphosphonates were obtained in high yields (80–95%) within 10 min. Recently, a microwave-assisted synthesis of arylphosphonates from aryl bromides and dialkyl *H*-phosphonates, using $Pd(OAc)_2$ and NEt_3 in a Pd-ligand- and solvent-free system, was promoted as an environmentally benign variant of the Hirao reaction [101].

An interesting and rare side reaction was observed during the cross coupling of bromoanilines with diethyl *H*-phosphonate under Hirao's conditions [102]. Together with the expected products, diethyl aminoarylphosphonates, significant amounts (up to 30%) of diethyl phenylphosphonate were formed, which the authors ascribed to an aryl–aryl exchange process in the $Pd(PPh_3)_2ArX$ complexes.

In contrast to arylpalladium(II) complexes, activation and functionalization of benzylic derivatives by palladium is far less common [103]. This is particularly true for cross-coupling reactions with phosphorus nucleophiles, for which a new, efficient method for the synthesis of benzylphosphonate diesters was recently developed [104, 105]. This protocol makes use of $Pd(OAc)_2$ [104] or $Pd_2(dba)_3(CHCl_3)$ [105] as a palladium source and Xantphos (Fig. 3) as a supporting ligand. Various glyceryl, cholesteryl, and dinucleoside benzylphosphonates, with a diverse substitution pattern in the benzyl moiety, could be obtained. Some mechanistic aspects of this reaction were also investigated [105]. An example of the application of this method to the synthesis of dinucleoside benzylphosphonates is shown in Scheme 15.

The catalytic cycle of the Hirao reaction consists of the oxidative addition of a Pd(0)-complex to aryl (or vinyl, benzyl) halides to form arylpalladium(II) species, followed by ligand exchange with a phosphorus nucleophile (usually deprotonated



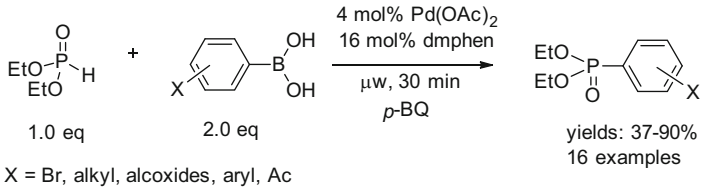
Thy = thymin-1-yl; R_1 = 4,4'-dimethoxytrityl; R_2 = *tert*-butyldimethylsilyl
DIEA = *N,N*-diisopropylethylamine

Scheme 15 Stereospecific synthesis of dinucleoside benzylphosphonates [104]

H-phosphonate), and reductive elimination which liberates the product (aryl-, vinyl-, or benzylphosphonate) and regenerates the Pd(0)-catalyst. Mechanistic aspects of this palladium-mediated cross coupling were investigated in depth in terms of palladium sources, supporting ligands, and the roles of various additives (halides, acetates) on the kinetics and efficiency of the catalytic cycle [106–109]. On this basis, a general, highly efficient protocol was developed for the synthesis of palladium-catalyzed arylphosphonates from *H*-phosphonate diesters and aryl electrophiles, in the presence of acetate ions [109]. The cross-coupling time (30 min vs 23 h, for phenyl triflate) was significantly shortened for bidentate and monodentate supporting ligands, as well as for different aryl electrophiles (iodo, bromo, and triflate derivatives) [100].

The stability, low toxicity, and easy availability of organobismuth compounds have made them attractive substrates in organic synthesis [110]. A novel and highly efficient cross coupling of triarylbismuths with a variety of H–P=O compounds was developed [111]. Since the C–Bi bond is week, it easily adds to Pd(0) species in the presence of 2,2′-bipyridine (bipy, Fig. 3). The catalytic cycle proceeds smoothly without the exclusion of moisture or air, and provides a convenient entry to various arylphosphonates. Some mechanistic aspects of this reaction were probed with DFT calculations [111].

Palladacycles are among the most efficient catalysts in the Heck-type reaction for C–C and C–X bond formation [112]. Wu, Yang, et al. [113] recently developed a new catalytic system based on cyclopalladated ferrocenylimines (cpf, Fig. 3) which efficiently performed synthesis of aryl- and benzylphosphonates. Also, inactive aryl chlorides with electron-donating substituents underwent cross coupling with diisopropyl *H*-phosphonates to afford the corresponding arylphosphonates in good to high yields (DMA, *t*BuOK, 130°C, 3 h). The same catalyst system (cyclopalladated ferrocenylimines, cpf), in combination with a weak, inorganic base (KF) was used for the cross coupling of aryl chlorides with



Scheme 16 Pd(II)-catalyzed arylphosphonate formation [115]

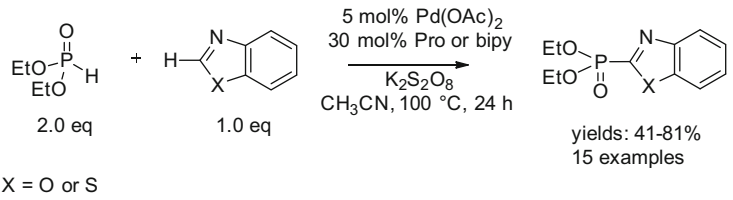
diisopropyl *H*-phosphonate in water [114]. In this case, however, addition of some isopropanol was necessary to suppress hydrolysis of the *H*-phosphonate diester. The method has wide substrate scope and conforms to the idea of green chemistry.

Larhead et al. [115] extended the Pd(II)-catalyzed oxidative Heck reaction [116] to P-arylation by cross coupling aryl boronic acids or aryl trifluoroborates with *H*-phosphonate diesters in the presence of $Pd(OAc)_2$ and rigid bidentate ligand dmphen (Fig. 3), under microwave irradiation (Scheme 16). The above coupling reactions were performed in DMF and occurred without the addition of acid or base. They were performed in the presence of *p*-benzoquinone (*p*-BQ), the most efficient reoxidant for the conversion of Pd(0) into the catalytically active Pd(II) species. Mechanistically, this reaction differs from Pd(0)-catalyzed arylations in the formation of aryl-palladium complexes via transmetallation instead of oxidative addition [104, 105].

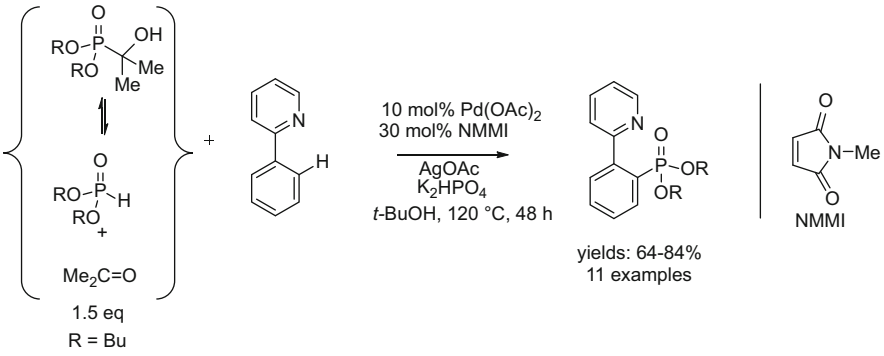
Recently, arylsulfinates have been proposed as new coupling partners in the Pd(II)-catalyzed formation of arylphosphonates [117]. In the presence of $PdCl_2/PPh_3$ as a catalyst system, tetrabutylammonium chloride as an additive, and Ag_2CO_3 as an oxidant, arylphosphonates with diverse substitution patterns could be obtained (yields 70–93%, 28 examples) [117].

In contrast to classical phosphonylation methods which require pre-functionalized Ar–H coupling partners (aryl halides, aryl boronic acid, etc.), a transition metal aromatic C–H activation recently emerged as a viable alternative for C–C and C–heteroatom bonds formation [118–121]. Scheme 17 depicts the first Pd-catalyzed direct phosphonylation of non-functionalized azoles with diethyl *H*-phosphonate (which occurs without the addition of acid or base) [122]. The method consists of an oxidative cleavage of the C–H and P–H bonds and proceeds probably via a Pd(II)/Pd(IV) catalytic cycle. An analogous catalyst system was used for direct phosphonylation (C–H activation) of coumarins with dialkyl *H*-phosphonates to produce the corresponding 3-phosphonylated coumarin derivatives in a highly regioselective manner, with moderate to good yields [123]. Although Pd(II)-catalyzed reactions typically proceed via a Pd(II)/Pd(0) catalytic cycle (Scheme 17), a Pd(IV) species [124] was postulated as an intermediate [122, 123].

A pyridine-directed, palladium-catalyzed phosphonylation of C(sp^2)–H bonds was reported by Murakami et al. [125] and Yu et al. [126]. A perennial problem in this type of reaction is a strong, competing coordination of phosphorus nucleophiles which may hamper the process of activation of less coordinative C–H bonds.



Scheme 17 Pd(II)-catalyzed direct phosphonylation of azoles with dialkyl *H*-phosphonates

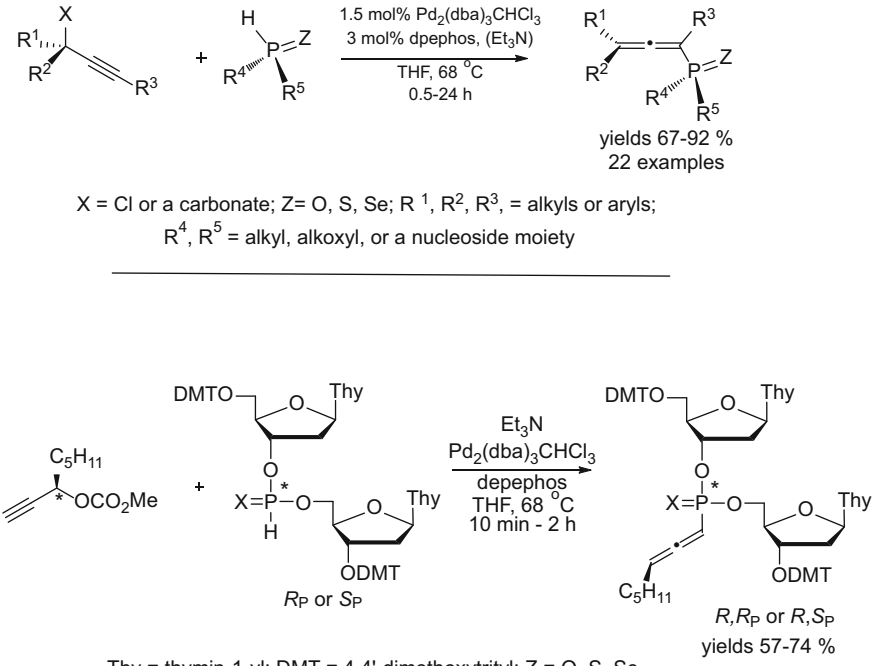


Scheme 18 Pyridine-directed palladium catalyzed phosphonylation of C(sp^2)-H bond

Scheme 18 presents the phosphonylation of 2-phenylpyridine via Pd(II)-catalyzed C–H bond activation [125]. To overcome the problem of catalyst deactivation caused by coordination by the *H*-phosphonate diesters, the corresponding α-hydroxyphosphonate was used as a substrate for a slow, in situ generation of the P-nucleophile.

Mechanistic studies revealed that the catalytic cycle for the reaction in Scheme 18 was of the Pd(II)/Pd(0) type, and silver acetate acted as an oxidant for regeneration of the Pd(II) catalyst. In addition, NMMI was found to be an indispensable reaction component which enabled reductive elimination of the products from the corresponding aryl(phosphonate)Pd(II) complexes. Also, Yu et al. [126] developed a catalytic system for C–H phosphonylation of 2-aminoaryl scaffolds, similar to the system shown in Scheme 18. In this instance, the Pd(II)-catalyst deactivation was attenuated by a slow addition of *H*-phosphonate diesters (ethyl, isopropyl), and *p*-benzoquinone was used to facilitate the reductive elimination step. The postulated Pd(II)/Pd(0) catalytic cycle was completed by oxidation of Pd (0)-species by silver acetate to afford arylphosphonate derivatives in up to 79% yields. This protocol did not work with dibenzyl and diphenyl *H*-phosphonates, but was compatible with various diarylphosphine oxides as coupling partners (yields of triarylphosphine oxides, 39–48%).

Although an allene moiety has been extensively used as a pharmacophore [127], allenylphosphonates have not been explored yet in this context [128]. However, a

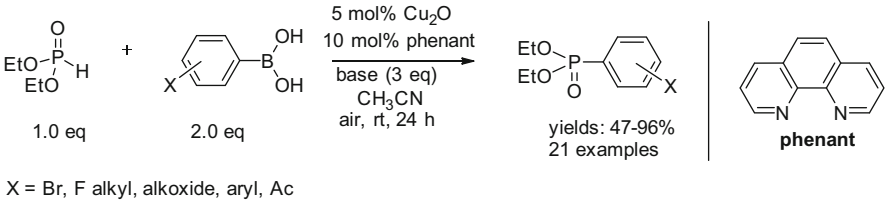


Scheme 19 Stereospecific synthesis of dinucleoside allenylphosphonates and their analogues [129, 130]

novel synthetic method was developed for the preparation of allenylphosphonates, applicable to biologically important natural product derivatives [129, 130]. The method shown in Scheme 19 is based on a palladium-catalyzed propargylic substitution with phosphorus nucleophiles, and represents a new means of formation of the P–C bond. With the proper choice of propargylic components and phosphorus nucleophiles (*H*-phosphonates and their analogues or *H*-phosphinate derivatives), complex organic structures can be generated. The reaction is stereospecific at the phosphorus center and occurs with complete center to axial chirality transfer in the propargylic partner moiety (Scheme 19). Some mechanistic aspects of this reaction were investigated through ab initio calculations [131].

5 Cu-, Ni-, and Other Metal-Catalyzed Reactions

Copper-catalyzed P–C bond formation has recently emerged as a cheaper and more convenient alternative to the Pd-catalyzed reactions. The first catalytic procedure for Cu(I)-mediated coupling of aryl halides with *H*-phosphonate diesters, based on the Ullmann-type of chemistry, was described in 2003 by Buchwald



Scheme 20 Copper-catalyzed cross coupling of arylboronic acids with *H*-phosphonate diesters

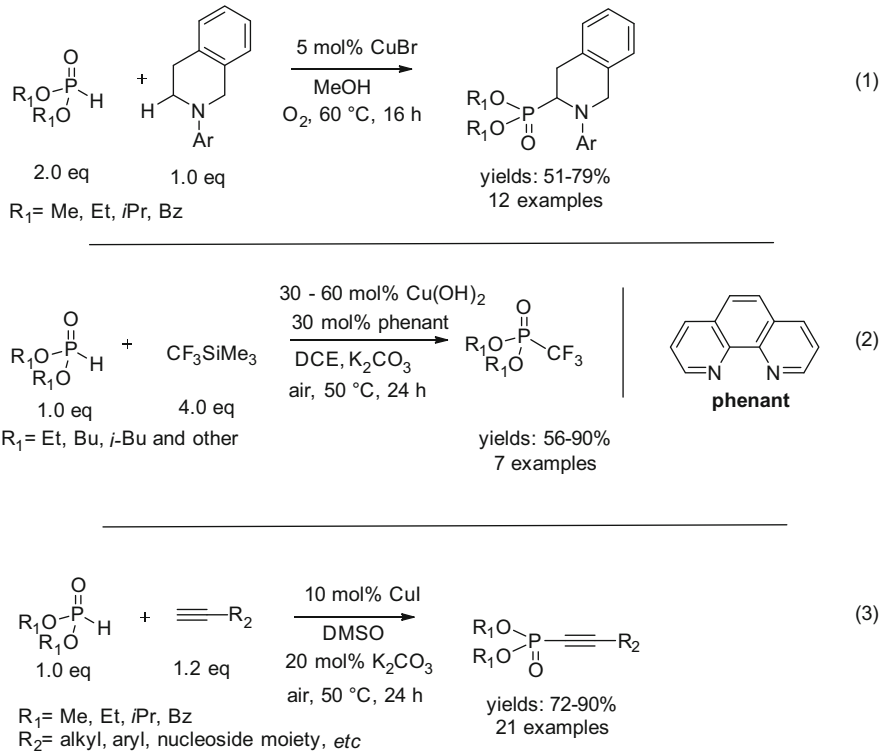
et al. [132]. Since then, the number of applications of copper as a catalyst has steadily increased [133–135].

Scheme 20 depicts a copper-catalyzed synthesis of arylphosphonates using arylboronic acid derivatives and diethyl *H*-phosphonate [136]. Among the bidentate-supporting ligands investigated, the best results were obtained with phenanthroline. The advantage of this method was that the cross coupling could be performed under milder conditions than those of the Hirao arylation protocol.

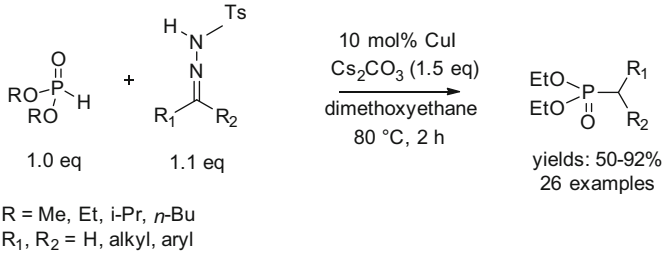
Some other examples for the catalytic construction of P–C linkages via an aerobic phosphonylation of sp^3 and *sp* C–H bonds are presented in Scheme 21. Reaction (1) depicts an efficient cross-dehydrogenative coupling of various dialkyl *H*-phosphonates via activation of an sp^3 C–H bond adjacent to the nitrogen atom in *N*-aryltetrahydroisoquinolines [137]. The reaction shows high regioselectivity and affords the corresponding α-aminophosphonates in high yields. Reaction (2) illustrates the first copper-catalyzed trifluoromethylation of *H*-phosphonate diesters in the presence of phenanthroline as a supporting ligand [138]. This method should allow for the introduction of the CF_3 group into biologically important compounds, thus modifying their electronic and hydrophobic properties. Finally, reaction (3) exemplifies an aerobic oxidative coupling of terminal alkynes with *H*-phosphonates, catalyzed by copper, to generate alkynylphosphonates in high yields under mild conditions [139]. This new method is highly general (examples include aromatic, aliphatic, and complex organic acetylenic compounds) and tolerates a variety of functional groups in the coupling partners (e.g., hydroxyl, alkoxyl, carboxyl, chloro, amino, etc.). In contrast to *H*-phosphonates and *H*-phosphinates, which reacted smoothly with terminal alkynes, no coupling products could be detected under the reaction conditions for secondary phosphine oxide $Ph_2P(O)H$. For this reaction, $CuSO_4$ [132] or recyclable silica-supported carbene-Cu(II) catalyst [140] was used.

Yang, Wu, et al. reported an alternative protocol for the synthesis of alkynylphosphonates via copper-mediated decarboxylative coupling in water, using 1,10-phenanthroline as a supporting ligand [141]. The reaction proceeded under mild conditions (60°C, 24 h) and afforded alkynylphosphonates in 51–88% yields. To suppress hydrolysis of *H*-phosphonate diesters, a few equivalents of isopropanol were used as an additive.

A copper-catalyzed reaction of *N*-tosylhydrazones with *H*-phosphonate diesters was recently investigated as a means for P–C(sp^3) bond formation

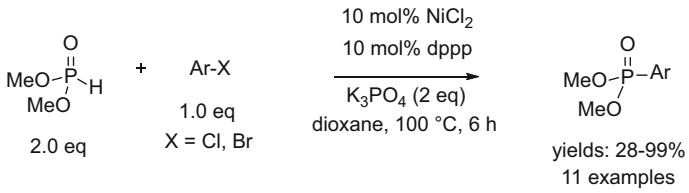


Scheme 21 Some copper-catalyzed aerobic oxidative coupling reactions



Scheme 22 Copper-catalyzed coupling of *H*-phosphonates with *N*-tosylhydrazones [142]

[142–144]. Scheme 22 shows a typical example of such a reaction which affords various alkyl- and benzylphosphonates [142]. This coupling reaction proceeds in good yields, does not require any ligand, and can be performed as a one-pot reaction from the corresponding carbonyl compounds, without isolation of tosylhydrazone intermediates. The above experimental conditions were extended to the cross coupling of *N*-tosylhydrazones with a secondary phosphine oxide $Ph_2P(O)H$ [143]. A modified version of this reaction was also developed, utilizing Cu(II)



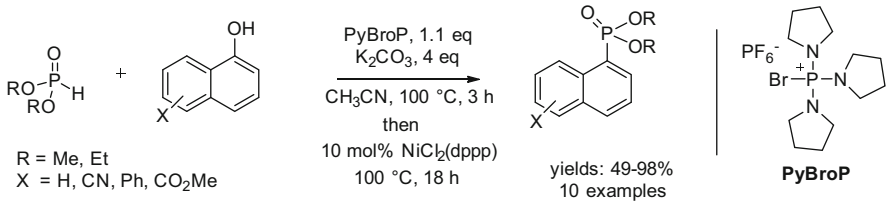
Scheme 23 Nickel-catalyzed coupling of *H*-phosphonates with aryl bromides [150]

precatalysts which undergo in situ reduction by tosylhydrazones to produce catalytically active Cu(I) species [144]. This protocol worked well with *H*-phosphonate diesters and $Ph_2P(O)H$, and with a variety of aliphatic and aromatic substrates bearing electron-rich as well as electron-deficient substituents. A Cu(I)-catalyzed direct oxyphosphonylation of alkenes with *H*-phosphonates in the presence of dioxygen to produce β-ketophosphonates [145], and a three-component, one-pot reaction of azides, alkynes, and *H*-phosphonates, to afford 1,2,3-triazolyl-5-phosphonates [146], were also recently reported.

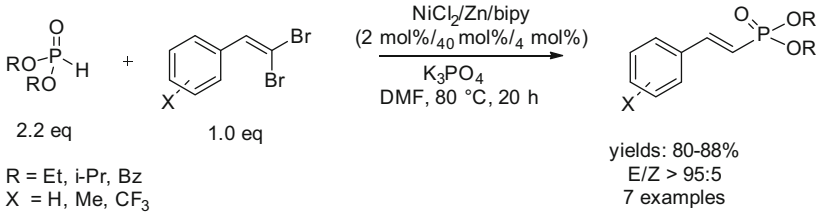
The reaction of trialkyl phosphites with aryl halides catalyzed by Ni(II)X_2 was developed in 1970 by Tavs [147], representing the first synthesis of a P–C bond catalyzed by transition metals; it is referred to as the Ni-catalyzed Arbuzov reaction or the Tavs reaction. It was postulated that the harsh conditions usually required for this reaction are necessary because of the high activation energy for the reduction of Ni(II) to Ni(0) and the oxidative addition step [148].

Tang et al. [149] recently developed milder reaction conditions for nickel-catalyzed cross coupling of aryl halides with $Ph_2P(O)H$, and these were modified by Han et al. [150] to become compatible with *H*-phosphonates as coupling partners (Scheme 23). Mechanistically, this reaction follows a pathway similar to the Hirao reaction pathway (see above), and the best results were obtained with 1,3-bis(diphenylphosphino)propane (dppp, Fig. 3) as a supporting ligand. Since aryl mesylates and tosylates are attractive substrates for cross-coupling reactions [151, 152], a method was developed for the nickel-catalyzed phosphonylation of this type of aromatic electrophiles with *H*-phosphonate diesters [153]. To facilitate cross coupling with these less reactive derivatives, zinc dust was used as a reducing agent for the in situ generation of an active Ni(0) catalyst. In addition, dppf (Fig. 3), a ligand with a bigger bite angle than dppp, was necessary. The reactions were carried out in DMF, in the presence of DIPEA as a base, and afforded the arylphosphonates in 55–90% yields [153]. The method is unsuitable for substrates with electron-donating groups or electron-withdrawing groups in the *para*-position of the aromatic ring. Recently, arylboronic acids were reported as new coupling partners with *H*-phosphonates, *H*-phosphinates, and *H*-phosphine oxides for nickel-catalyzed P–C bond formation [154].

For electron-deficient phenols which are usually difficult to phosphonylate, a new Ni-catalyzed cross-coupling protocol was developed (Scheme 24). The method involves activation of a phenol with bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP), followed by Ni-catalyzed coupling with *H*-phosphonate



Scheme 24 One-pot Ni(II)-catalyzed cross-coupling reaction mediated by PyBroP [155]



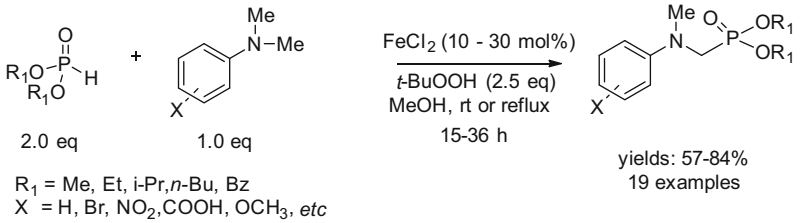
Scheme 25 Ni-catalyzed cross coupling of *gem*-dibromoalkenes with *H*-phosphonate diesters

diesters or diaryl phosphine oxides [155]. The reaction can be carried out as a one-pot procedure without the need for isolating the activated phenol intermediate.

Alkenyl–phosphorus compounds bearing a vinyl group attached to the phosphorus center are an important class of chemicals which are used extensively in pharmaceuticals and material sciences [156–158]. Scheme 25 depicts a new synthetic approach to vinylphosphonates, utilizing Ni(0)-catalysis [159]. The reaction consists of two steps: (1) the Hirao-type of reduction which generates a bromovinyl intermediate, followed by (2) Ni(0)-catalyzed cross coupling with *H*-phosphonate diesters. This is a highly stereospecific process which produces, in a one-pot procedure, the corresponding vinylphosphonate derivatives. Zinc dust acts as a reducing agent for converting Ni(II) into the catalytically active Ni(0) species which is stabilized by the supporting 2,2′-bipyridine (bipy, Fig. 3) ligand. A mechanism proposed for this reaction was substantiated by computational and ^{31}P NMR studies [159].

Although typical reactions for the synthesis of α-aminophosphonates are those of the Pudovik and the Kabachnik–Fields types (see Sect. 2, Scheme 1), these compounds are also accessible via transition metal-catalyzed cross couplings (e.g., see Scheme 21, Reaction 1). Scheme 26 shows an example of a selective C–H to C–P bond transformation with aryl tertiary amines which is catalyzed by $FeCl_2$ [160, 161].

Aniline derivatives bearing various alkyl groups, or having a nitrogen atom as part of their cyclic systems (e.g., pyrrolidine, piperidine), also smoothly underwent this oxidative α-phosphonylation. Mechanistic investigations showed that the reactions proceeded with intermediate *N*-aryl iminium ions (mediated by Fe/BuOOH), which were reactive enough to be intercepted by *P*-nucleophiles [160].



Scheme 26 Iron-catalyzed α-phosphonylation of the C(sp^3)-H bond in *N*,*N*-dimethylanilines [160]

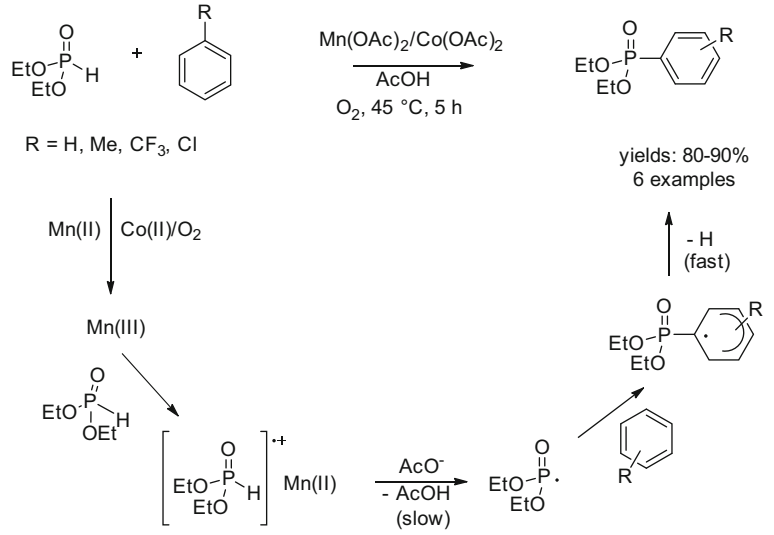
6 Free Radical Reactions

Because of the presence of a medium-strong P–H bond (ca 77 kcal/mol; actually weaker than the N–H or C–H bond), *H*-phosphonate diesters can relatively easily generate phosphorus-centered radicals which may undergo various transformations relevant to synthetic organic chemistry [162, 163]. In 1958, Stiles et al. [164] reported on the first radical addition of *H*-phosphonate diesters to various olefins using light or peroxides as initiators. However, it was not until recently that Ishii et al. [165] disclosed their results on manganese-mediated activation of *H*-phosphonate diesters, and that a free-radical phosphonylation, via C–H bond functionalization, became an important way to form the P–C bond [17].

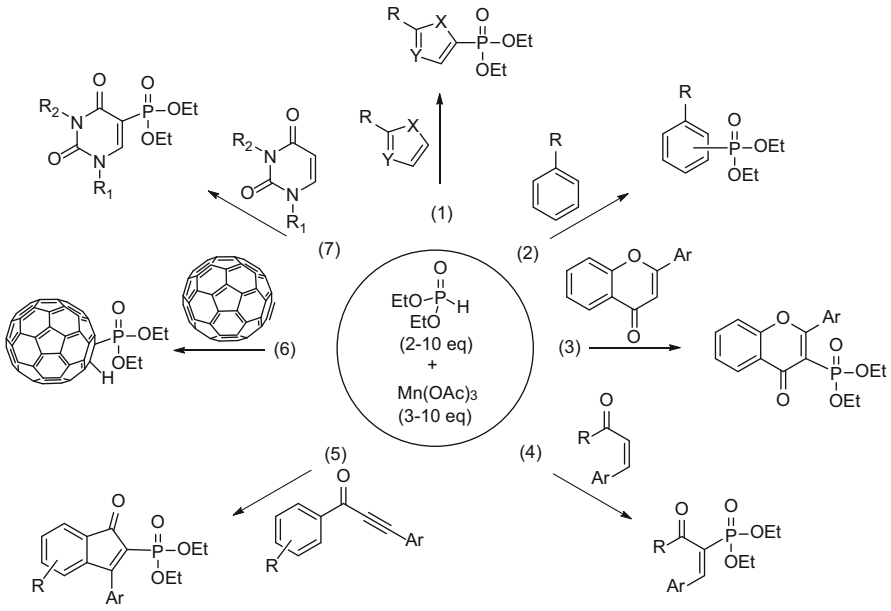
In 2006, Ishii et al. [153] developed the first catalytic phosphonylation of arenes using a $Mn(OAc)_2/Co(OAc)_2/O_2$ redox system [166] (Scheme 27).

The authors proposed that the reaction involved a phosphonyl radical intermediate, generated in situ by a one-electron oxidation of the *H*-phosphonate by Mn(III). This is followed by the addition of the radical to the aromatic system, and, ultimately, formation of arenephosphonates (see Scheme 27). Consistent with the proposed mechanism, the reaction was markedly accelerated by KOAc. In some instances, formation of bisphosphonylated products (up to 9%), was observed.

This method was further simplified by using Mn(III) as a stoichiometric oxidant. Some synthetic transformations based on this reaction are shown in Scheme 28. Zhang et al. [167] developed direct phosphonylation of heteroaromatic compounds, such as thiazoles, furans, and pyrroles (Reaction 1, Scheme 28). These transformations were carried out in acetic acid (3 h, 80°C), and afforded the phosphonylated products in high yields (84–95%) with complete regioselectivity. A free-radical mechanism, similar to the one shown in Scheme 27, was proposed. The same reaction conditions were recently applied to the phosphonylation of mono- and disubstituted arenes [168] (Reaction 2, Scheme 28). To secure high yields (80–90%), threefold molar excess of Mn(III) relative to the *H*-phosphonate component was required. The observed regioselectivity was rationalized on the basis of the assumed free radical mechanism [168]. The same authors observed that phosphonyl radicals generated from *H*-phosphonate diesters and Mn(III) added



Scheme 27 Free radical, manganese-catalyzed arene phosphonylation [166]



Scheme 28 Free radical, Mn(III)-catalyzed phosphonylation reactions

selectively to the three-position of flavones and coumarins (Reaction 3, Scheme 28), producing the corresponding phosphonates in moderate to good yields [168].

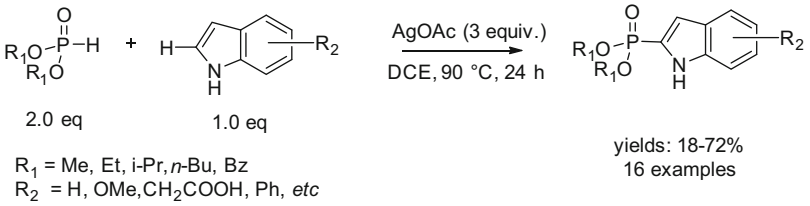
In contrast to aromatic/heteroaromatic phosphonylation, the synthesis of vinylphosphonates turned out to be more challenging. This was because of the competing polymerization of the alkenes used for the reaction, and problems with controlling regio- and stereo-(*E*/*Z*)-selectivity (Reaction 4, Scheme 28). To address these problems, Zhang et al. [169] developed reaction conditions for the regioselective phosphonylation of conjugated arylalkenes bearing a keto, nitro, or ester functionality in the α-position (Reaction 4, Scheme 28). Both the carbonyl and aryl groups in the substrates were necessary to control reactivity and regioselectivity of the phosphonylation process. Reaction 5 in Scheme 28 is similar to this wherein phosphonylated indenone derivatives are formed in 70–80% yield from the corresponding arylalkynes [169]. The reaction consists of the addition of a phosphonyl radical to the triple bond, followed by an intramolecular free radical cyclization.

Wang et al. [170] investigated phosphonylation of fullerene with *H*-phosphonate diesters or phosphine oxides mediated by Mn(III) (Reaction 6, Scheme 28). The phosphonylated fullerene shown in the scheme was formed in 62% yield; however, depending on the ratio of the reactants, other fullerene derivatives can be formed as major products (e.g., single bonded phosphonylated fullerene dimers or hydrophosphonylated fullerenes with the acetoxy group) [159].

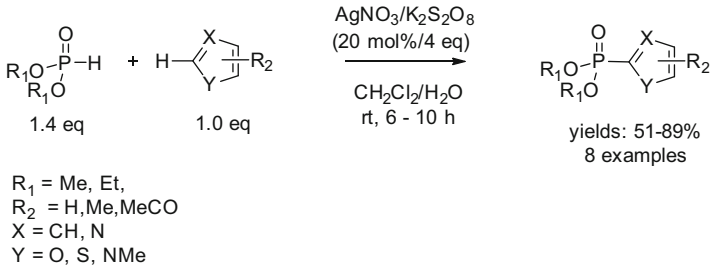
An efficient synthesis of 5-phosphonylated uracil derivatives (Reaction 7, Scheme 28) via an Mn(III)-mediated coupling of *H*-phosphonate diesters with various uracil precursors was also developed [171]. The starting materials for this reaction, besides simple alkyl derivatives, included ribo-, deoxy-, and dideoxyuridines; they afforded the phosphonylated products in 68–99% yields. As in the other protocols for this type of free radical reactions, acetic acid was used as a solvent. These reaction conditions were later extended to phosphonylation of pyridine-2-ones and pyrimidine-4-ones [172].

Apart from manganese, silver is another metal frequently used in free radical oxidation reactions [173]. Recently, Wan et al. [174] developed direct phosphonylation of indoles using Ag(I) as a stoichiometric oxidant (Scheme 29).

This method provides a convenient access to biologically important indolylphosphonates, albeit in moderate yields. A free radical mechanism for this reaction was proposed on the basis of influence of the substituents and sensitivity to radical inhibitors (butylated hydroxytoluene, BHT).



Scheme 29 Ag(I)-mediated oxidative coupling of indoles with *H*-phosphonate diesters



Scheme 30 Silver-catalyzed dehydrogenative phosphonylation of five-membered heteroarenes

A catalytic system for phosphonylation of various heteroaromatic compounds (Scheme 30) was developed [175] to reduce the amount of silver used.

It was hypothesized that Ag(II) was catalytically active in this reaction; it was formed from Ag(I) via oxidation with peroxydisulfate $K_2S_2O_8$ during the course of the reaction which converted the *H*-phosphonate diester into a cation radical. The mechanism is similar to the mechanism proposed by Effenberger et al. [173]. The best results were obtained in methylene chloride/water using 13 mol% of $AgNO_3$ and fourfold excess of the oxidant. These reaction conditions were extended to phosphonylation of pyridines and quinolines, but the yields were lower because of competing formation of the corresponding *N*-oxides [175]. To remedy this problem, an additional step was added to the synthetic protocol, namely the reduction of *N*-oxides with $Na_2S_2O_3$. This significantly increased the yields (53–81%) of pyridyl- and quinolylphosphonates.

A similar catalytic system was also successfully developed for dehydrogenative cross coupling of *H*-phosphonate diesters with arenes bearing strongly electron-withdrawing substituents (e.g., nitro, sulfonyl groups) [176]. This protocol for the C–H-functionalization (Ag_2SO_4, 10 mol%; $K_2S_2O_8$, 3 equiv.; CH_3CN/water, 1:1, v/v; 90°C; 1–12 h) has a broad substrate scope and is suitable for the preparation of *ortho*-phosphonylated aromatic compounds (yields 55–82%, 25 examples). This catalytic system also worked well in the phosphonylation of various pyrroles [177].

New types of electrophilic components, diaryliodonium salts [178], have recently been promoted as superior substrates for room temperature synthesis of arylphosphonates from *H*-phosphonate diesters. This reaction is catalyzed by CuCl (5 mol%), and affords the coupling products in high yields (75–95%) within 10 min. A free radical mechanism for this reaction was suggested.

Other free radical reactions, not involving metal catalysis, were also reported for C–P bond formation. These include photochemical activation of the P–H bond by eosin Y [179], 2,2-dimethoxy-2-phenylacetophenone (DPAP) [180], an Ru(II)- or Ir(III)-bipyridyl photocatalyst [181], a microwave-assisted reaction of dimethyl *H*-phosphonate with cyclohexane and alkene oxides [182], and radical telomerization of fluorinated alkenes with *H*-phosphonate diesters acting as telogens [183].

7 Other Types of Reactions

The addition of H–P=O compounds to unsaturated carbon frameworks (e.g., acetylenes, olefins, allenes, dienes, isocyanides) is another powerful strategy for preparing organophosphorus compounds. In these instances, Ni- and Pd-based catalysts are commonly used [184–187]. Chemical, stereochemical, and mechanistic aspects of these reactions, along with studies on the development of new catalysts, have been thoroughly covered in a recent review by Tanaka [188]; they are not the subject of this survey.

8 Final Remarks

Because of the chemical, biological, medicinal, and industrial importance of phosphorus compounds containing P–C bonds, synthetic methods for preparing C-phosphonates and related compounds are of great importance in contemporary bioorganic phosphorus chemistry. In this respect, *H*-phosphonate diesters, with their ability to act as nucleophiles, electrophiles, and P-centered free radicals, provide a plethora of mechanistic ways in which the phosphorus–carbon bond can be formed; they are unrivalled phosphorus substrates. Currently, both classical methods for P–C bond formation (the Michaelis–Arbuzov, the Michaelis–Becker, the Pudovik, the Abramov, and the Kabachnik–Fields reactions) and those based on organocatalysis or transition-metal catalyzed cross couplings are still viable synthetic options.

It seems that further progress in developing (1) enantioselective methods for the formation of C(sp^3)–P bonds using chiral auxiliaries, (2) broadening the scope of the reactions catalyzed by Fe, Cu, Ni, and various chiral organocatalysts, and (3) designing new methods for diverse, direct C–H bond functionalization under environmentally friendly conditions will all be of particular importance in the future.

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Carbon–Hydrogen to Carbon–Phosphorus Transformations

Jean-Luc Montchamp

Abstract Literature published between 2008 and 2013 concerning the functionalization of carbon–hydrogen into carbon–phosphorus bonds is surveyed. The chapter is organized by reaction mechanism. The majority of methods still proceed via deprotonation of C–H into C–M (M=Li, Na, etc.) followed by reaction with a phosphorus electrophile P–X, where X is usually chlorine. A few examples of electrophilic aromatic substitution and related processes have also been reported, although this approach has not yet been developed significantly. Over the past 5 years a rapidly growing family of reactions includes transition metal "C–H activation" and formally related radical-based processes has been developed. The latter processes offer exciting prospects for the synthesis of organophosphorus compounds.

Keywords C–H activation, Metallation, Phosphanyl, Phosphinyl, Phosphonyl, Phosphorus electrophiles, Radical reactions

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Abbreviations

Ac	Acetyl
Ar	Aryl
BIPHEP	2,2′-Bis(diphenylphosphino)-biphenyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
Bp	Boiling point
Bpy	2,2′-Bipyridyl
BQ	1,4-Benzoquinone
brsm	Based on recovered starting material
Bu	Butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
cat	Catalyst
concd	Concentrated
Cy	Cyclohexyl
d	Day(s)
$(DHQD)_2PYR$	Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DOPO	6*H*-Dibenzo[*c,e*][1,2]oxaphosphorine 6-oxide
dppe	Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppm	Bis(diphenylphosphino)methane
ee	Enantiomeric excess
equiv.	Equivalent(s)
Et	Ethyl
h	Hour(s)
i-Pr	Isopropyl
KHMDS	Potassium hexamethyldisilazide potassium bis(trimethylsilyl) amide
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide lithium bis(trimethylsilyl)amide
Me	Methyl
Mes	Mesityl 2,4,6-trimethylphenyl (not methanesulfonyl)
min	Minute(s)

mol	Mole(s)
MTBE	Methyl *tert*-butyl ether
Nu	Nucleophile
Oct	*n*-Octyl
Ph	Phenyl
Pr	Propyl
py	Pyridine
rt	Room temperature
s	Second(s)
s-Bu	*sec*-Butyl
t-Bu	*tert*-Butyl
THF	Tetrahydrofuran
THP	Tetrahydropyran, tetrahydropyranyl
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	4-Methylphenyl
Tr	Triphenylmethyl (trityl)

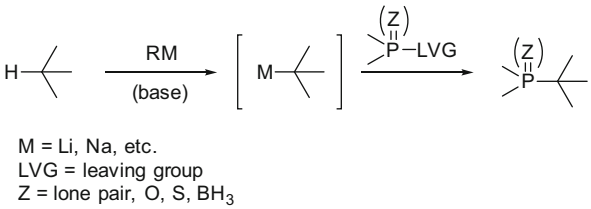
1 Introduction

This chapter surveys the literature dealing with the conversion of carbon–hydrogen bonds into carbon–phosphorus bonds published between 2008 and 2013. Three general types of reactions are considered: (1) C–H deprotonation followed by reaction with a phosphorus electrophile; (2) electrophilic aromatic (and related) substitution with phosphorus electrophiles; and (3) oxidative arylation and related processes, including transition metal "C–H activation" and radical processes.

The first approach is by far the most commonly employed and this chapter cannot review every single example of this type of reaction, even for just the last 5 years. Instead, representative examples are discussed. The second approach is still relatively underdeveloped (although it has industrial importance) and up-to-date examples are rare. Unlike the other two approaches, the third is very up-to-date and growing rapidly.

2 Reactions via Carbon–Metal Intermediates with Phosphorus Electrophiles

The deprotonation of acidic C–H precursors with a strong base, followed by reaction of the intermediate with a phosphorus electrophile (Scheme 1), is by far the most common "classic" approach to prepare a wide range of organophosphorus compounds. The vast majority of examples relate to the deprotonation–phosphinylation of C_{sp2}–H and C_{sp}–H, usually for the synthesis of aryl- and



Scheme 1 The C–H deprotonation approach

alkynyl-phosphine ligands. Because numerous examples are available, only selected representative examples are discussed in this section. The most common phosphorus electrophiles used are disubstituted chlorophosphanes R_2PCl. Other electrophiles include $R_2P(BH_3)Cl$ and $(RO)_2P(O)Cl$.

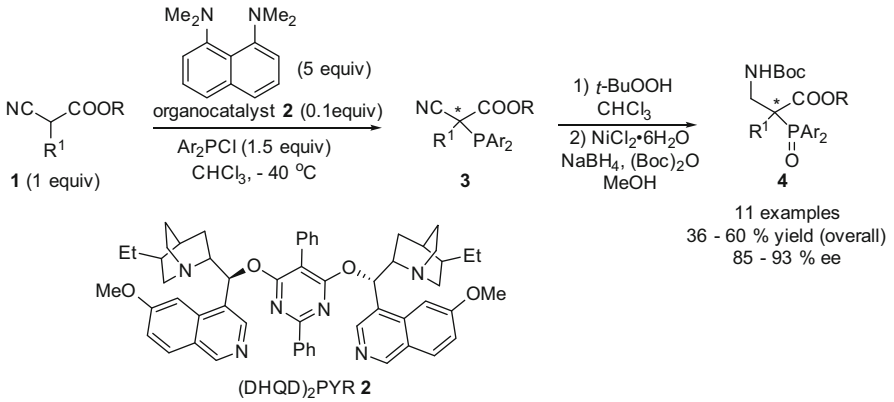
2.1 Deprotonation of C_{sp3}–H

In this class of reaction, the deprotonation of C_{sp3}–H is less common than with other hybridization of carbon. Nonetheless, several recent examples have been reported. Jørgensen and coworkers [1] reported the asymmetric electrophilic phosphination of α-substituted cyanoacetates **1** with cinchona organocatalyst **2** (Scheme 2). The intermediate **3** is converted into the phosphine oxide, after which the nitrile is reduced into an amine and protected in the presence of di-*tert*-butyl dicarbonate (Boc_2O). The entire sequence proceeds in moderate to good overall yields and excellent enantiomeric excesses.

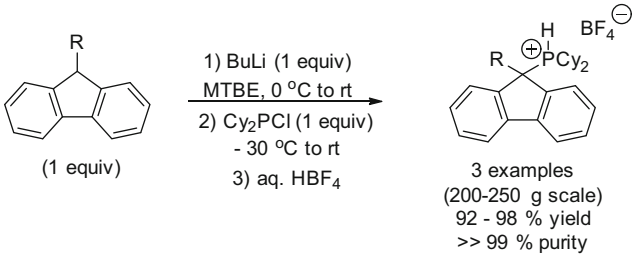
The phosphination of fluorene derivatives has been investigated by the Plenio group. For example, Plenio and coworkers [2] deprotonated 9-alkylfluorene with *n*-butyl lithium in MTBE as solvent to prepare phosphine ligands for palladium-catalyzed processes (Scheme 3). The reactions are conducted on a large scale. The intermediate phosphines are protonated with aqueous tetrafluoroboric acid to deliver crystalline phosphonium salts in excellent yield and purity.

Similarly, Xie and coworkers [3] deprotonated fluorene and isolated the resulting anion, which was subsequently reacted with dichloro(diisopropylamino) phosphine $i\text{-}Pr_2NPCl_2$ (Scheme 4). The product was used to prepare carborane-containing derivatives.

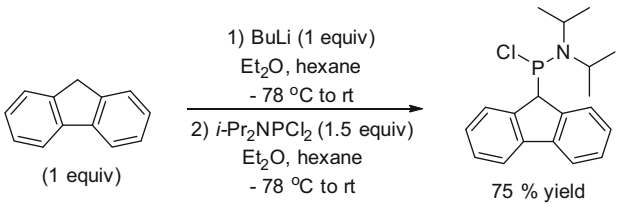
Smits and Wiemer [4] synthesized alkyl-1,1,1-trisphosphonate esters through the deprotonation of alkyl-1,1-bisphosphonate esters followed by reaction with chlorodiethoxyphosphine $(EtO)_2PCl$ and subsequent oxidation with hydrogen peroxide (Scheme 5). Interestingly, the direct alkylation of the unsubstituted 1,1,1-trisphosphonate ester $[(EtO)_2P(O)]_3CH$ with NaH as the base did not give the corresponding product. This was attributed to the steric hindrance of the carbon



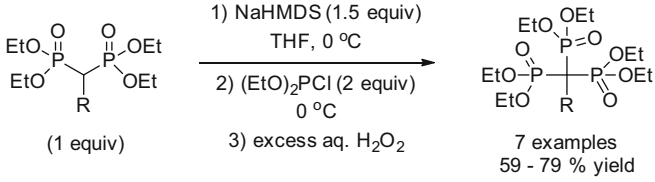
Scheme 2 Organocatalytic asymmetric electrophilic phosphination of α-substituted cyanoacetates [1]



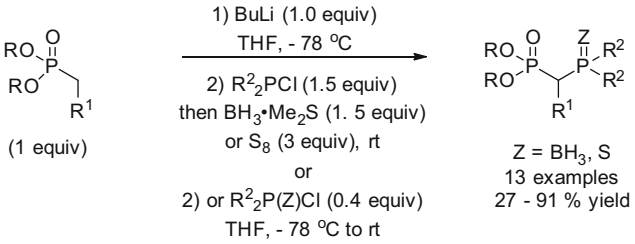
Scheme 3 Large scale synthesis of 9-alkylfluorenyl-dicylohexyl phosphines [2]



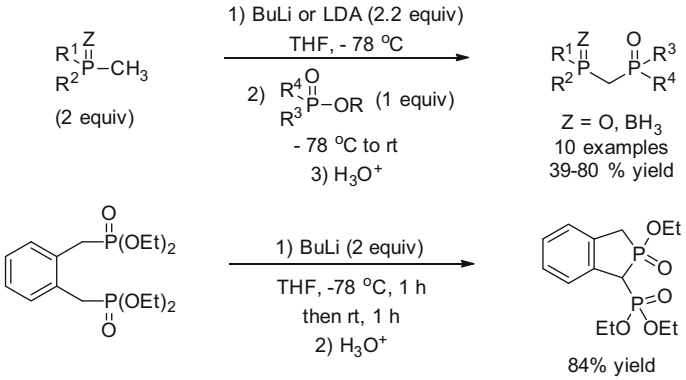
Scheme 4 Fluorene functionalization [3]



Scheme 5 Preparation of alkyl-1,1,1-trisphosphonate esters [4]



Scheme 6 Preparation of mixed 1,1-bisphosphorus compounds [5]



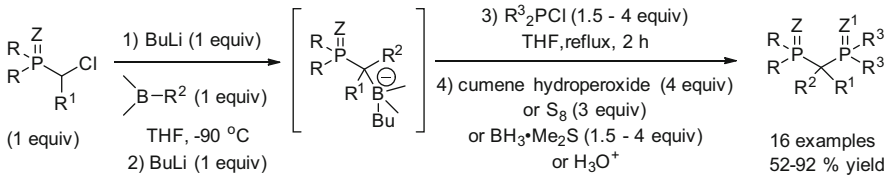
Scheme 7 The phosphorus-Claisen/Dieckmann condensation [6]

because the anion could form ($pK_a \sim 6.5$). Many other compounds were synthesized from the allylated trisphosphonate (R=allyl).

Montchamp and coworkers [5] reported a study of the reaction between phosphonomethyl anions and various phosphorus electrophiles for the preparation of mixed 1,1-bisphosphorus compounds (Scheme 6).

While the self-condensation of phosphonomethyl anions had been occasionally reported and used, Montchamp and coworkers [6] explored the generality of the phosphorus-Claisen (and Dieckmann) condensations in which the electrophile is a phosphorus ester P(O)(OR) instead of a chlorophosphine (Scheme 7). The reaction appears to be widely applicable and convenient because it alleviates the need for phosphorus–chlorine electrophiles, which are sometimes not readily available.

A final example, from Antczak and Montchamp [7], uses phosphorus carbenoids for the functionalization of an acidic C_{sp3}–H. The reaction proceeds via formation of an organoborane intermediate after one group has migrated. Addition of *n*-butyl lithium is then required to activate the P–C–B moiety toward electrophilic attack. Various phosphorus electrophiles can be used. The entire process is conducted in a single vessel without intervening isolation, and delivers a broad range of mixed 1,1-bisphosphorus compounds in good yield (Scheme 8).



Scheme 8 Synthesis of 1,1-bisphosphorus compounds from phosphorus-carbenoids via organoboranes. Z, Z^1 = O, S, BH_3, lone pair; R, R^3 = EtO, Ph; R^1, R^2 = carbon chain [7]

2.2 *Deprotonation of C_{sp2}–H*

This is the most widely employed method and complete coverage for the past 5 years is impossible. Instead, only a few illustrative examples are discussed below. The reader should consult the references and the earlier literature cited therein. This approach is used extensively for the synthesis of phosphine ligands. Typically, C_{sp2}–H deprotonation (with *n*-, *sec*-, or *tert*-BuLi) is directed by a chelating functional group, or in some cases the phosphorus electrophile is already part of the directing group so a rearrangement takes place (Scheme 9). More acidic ferrocene can be deprotonated directly without any directing group to prepare 1,1′-bis(diphosphino)ferrocene derivatives, such as dppf.

A highly representative example from Asensio and coworkers [8] is shown in Scheme 10. Room temperature deprotonation of 9,9-dimethylxanthene with *s*-BuLi/TMEDA and then reaction with chlorodiisopropylphosphine provides the corresponding bisphosphine ligand in excellent yield.

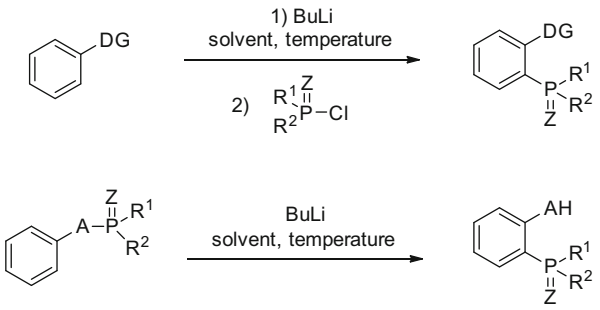
Mathey and coworkers [9] deprotonated furan with *n*-butyl lithium and reacted the intermediate with 1-cyano-3,4-dimethylphosphole **5** to give compound **6** in 60% yield (Scheme 11).

Cowie and coworkers [10] investigated the phosphinylation of *N*-methylaniline with various chlorophosphines (Scheme 12). As others have also reported [11, 12], *N*-methylaniline can be converted into the *o*-lithiocarbamate (*n*-BuLi, CO_2), which is then lithiated with *tert*-butyl lithium to form intermediate **7**. Reaction of **7** with chlorophosphines gives the corresponding 2-*N*-methylaniline derivatives **8**. Only diphenylchlorophosphine gave a good yield of product **8** (R^1=R^2=Ph).

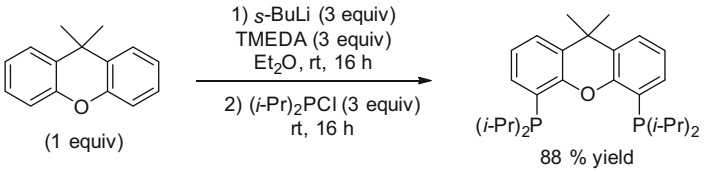
Li and coworkers [13] prepared various 2-(diphenylphosphino)phenol ligands **9** using THP as a directing group (Scheme 13). If a second lithiation is conducted before hydrolysis, compound **10** can be obtained in moderate yield.

Claverie and coworkers [14] synthesized a variety of (arylsulfonyl)phosphines using the sulfonate as a directing group (Scheme 14). The phosphines were used to prepare palladium catalysts for the polymerization of ethylene.

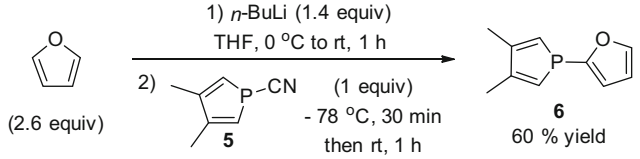
Woollins and coworkers [15] prepared 8-methoxynaphthyl derivatives using lithiation of 8-methoxynaphthalene with *tert*-butyl lithium. The intermediate organolithium was reacted with chlorodiphenylphosphine and chlorodiethoxyphosphine (Scheme 15). The phosphines were converted to other products.



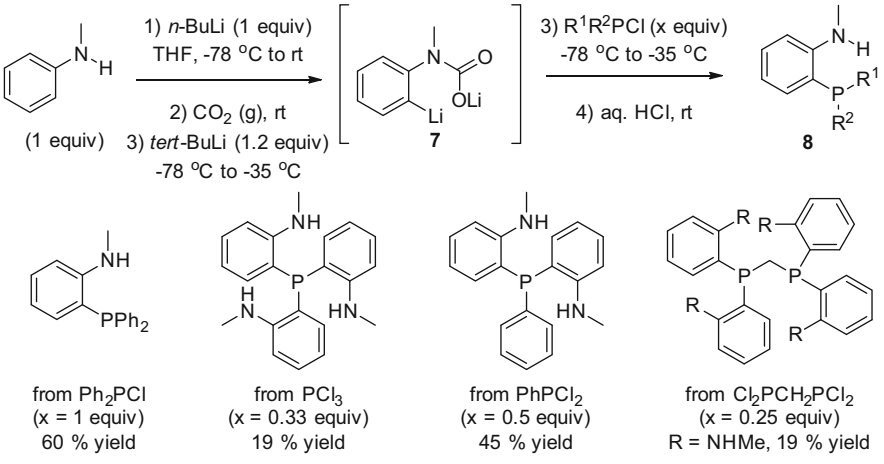
Scheme 9 General method for the functionalization of arylic C–H bonds (*DG* = directing group, A = O, NH, etc., Z = O, lone pair, etc.)



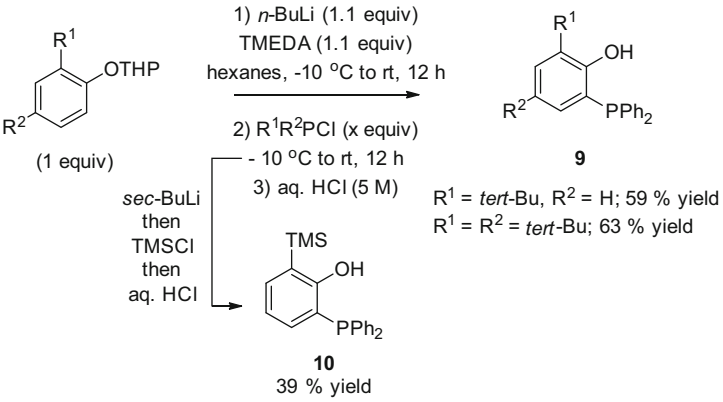
Scheme 10 Representative example of the lithiation/phosphinylation approach [8]



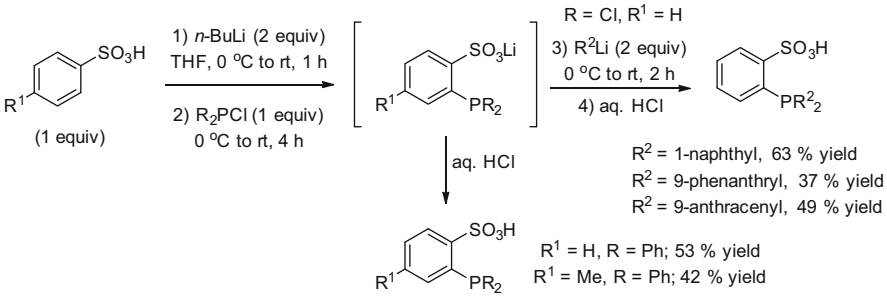
Scheme 11 Synthesis of phosphole **6** [9]



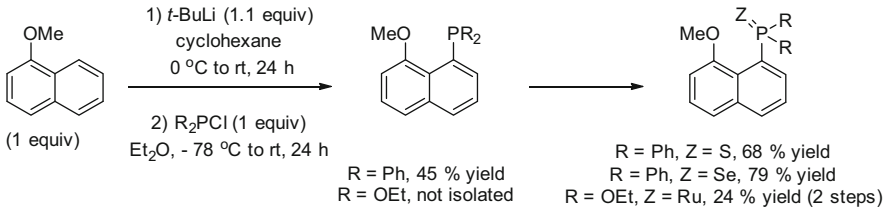
Scheme 12 *O*-Lithiocarbamate as a directing group: synthesis of 2-*N*-methylaniline phosphines [10]



Scheme 13 Tetrahydropyranyl as a directing group: synthesis of 2-(diphenylphosphino)phenols [13]



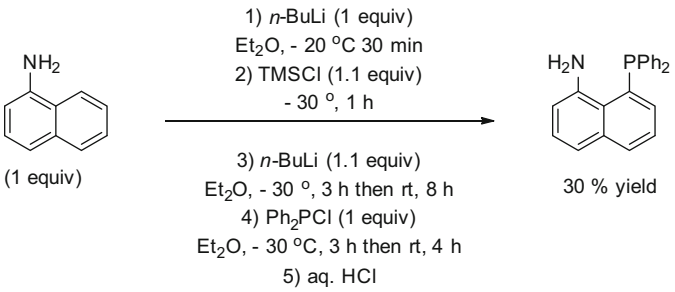
Scheme 14 Sulfonate as a directing group: synthesis of 2-(arylsulfonyl)phosphines [14]



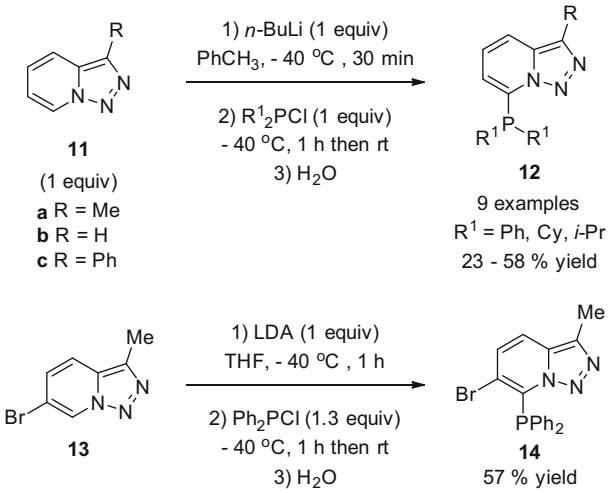
Scheme 15 (8-Methoxynaphth-1-yl)diphenylphosphine and related compounds [15]

Zheng and coworkers [16] prepared 1-(8-diphenylphosphino)naphthylamine from 1-naphthylamine (Scheme 16). The reaction gives a mixture of the 2- and 8-isomers, but the 8-isomer can be isolated in high purity by chromatography. This compound was then elaborated into novel chiral phosphine–phosphoramidite ligands for asymmetric hydrogenation.

Ballesteros, Leroux, and coworkers [17] prepared a range of phosphines **12** through regioselective lithiation of the triazolopyridines **11** (Scheme 17). The



Scheme 16 Synthesis of 1-(8-diphenylphosphino)naphthylamine [16]

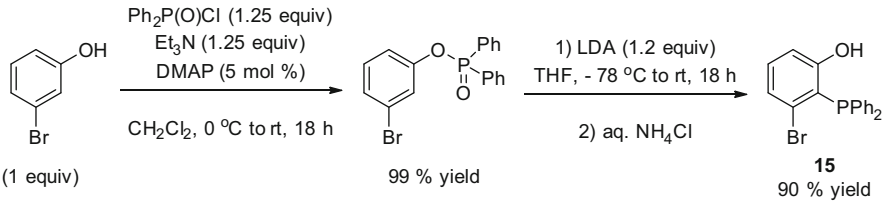


Scheme 17 Synthesis of 1-(8-diphenylphosphino)naphthylamine [17]

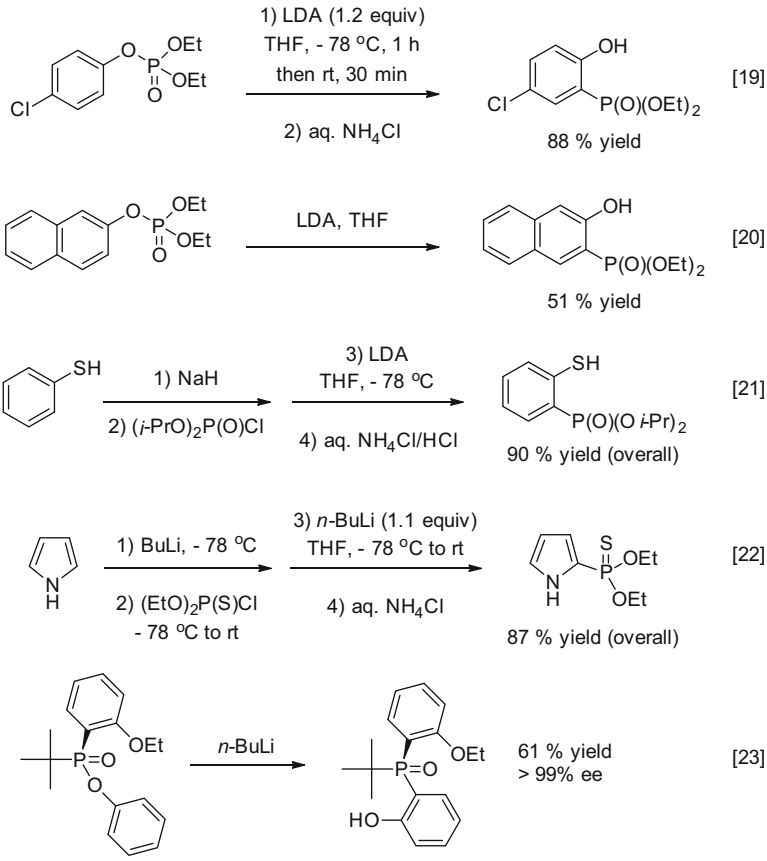
yields of **12** were generally around 50%. The 6-bromo derivative **13** could also be converted into **14**, but using LDA instead. Compounds **12** and **14** were carefully characterized spectroscopically to probe the conformational preference of the phosphorus lone pair.

The rearrangement route (anionic phospho-Fries rearrangement, bottom of Scheme 9) was employed in the preparation of various organophosphorus compounds used in a broad range of studies.

Brown and coworkers [18] prepared 3-bromo-2-(diphenylphosphoryl)phenol **15** from 3-bromophenol in excellent overall yield (Scheme 18). Compound **15** was then elaborated into 3,3′-dialkoxy-BIPHEP derivatives through Ullmann coupling. These ligands were resolved in situ by a chiral rhodium complex and used in asymmetric hydrogenation.



Scheme 18 Synthesis of 3-bromo-2-(diphenylphosphoryl)phenol **15** [18]



Scheme 19 Anionic phospho-Fries rearrangement [19–23]

Similar rearrangements have been conducted on 4-substituted-phenol [19], 2-naphthol [20], thiophenol [21], pyrrole [22], and *P*-stereogenic phenyl phosphinate esters [23] (Scheme 19).

2.3 *Deprotonation of C_{sp}–H*

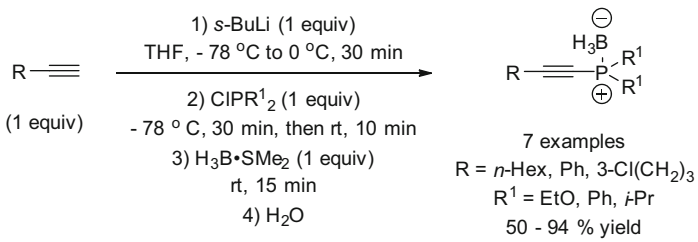
As with C_{sp2}–H, the deprotonation of C_{sp}–H followed by reaction with a phosphorus electrophile is a standard method in organophosphorus synthesis. Because the pK_a of terminal alkynes is lower than arylic hydrogens, the reaction is usually easier. Below are some representative examples of this approach.

Ortial and Montchamp [24] prepared a series of alkynylphosphine borane complexes through deprotonation of terminal alkynes with *s*-BuLi, followed by reaction with chlorophosphines (Ph_2PCl, *i*-Pr_2PCl, $(EtO)_2PCl$) and complexation with boranes (Scheme 20).

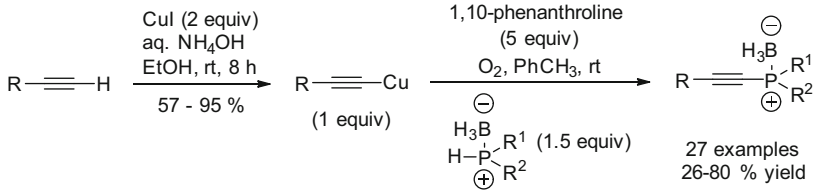
Alayrac, Gaumont, Evano, and coworkers [25] recently reported the synthesis of similar compounds, but through the oxidative coupling of alkynylcopper reagents with secondary phosphine borane complexes ($R^1R^2P(BH_3)H$) (Scheme 21). With *P*-stereogenic phosphine boranes, retention of configuration is observed. The alkynylcopper reagents are isolated before the coupling step.

Traditional lithiation has been used in numerous cases to prepare alkynylphosphorus compounds through reaction with electrophiles usually containing P–Cl bonds. One example using P–F bonds was recently reported by Elias and coworkers [26] for the preparation of alkynylphosphazene derivatives **16** and **17** (Scheme 22). Selective monosubstitution could not be achieved, but each compound was isolated. Compound **16** was also reacted with other alkynyllithium reagents to give disubstituted products similar to **17**.

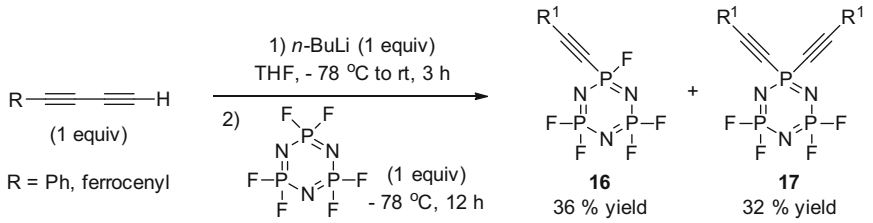
Other examples [27–31] of various synthesized phosphines are shown in Scheme 23. Compounds **18**–**26** were synthesized for a wide variety of applications.



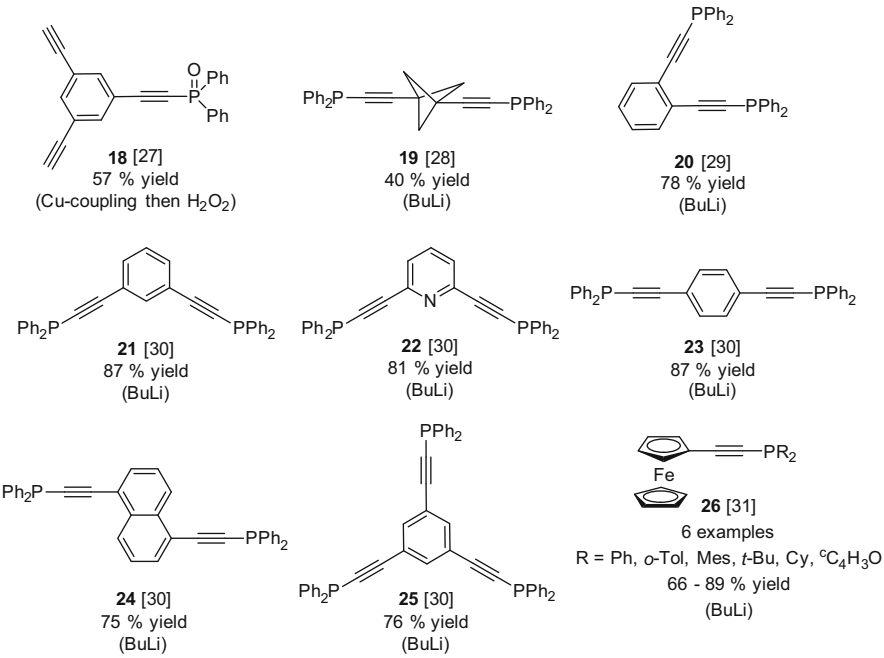
Scheme 20 Preparation of alkynylphosphine borane complexes [24]



Scheme 21 Preparation of alkynylphosphine borane complexes through oxidative coupling [25]



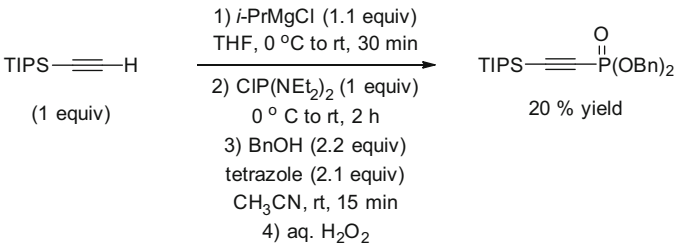
Scheme 22 Preparation of alkynylphosphazenes [26]



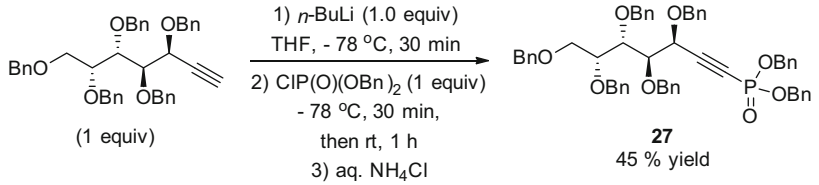
Scheme 23 Various alkynylphosphorus compounds synthesized from the corresponding alkyne [27–31]

Allister and Webb [32] synthesized dibenzyl and di-*tert*-butyl alkynylphosphonate derivatives. Scheme 24 is representative of this approach. All attempts to prepare the ethynyl compounds by transesterification of the diethyl ethynylphosphonate failed.

Vincent and coworkers [33] prepared 1,1′-dideoxy-1′-(dibenzyl phosphinyl)-2,3,4,5,6-penta-*O*-benzyl-D-galacto-hept-1′-ynitol **27** (Scheme 25) en route to UDP-galactopyranose mutase (UGM) inhibitors.



Scheme 24 Synthesis of dibenzyl (triisopropylsilyl)ethynylphosphonate [32]



Scheme 25 Synthesis of dibenzyl (triisopropylsilyl)ethynylphosphonate **27** [33]

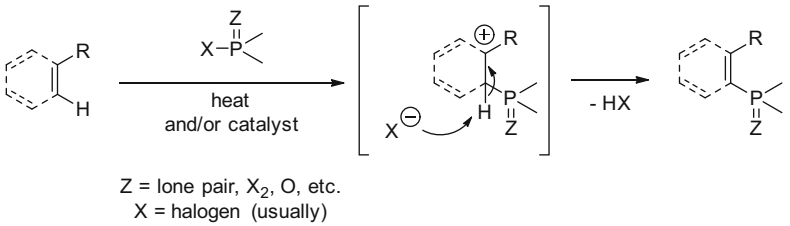
3 Reactions of Carbon–Hydrogen Bonds with Phosphorus Trichloride and Related Reagents

Another approach is the direct reaction of unsaturated compounds with phosphorus electrophiles (Scheme 26). Not surprisingly, the reaction generally proceeds in a similar way to electrophilic aromatic substitutions (Friedel–Crafts). Few examples are therefore available with aromatic nucleophiles. Fewer still are available with rather special alkenes. With alkanes, the reaction is known and it proceeds via a radical mechanism, but little recent work is detailed in the literature.

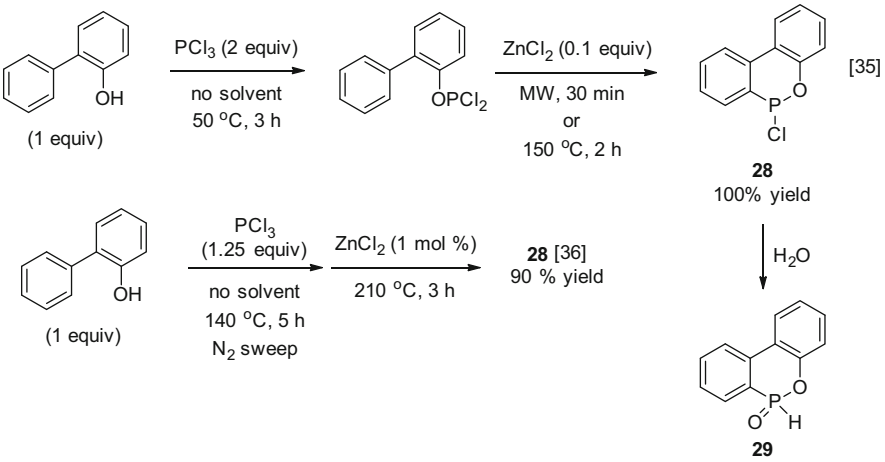
3.1 Electrophilic Aromatic Substitution

The reaction of benzene with phosphorus trichloride PCl_3 in the presence of stoichiometric amounts of aluminum chloride $AlCl_3$ has been known for a long time and is the basis for the large scale preparation of dichlorophenylphosphine ($PhPCl_2$). Some attempts at improving this reaction have been made. For example, Wang and Wang [34] conducted the reaction in ionic liquids, allowing the easy isolation of $PhPCl_2$, a process normally complicated under standard conditions. Using petroleum ether as the extractant, Wang and Wang were able to obtain $PhPCl_2$ in 56–68% yields (based on benzene).

Not surprisingly, the Friedel–Crafts reaction of P–Cl compounds is rarely employed because of the forcing conditions generally required, the evolution of HCl, and the difficulty in isolating the products. However, it is a good method in



Scheme 26 General scheme for the electrophilic C–H to C–P functionalization



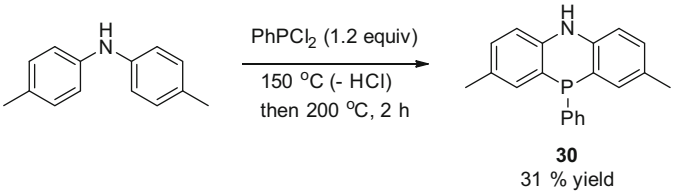
Scheme 27 Preparation of 6-chloro-dibenzo[*c*,*e*][1,2]oxaphosphorine **28** and DOPO **29** [35, 36]

some cases, one important example being the preparation of 6-chloro-dibenzo[*c*,*e*][1,2]oxaphosphorine **28**, which is used industrially to manufacture the commercially important flame-retardant 6*H*-dibenzo[*c*,*e*][1,2]oxaphosphorine 6-oxide (DOPO) **29** (Scheme 27). Keglevich and coworkers [35] investigated the synthesis of **28** while Zhang and coworkers [36] used it to prepare phosphine–oxazoline ligands (Scheme 27).

Van Leeuwen, Kamer, and coworkers [37] used the reaction of $PhPCl_2$ to prepare heterocycle 2,8-dimethyl-10-phenyl-5,10-dihydrophenophosphazinine **30** (Scheme 28).

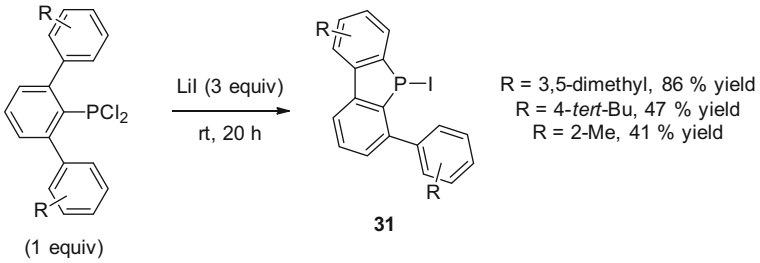
Wehmschulte and coworkers [38] reported an interesting observation when investigating the heterocyclization of terphenyl derivatives into 9-phosphafluorene **31** (Scheme 29). When the precursor P–Cl is replaced with P–I, a dramatic drop in reaction temperature, from 200–220°C for $ArPCl_2$ to room temperature for $ArPI_2$ was achieved.

Scheme 30 summarizes other compounds **32**–**35** which have recently been described [39–42]. Chaikovskaya and coworkers have examined the electrophilic aromatic substitution of pyrroles and indoles, and observed interesting isomerization reactions [40, 41]. Kostyuk and coworkers studied imidazoles [42].

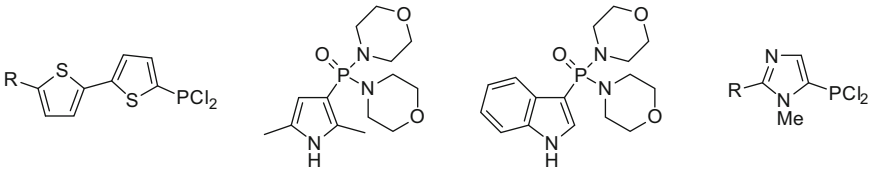


30
31 % yield

Scheme 28 Preparation of phosphorus heterocycle **30** [37]



Scheme 29 Room-temperature preparation of 9-phosphafluorenes **31** [38]



32 [39]
R = H, 75 % yield
R = PCl_2, 17 % yield
(PCl_3/$SnCl_4$)

33 [40]
85 % yield
(PCl_3/Pyr)

34 [41]
90 % yield
(PCl_3/Pyr)

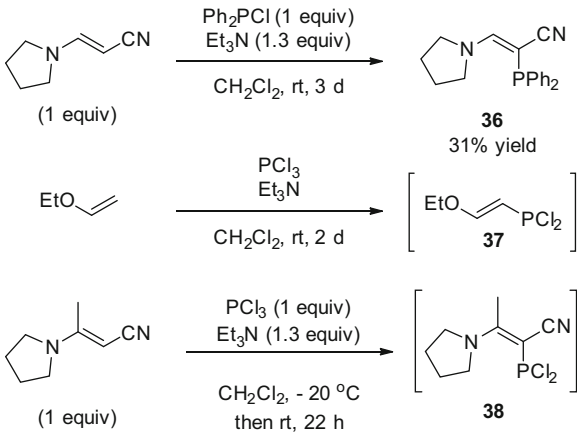
35 [42]
R = Ph, NMe_2, SMe
R = *i*-Pr, 70 % yield
(PCl_3/Pyr)

Scheme 30 Heterocyclic compounds prepared by electrophilic aromatic substitution [39–42]

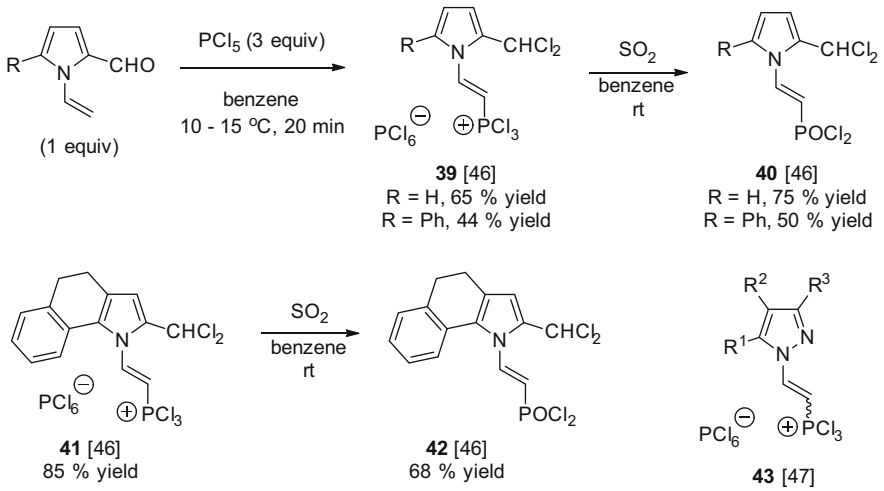
3.2 Miscellaneous

A few exceptional cases of C–H to C–P transformation using PCl_3 (and related electrophiles) and alkenes have been disclosed. In particular, Kostyuk and coworkers [43–45] have prepared some building blocks **36**–**38** using this approach (Scheme 31). These have been used for an elegant synthesis of λ^5-phosphinine derivatives [43, 44]. It is possible that the mechanism proceeds through addition–elimination.

The reactions of some *N*-vinyl heterocycles with phosphorus pentachloride PCl_5 have been reported [46, 47] to produce *N*-vinylphosphonium trichloride ions **39**, **41**, and **43**. These can be converted into the corresponding phosphonic dichlorides **40** and **42** (Scheme 32).



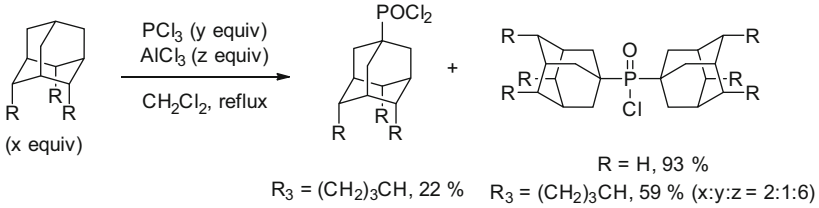
Scheme 31 Electrophilic substitution on alkenes [43–45]



Scheme 32 Formation of *N*-vinylphosphonium trichloride ions from the alkene [46, 47]

It should be noted that the functionalization of alkanes with phosphorus trichloride under radical conditions has been known for a long time (in a process similar to photohalogenation) [48–50].

The overall reaction is $RH + 2\ PCl_3 + O_2 \rightarrow RP(O)Cl_2 + POCl_3 + HCl$. Little could be found in recent literature, except for the "C–H activation" of adamantane-like structures. Indeed, examples of this reaction were recently reported by Schreiner and coworkers [51] (Scheme 33).



Scheme 33 Functionalization of adamantane-like ("nanodiamonds") structures [51]

4 Oxidative Arylation and Related Processes

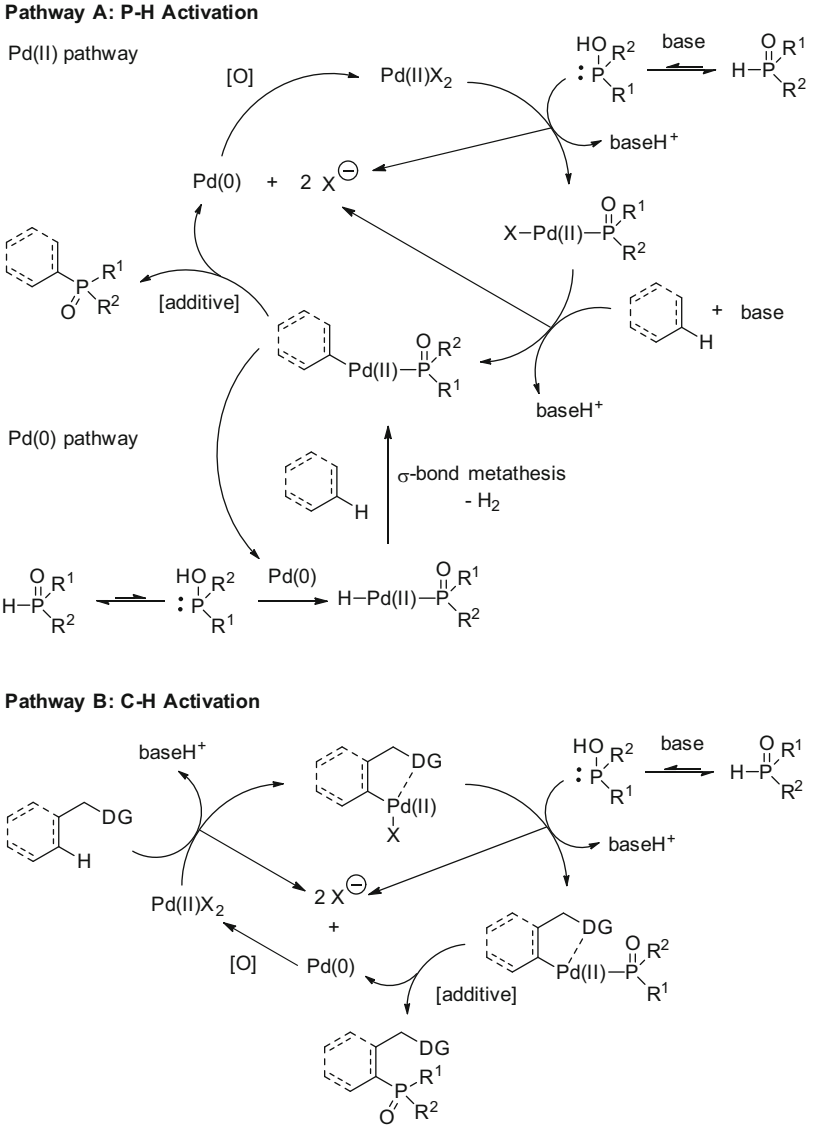
The last class of reactions encompasses two types of processes: (1) oxidative arylation and alkynylation under transition metal catalysis with palladium and copper, respectively, in the presence of an oxidant; and (2) oxidative radical arylation (silver, manganese, etc.). The distinction between the two types is concerned with the presumed reaction mechanisms. This research is generally much later than that discussed in Sects. 2 and 3 and is rapidly growing. The early literature is discussed in the relevant sections.

4.1 Processes Involving Transition Metals

Recent reports have described the first examples of palladium-catalyzed arylations. Mechanistically, two possibilities exist depending on whether the palladium inserts into a P–H or a C–H bond (Scheme 34). Montchamp [52] provided a related discussion of Pd(0) insertion into P–H vs C–X bonds.

Pathway A (Scheme 34) involves the insertion of palladium(II) into the P–H bond. A potential alternative mechanism, albeit less likely, would involve only palladium(0). Pathway B (Scheme 34) involves the insertion of palladium(II) into a C–H bond as with other transition metal-catalyzed "C–H activation" processes. It is likely that both pathways can be operative depending on the situation. Perhaps intramolecular reactions follow pathway A, while intermolecular reactions follow pathway B, depending on their regioselectivities and the need for a directing group (DG). However, even intramolecular reactions may follow pathway B as either the oxygen atom of the P(V) tautomer or, more likely, the phosphorus lone pair of the P(III) tautomer (the broad literature on palladacycles supports this) may act as an excellent directing group. There certainly is tremendous and extremely recent precedent for P = O directed C–H activation [53–64].

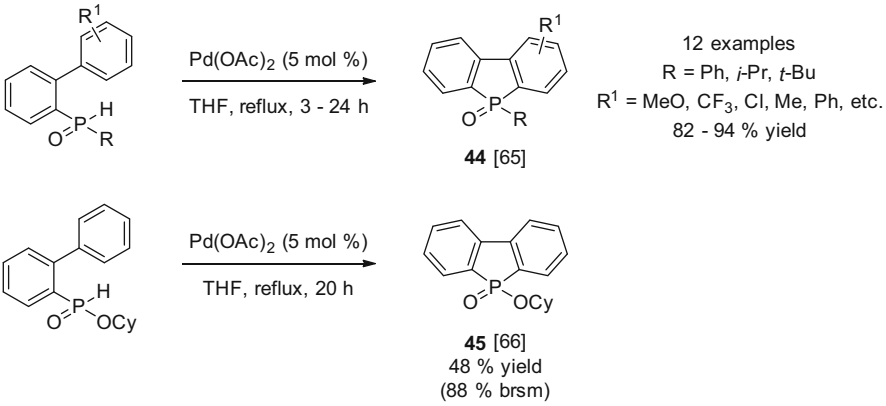
In 2011, Kuninobu, Yoshida, and Takai [65] reported the catalytic cyclization of secondary arylphosphine oxides into dibenzophospholes **44** (Scheme 35). The reaction appeared general and the yields were excellent. Subsequently Montchamp and coworkers [66] showed that cyclohexyl 2-biphenyl-*H*-phosphinate also



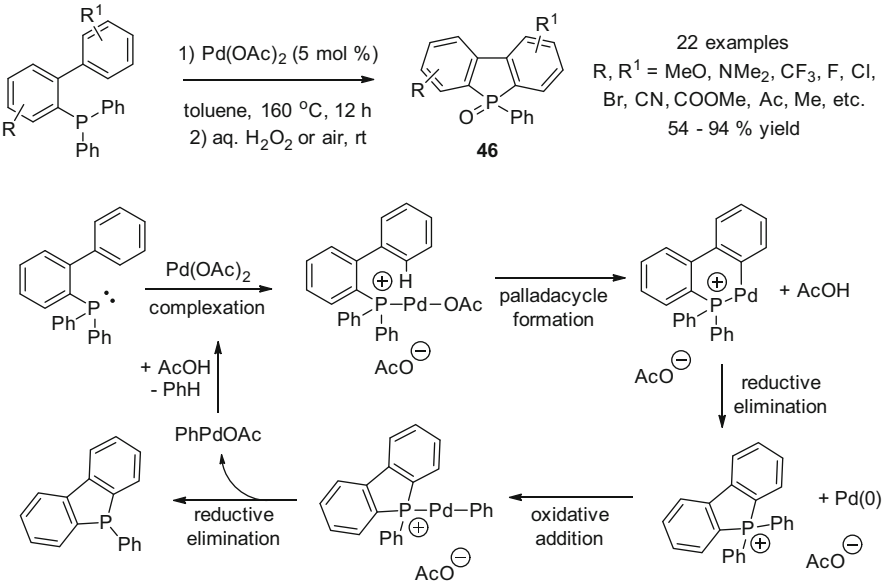
Scheme 34 Possible mechanisms in palladium-catalyzed oxidative arylation

undergoes the reaction, albeit in lower yield, to form **45**. The reaction was not optimized, and it is expected the yield could be improved. Mechanistically, these reactions might proceed through any of the pathways shown in Scheme 34 (see above).

Very recently, Baba, Tobisu, and Chatani [67] reported an intriguing related reaction, but using triarylphosphines as starting materials (Scheme 36). The

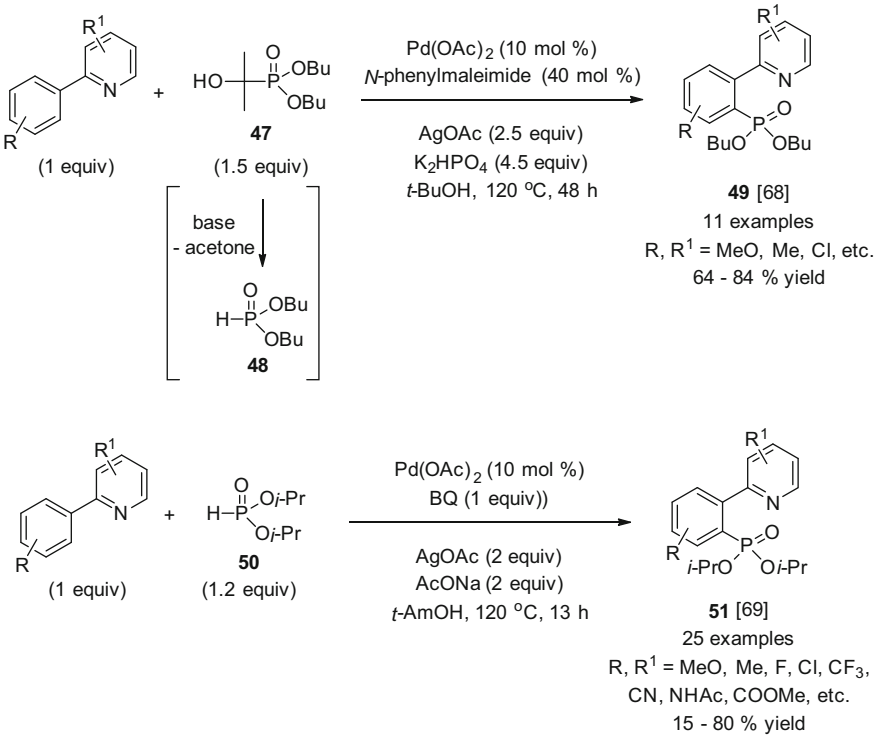


Scheme 35 Palladium-catalyzed cyclization of P(O)H compounds into dibenzophospholes [65, 66]



Scheme 36 Palladium-catalyzed cyclization of triarylphosphines into dibenzophospholes, and postulated mechanism [67]

tolerance for functional groups is superb. Presumably the reaction proceeds through a palladacycle as before, but this time the intermediate tetraarylphosphonium salt collapses to give the corresponding triarylphosphine. The authors also conducted experiments supporting the key steps of the mechanism, such as the reductive elimination step and oxidative addition into the phosphonium ion. Scheme 36 shows a slightly more detailed version of the authors' proposed mechanism.

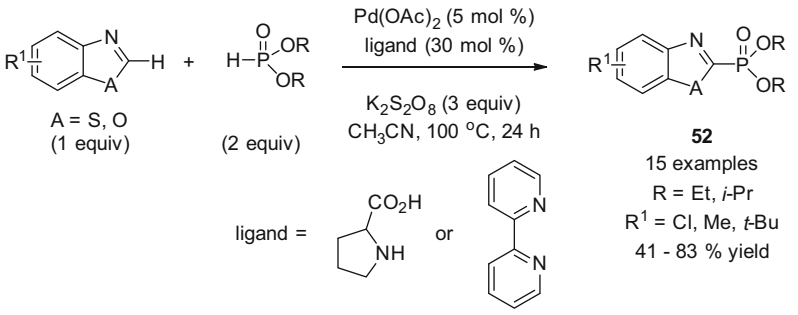


Scheme 37 Palladium-catalyzed and pyridine-directed phosphonylation [68, 69]

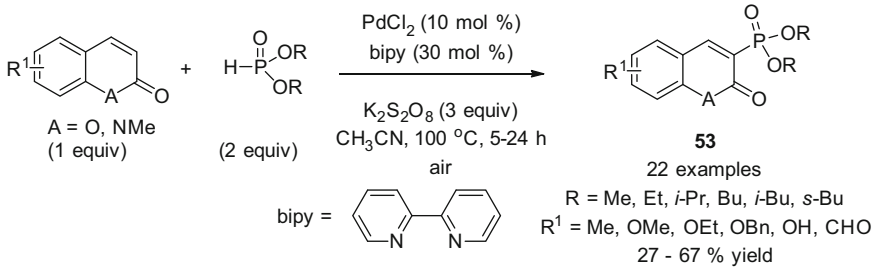
It also shows the role of the phosphorus lone pair as a directing group for C–H activation (see also Scheme 34, path B).

Murakami [68] and Yu [69] simultaneously reported essentially the same pyridine-directed phosphonylation, both using 10 mol% palladium acetate, AgOAc as the stoichiometric oxidant, and a tertiary alcohol as solvent (Scheme 37). In both instances the mechanism is presumably as shown in Scheme 34, pathway B. Murakami [68] used phosphonate **47**, which acts as a slow-release precursor of dibutyl-*H*-phosphonate **48** under basic conditions. If **48** is employed directly, the yield of product **49** is much lower, presumably because of competing oxidation of **48** into the phosphate diester. *N*-Phenylmaleimide is used as an additive to promote reductive elimination. Silver acetate was superior to either $Cu(OAc)_2$ or Ag_2CO_3 as the oxidant. The work also reported an interesting phosphonylation of an alkene and a detailed mechanistic study.

Yu [69] used diisopropyl-*H*-phosphonate **50**, and benzoquinone (BQ) as an additive to promote reductive elimination. Other parameters such as *H*-phosphonate diesters, solvents, bases, oxidants, and even acids were also tested. The reaction has a broad scope and other nitrogen-directing groups can be employed. The same conditions were also successful with diarylphosphine oxides (five examples, 39–48% yield).



Scheme 38 Palladium-catalyzed phosphonylation of thiazoles and oxazoles [70]



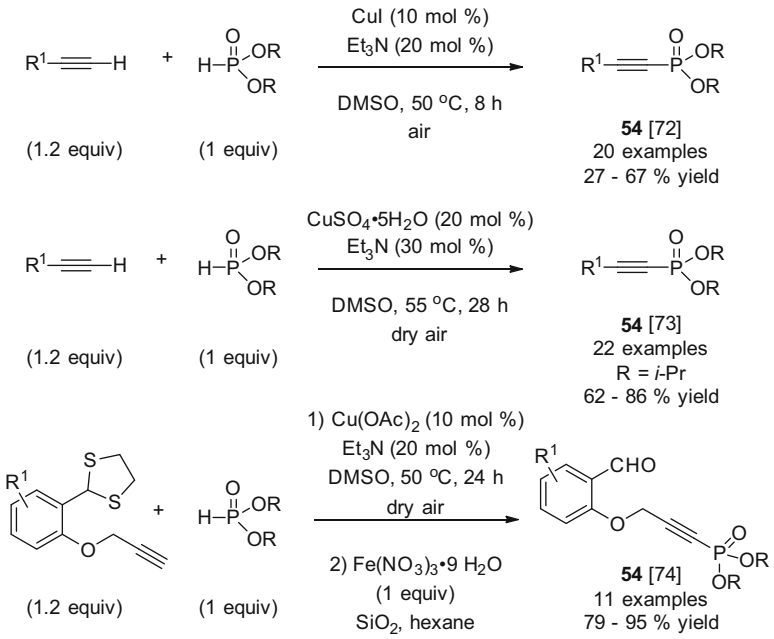
Scheme 39 Palladium-catalyzed phosphonylation of coumarins [71]

The clear advantage of this reaction is its regioselectivity, as a nitrogen group determines which C–H reacts. Similar levels of regioselectivity would otherwise require cross-coupling with ArX. However, and as is the case in most "C–H activation" methodologies, the disadvantages are the high loading of an expensive catalyst and the large number of reagents and additives required. In the present examples, 2–2.5 equiv. of AgOAc are used, adding to the cost of the process.

Li and coworkers [70] reported the palladium-catalyzed phosphonylation of thiazoles and oxazoles (Scheme 38). The authors propose a P–H activation mechanism (Scheme 34, pathway A), but with complexation of P(O)-Pd-X to the azole nitrogen for intramolecular C–H activation. The reaction is regiospecific and introduced the phosphorus at the 2-position.

Huang, Wu, and coworkers [71] reported a closely related reaction but with coumarins as substrates to produce phosphonates **53** (Scheme 39). The presence of a radical inhibitor did not change the yield of the reaction, and a complex corresponding to P(O)-Pd-X was detected by mass spectrometry. Other conditions were investigated.

Finally, the copper-catalyzed oxidative alkynylation of P(O)H compounds with terminal alkynes has been achieved (it should be remembered that Scheme 21 describes a stoichiometric process in copper using $P(BH_3)H$ compounds.) The pioneering work by Zhao and Han [72] was published in 2009 (Scheme 40). Copper acetate and diethylamine were sometimes used. The authors also provided an



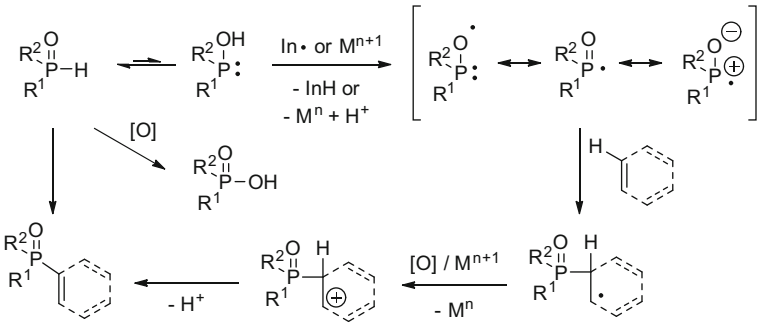
Scheme 40 Oxidative copper-catalyzed phosphonylation of terminal alkynes [72–74]

example of alkynylation of an *H*-phosphinate ester (phenylacetylene + PhP(O)(O*i*-Pr)H, 87% yield). Subsequently, two more reports [73, 74] have appeared (Scheme 40).

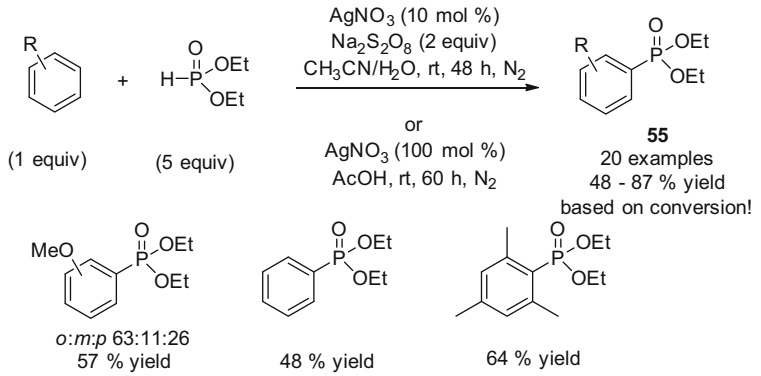
All the references in this section are less than 5 years old (and more often than not from 2013), demonstrating the current intense and increasing activity in this area of research. Undoubtedly many more reports will soon appear on this subject.

4.2 Radical Reactions

Last, but not least, C–H bonds can be converted into C–P bonds under radical conditions. Although the reaction of PCl_3 with alkanes was discussed in Sect. 3.2 [48–51], it could equally well have been discussed in this section. However, this section will instead focus exclusively on the functionalization of C_{sp2}–H bonds, and mainly on the arylation of P(O)H compounds. This process can indeed be conducted under radical conditions, although metals are often used to catalyze or to promote the formation of the phosphorus-centered radicals. However, even when metals are involved, this section is separate from Sect. 4.1, which involves discrete and familiar organometallic intermediates.



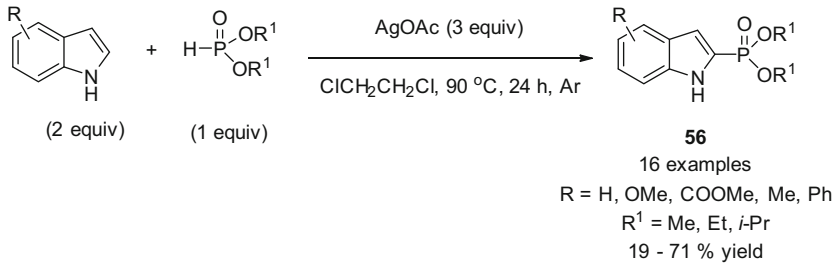
Scheme 41 Postulated mechanism in radical arylation (alkenylation) of P(O)H compounds



Scheme 42 Silver-catalyzed and promoted arylation of diethyl *H*-phosphonate [75]

A general mechanism for the radical arylation/alkenylation of phosphinylidene P(O)H compounds is shown in Scheme 41. With a standard radical initiator, air must be the oxidant of the intermediate (cyclohexadienyl) radical, and peroxide the byproduct. With a metal, if air reoxidizes the reduced metal from M^n to M^{n+1}, then a catalytic process is possible. In the vast majority of cases, however, a stoichiometric amount of oxidant is necessary for the reactions to proceed efficiently. Furthermore, under oxidative conditions, the competing oxidation of P(O)H into P(O)OH takes place, explaining why the phosphorus reagent is usually used in excess.

The pioneering study seems to be Effenberger's 1985 seminal paper [75] which included both electrochemical and silver-catalyzed (or promoted) arylation reactions for the synthesis of diethyl arylphosphonates **55** (Scheme 42). Isomeric mixtures are obtained usually favoring the ortho isomer. The electrochemical process employed triethylphosphite $(EtO)_3P$ to give the aryl phosphonates in moderate to good yield, but often as isomeric mixtures. Soon after (1987) he reported on the reaction promoted by ceric ammonium nitrate (CAN, $(NH_4)_2Ce(NO_3)_6$) [76]. Apparently this publication has not yet generated any follow-up.



Scheme 43 Silver-promoted reaction of dialkyl *H*-phosphonates with indole derivatives [77]

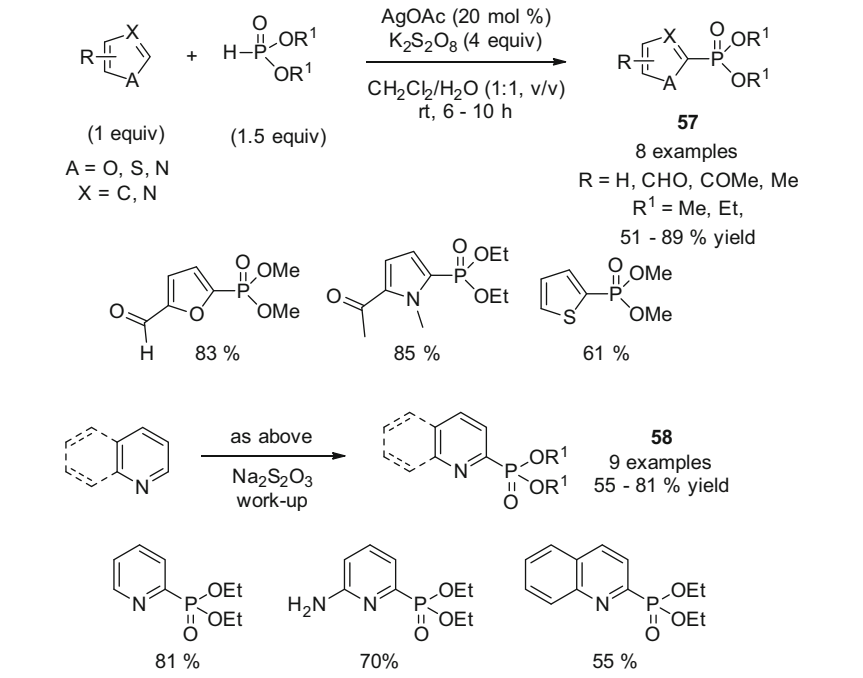
In spite of the fact that CAN cannot be classified as "cheap," it is still considerably cheaper than noble metals and its molar cost is essentially the same as that of silver acetate (both about $ 220/mol at the time of writing).

This reaction was apparently dormant for more than 25 years, until silver-promoted and catalyzed reactions were being reported again in 2012. (The manganese version apparently started in the early 2000s, see below.)

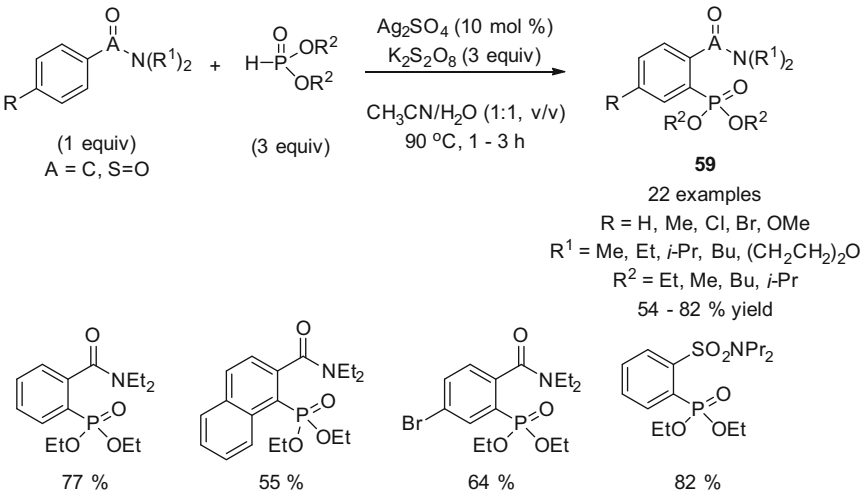
Wang, Li, and Wan [77] reported the phosphonylation of indole derivatives to produce phosphonates **56** essentially regiospecifically at C-2 (Scheme 43). The yields are generally low (<50%) with only three cases above 50%. In this reaction, the indole is used in excess. Other conditions were examined but other solvents gave poorer results. The reaction of indole conducted with $Mn(OAc)_3$ instead of AgOAc gave the phosphonate product in 28% yield instead of 44% yield. The choice of the *H*-phosphonate diester did not have a great impact (Me ~ Et > *i*-Pr).

Huang and coworkers [78] used similar conditions to Effenberger [75] but used dichloromethane instead of acetonitrile. Various heterocycles (furan, thiophene, thiazole, pyrrole, pyridine, and quinoline derivatives) gave good yields of the corresponding phosphonylated products **57** and **58** with good regioselectivities for the hydrogen closest to the heteroatom (Scheme 44). CAN did not give the product under otherwise similar conditions. Other silver salts (Ag_2CO_3, AgOAc, Ag_2O) also catalyzed the reaction, but were slightly inferior to $AgNO_3$. Other oxidants (H_2O_2, MnO_2, *t*-BuOOH, etc.) did not give any product. Interestingly, acetonitrile as the solvent (Effenberger's conditions) only gave a trace amount, as in DMF. On the other hand, acetone was satisfactory. With pyridines, the addition of $Na_2S_2O_3$ before work-up considerably improved the isolated yield.

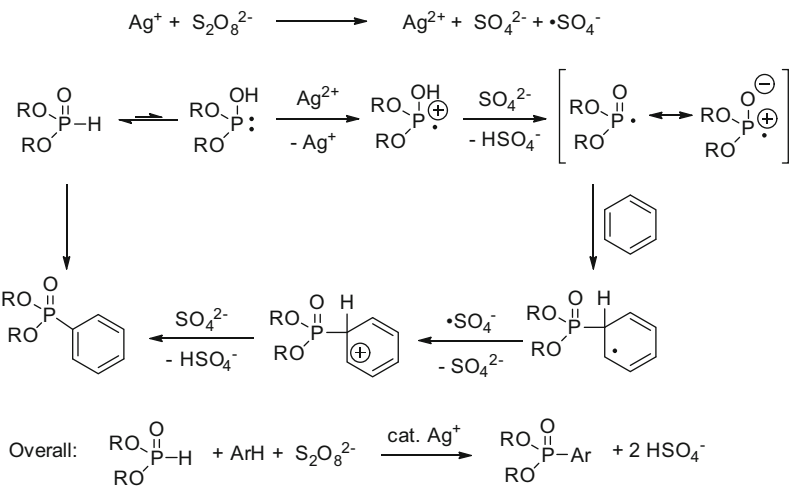
Zhu, Cheng, and coworkers [79] have examined the reaction of arenes substituted by electron-withdrawing group – mainly *N*,*N*-dialkylbenzamides and *N*,*N*-dialkylbenzenesulfonamides (Scheme 45). Acetanilide and nitrobenzene also reacted successfully (54% and 50% yields, respectively). The high regioselectivity was attributed to the stability of the cyclohexadienyl radical intermediate. Another possible explanation might be that the silver is complexed to the substrate so that formation of the phosphorus radical takes place in the vicinity of the ortho C–H. Various reaction parameters were examined. The choice of dialkyl *H*-phosphonate had no influence on yield. The difference with Effenberger's reaction is that it is



Scheme 44 Silver-catalyzed reaction of dialkyl *H*-phosphonates with heterocycles [78]



Scheme 45 Silver-catalyzed regioselective phosphonylation of electron-poor arenes [79]



Scheme 46 Proposed mechanism for the $Ag^{+}/K_2S_2O_8$ reaction [75, 78, 79]

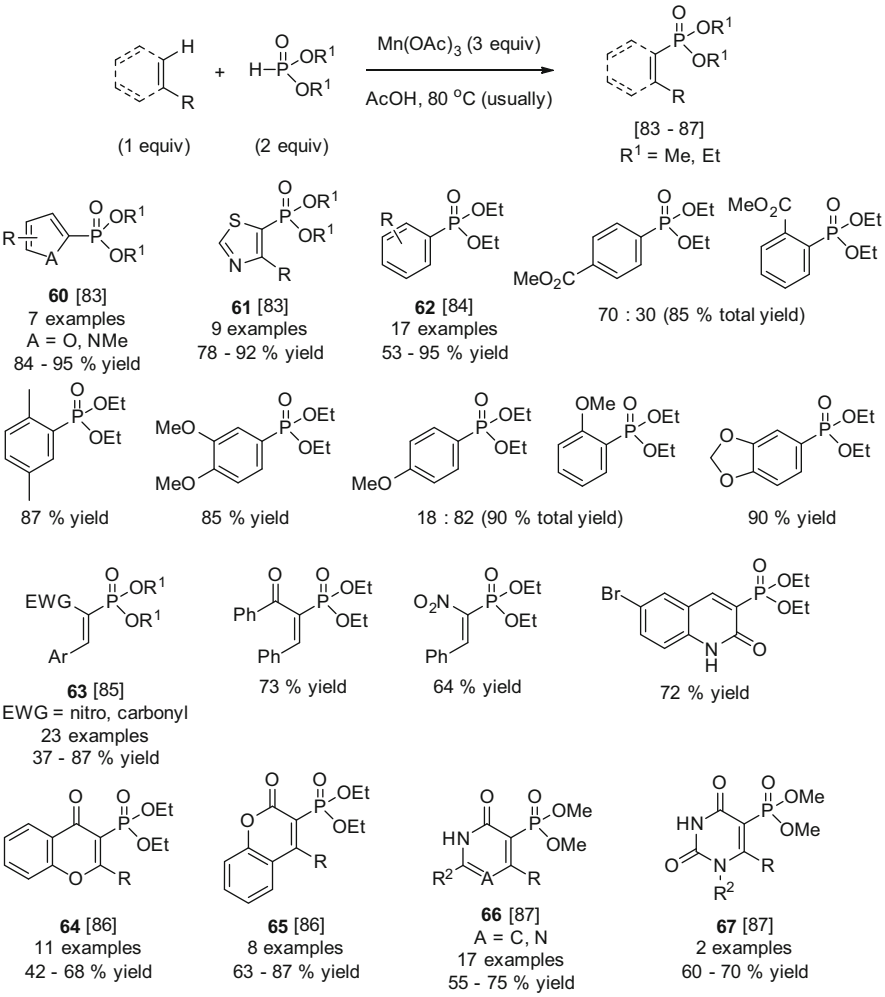
conducted at 90°C in air, and Ag_2SO_4 was found to be slightly better than $AgNO_3$ (which gave some mono-dealkylated amide), and, of course, 10 mol% of the sulfate corresponds to 20 mol% of silver. Interestingly, $Mn(OAc)_3$ (3 equiv.) or $Mn(OAc)_2/Co(OAc)_2$ in acetic acid only gave traces of product.

A generally accepted [75, 78, 79] mechanism for the $Ag^{+}/K_2S_2O_8$ reaction is shown in Scheme 46.

For silver- and manganese-mediated reactions, Scheme 41 can be consulted.

Over the past few years, manganese has generated a lot of interest for the radical arylation of *H*-phosphonates and reviews are available [80, 81]. A catalytic process was reported by Ishii and coworkers [82] in 2006. The reaction conditions are: arene (1 equiv.), $(EtO)_2P(O)H$ (3 equiv.), $Mn(OAc)_2$ (5 mol%), and $Co(OAc)_2$ (1 mol%), in acetic or propionic acid at 45°C (3–15 h) under 0.5 atm O_2 and 0.5 atm N_2. Under air the conversion was low, whereas 1 atm of oxygen gave better conversion but low yield. The inefficiency of this reaction is probably because of the oxidation of the cyclohexadienyl radical intermediate which is slow, and competing oxidation of diethyl *H*-phosphonate. Unfortunately, not a single isolated yield is specified. Instead, a selectivity yield (based on the starting material consumed) is used and calculated by gas chromatography. Thus, GC yields of products are around 48–63% for six examples. The ortho:meta:para ratio was 59:24:17 with toluene as the substrate. With naphthalene the ratio of substitution at C-1 vs C-2 was 87:13. Although it is catalytic, Ishii's arylation appears impractical.

Virtually all other reactions in the literature typically employ 3 equiv. of manganese(III) acetate. Most of the reports come from Zou, Zhang, and coworkers [83–87] (Scheme 47). Thiazoles, furans, and one *N*-methylpyrrole were successfully phosphonylated in excellent yields to give products **60** and **61** [83]. The reactions were conducted at 80°C for 3 h. Refluxing acetonitrile, methanol, or



Scheme 47 Zou, Zhang, and coworkers' phosphonylation with $Mn(OAc)_3$ [83–87]

ethanol gave yields 10–15% below what is obtained in acetic acid (92% yield). The reaction could also be conducted neat at 80°C (76% yield). On some thiazoles, mixtures of isomers were obtained.

Various arenes were phosphonylated into **62** under similar conditions but at 60°C for 5–7 h [84]. With only 1 equiv. of $Mn(OAc)_3$ the yield drops dramatically (32% vs 90%). In many cases mixtures of isomers are obtained. Benzaldehyde and acetophenone give complex mixtures while nitrobenzene is completely unreactive.

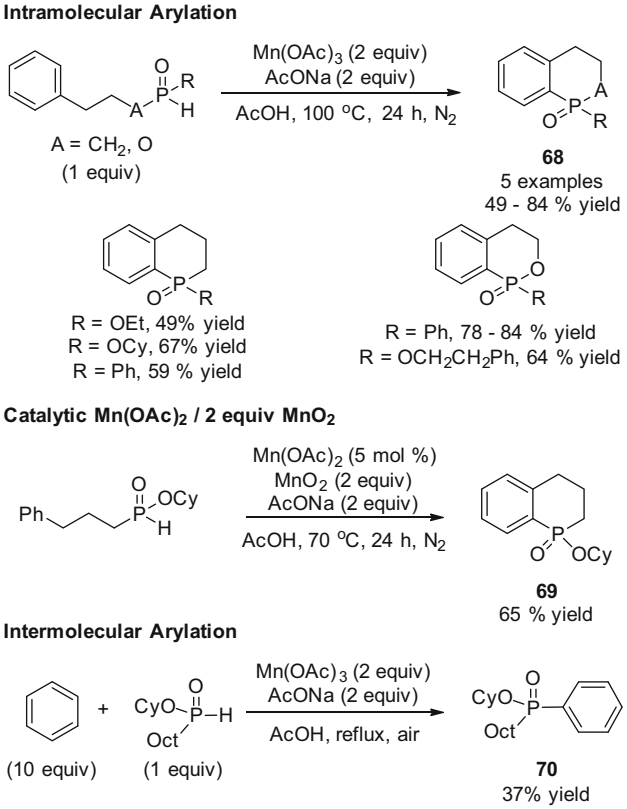
Arylalkenes containing a conjugated nitro or carbonyl group (such as chalcones) can be phosphonylated regioselectively to afford compounds **63** [85]. The reactions are conducted at 60°C for 1 h.

Flavones and coumarins were converted to the phosphonylated products **64** and **65**, respectively [86]. The reactions are conducted at 80°C for 1–2 h. Pyridones and pyrimidinones, as well as uracil derivatives, also reacted to produce **66** and **67** [87].

Kim and coworkers [88] recently investigated uracil derivatives and related compounds. The best conditions were the C–H compound (1 equiv.), $(EtO)_2P(O)H$ (4 equiv.), and $Mn(OAc)_3$ (3 equiv.) in acetic acid at 80°C for 3 h. In this way, 12 compounds were synthesized in yields ranging from 68% to 99%. Other conditions such as $AgNO_3/K_2S_2O_8$ and CAN were investigated but the results were poor.

Wang, Wang, and Zou [89] investigated the $Mn(OAc)_3$-mediated reaction between [60]fullerene and various P(O)H compounds ($(MeO)_2P(O)H$, $(EtO)_2P(O)H$, $Me_2C(CH_2O)_2P(O)H$, and $Ph_2P(O)H$). The reactions were generally conducted at high temperature and under argon. Yields were in the 30–40% range. This appears to be the first time a phosphorus reagent $Ph_2P(O)H$ other than an *H*-phosphonate diester was employed.

Very recently, Montchamp and coworkers [90] disclosed the first examples of reactions using *H*-phosphinates (Scheme 48). The heterocyclization worked well



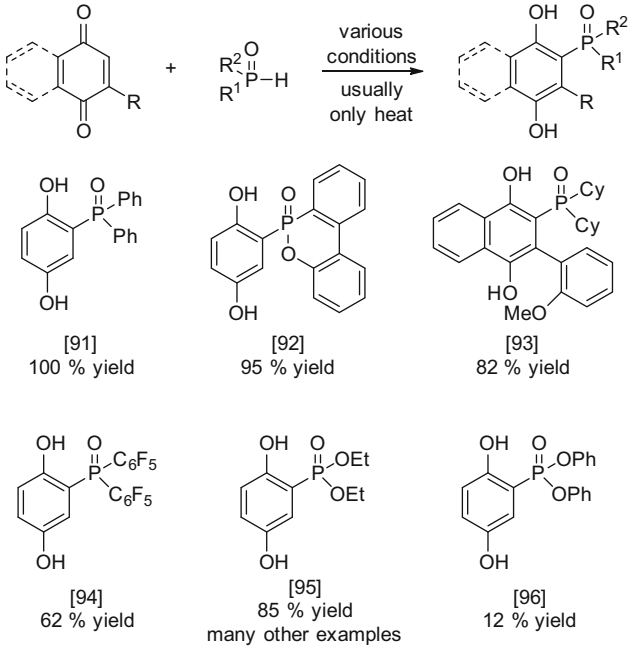
Scheme 48 Manganese-mediated synthesis of *P*-heterocycles through intramolecular radical arylation, and intermolecular arylation of an *H*-phosphinate ester [90]

for *H*-phosphonate, *H*-phosphinate, and secondary phosphine oxide, all leading to heterocycles **68**. Only 2 equiv. of $Mn(OAc)_3$ were employed. This compound is very expensive (~$ 1,000/mol) although it can be made cheaply using $Mn(OAc)_2$ (~$ 15/mol) and $KMnO_4$ (~$ 14/mol). In fact, in one of the heterocyclizations the manganese was recycled through oxidation with $KMnO_4$ and a subsequent run proceeded in even slightly higher yield (84% vs 78% yield).

Montchamp also disclosed an exciting innovation: the 5 mol% $Mn(OAc)_2/MnO_2$ (2 equiv.) system (Scheme 48). With this system, heterocycle **69** was obtained in virtually identical yield to that obtained under the $Mn(OAc)_3$ conditions (65% and 67% yield, respectively). Technical activated MnO_2 was employed. This is important because MnO_2 costs ~ $ 15/mol and is actually more than 50% cheaper than $K_2S_2O_8$ (~$ 36/mol).

The intermolecular arylation was also accomplished (compound **70**, Scheme 48), albeit in low isolated yield. However, conditions have now been improved significantly so that intermolecular arylation is efficient [91].

Although it is not a radical process, a final example of special C–H to C–P transformation is included here, at the end of this chapter. There are numerous literature reports on the reaction between benzoquinone derivative and phosphorus compounds (Scheme 49). Because of the commercial importance of DOPO in flame-retardant materials (see Scheme 27), there are also numerous patents using this reaction. Therefore, only a few representative publications are cited here [92–97]. The reaction proceeds via conjugate addition and subsequent



Scheme 49 Addition of P(O)H compounds to hydroquinone derivatives [92–97]

tautomerization. A detailed study of this reaction was published by Yin, Han, and coworkers [96]. Döring examined disubstitution through oxidation of the initially formed hydroquinone with MnO_2. In all cases the 2,3-disubstituted products were obtained.

5 Summary, Conclusions, and Outlook

The carbon–hydrogen to carbon–phosphorus transformations are a mixture of old and (sometimes very) new methodologies. There is no doubt that the lithiation approach (Sect. 2) remains a very significant component of organophosphorus synthesis for the future, although it is not practical for large-scale work.

The reaction of phosphorus trichloride with arenes (and to a lesser extent alkenes and to an even lesser extent alkanes) remains quite marginal, although some Friedel–Crafts phosphinylations are already of industrial importance (Sect. 3). This chemistry certainly deserves more attention.

According to the literature, it is clear that both oxidative transition metal-catalyzed and radical arylation are the up-and-coming methodologies (Sect. 4). However, no matter how popular the "C–H bond activation" approaches (especially intermolecular) are becoming, it seems unlikely these methodologies will be sustainable or practical in the foreseeable future. This is because these still require very expensive catalysts (palladium, ruthenium, rhodium, etc.) in high loadings, together with numerous additives and reagents. The ready availability of C–H compounds as opposed to C–X compounds (necessary for metal-catalyzed cross-couplings) will probably not offset the cost of these reactions in the near future (Sect. 4.1). Even copper, while inexpensive, typically is not a particularly good option because of loading, toxicity, and the cost of the ligands which are usually necessary.

On the other hand, radical arylation methodologies (Sect. 4.2) are poised to make a significant difference in the near future, especially if air can be used as the oxidant. Here too, significant developments are taking place, although usually the C–H substrates are specialized. Of the two major current options, silver vs manganese, manganese wins outright. Manganese is inexpensive in many oxidation states and is largely non-toxic. While $Mn(OAc)_3$ is not inexpensive, recycling or cheaper alternatives are becoming viable possibilities. Although MnO_2 is not as cheap as air, it must be one of the cheapest stoichiometric oxidant available, apart from Fe_2O_3 ("rust"). Our own catalytic $Mn(OAc)_2$/stoichiometric MnO_2 system seems very promising. In fact, unless iron(III) methodologies are developed, or greatly improved highly catalytic processes with air as the oxidant are found, nothing appears to be superior to manganese at present. Ishii and coworkers [82] appear to have the best system on paper so far, although the practicality and generality of the process were certainly not demonstrated. Obviously, methodologies using palladium and other very expensive catalysts should not be presented as viable, let alone as practical, alternatives to already existing, simpler and cheaper processes.

Finally, the development of C–H to C–P transformations is a "hot" area of organophosphorus research with a very promising future. The outlook is clear: greener, cheaper, and catalytic methods are still needed. It is hoped this chapter will stimulate useful research in this field by providing a broad perspective on state-of-the-art methodologies.

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Phosphate Tethers in Natural Product Synthesis

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Abstract Recent advances in phosphate tether-mediated natural product synthesis are reviewed. Synthetic approaches toward dolabelide C, (−)-salicylihalimide A, (−)-tetrahydrolipstatin, and (+)-strictifolione are included. In addition, current efforts in method development are briefly reviewed, including a detailed study on the effect of stereochemical complexity on the phosphate-mediated, diastereoselective ring-closing metathesis reaction and recent advances in multi-reaction, one-pot sequential processes mediated by the phosphate tether. Overall, this review seeks to highlight the utility of phosphate triesters to serve as multifunctional tethers with protecting group and latent leaving group characteristics and the ability to orchestrate multiple, orthogonal reaction pathways to allow for the facile synthesis of complex, bioactive small molecules and their analogs.

Keywords Chemical methods · Chemoselective transformations · Cross metathesis (CM) · Natural product synthesis · One-pot · Phosphate · Phosphorus-based tether systems · Ring-closing metathesis (RCM) · Sequential processes · Tether methodologies

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Abbreviations

2,2-DMP	Dimethoxypropane
9-BBN	9-Borabicyclo(3.3.1)nonane
BOPCl	Bis(2-oxo-3-oxazolidinyl)phosphonic chloride
CH_2Cl_2	Dichloromethane
CM	Cross metathesis
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
Et_3N	Triethylamine
G-I	Grubbs first generation catalyst $[(PCy_3)_2(Cl)_2Ru{=}CHPh]$
G-II	Grubbs second generation catalyst $[(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh]$
HG-II	Hoveyda–Grubbs second generation catalyst
$LiAlH_4$	Lithium aluminum hydride
LiDBB	Lithium di-*tert*-butyl biphenylide
LLS	Longest linear sequence
Me_2SO_4	Dimethylsulfate
MeCN	Acetonitrile
MES	Mesityl
MOM	Methoxymethyl
NaHMDS	Sodium bis(trimethylsilyl)amide
NMO	*N*-Methylmorpholine-*N*-oxide
o-NBSH	*o*-Nitrobenzene sulfonyl hydrazine
PMB	*para*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
RCM	Ring-closing metathesis
TBAF	Tetra-*n*-butylammonium fluoride
TBSCl	*tert*-Butyldimethylsilyl chloride
TES	Triethylsilyl
TIPS-	Triisopropylsilyl-
TMS-diazomethane	Trimethylsilyldiazomethane

1 Introduction

Streamlining of natural product syntheses through the development of new step-, atom-, and redox-economical methods stands at the forefront of modern-day synthesis and drug discovery [1–3]. In this regard, some of the most efficient synthetic methods are those which couple a wide array of simple, as well as complex, chemical fragments – preferably in an iterative and manipulatable fashion – to rapidly access key portions of a wide array of bioactive small molecules. While silicon-based tethers are the most prevalent systems reported in the literature [4–8], the vast majority of applications couple fragments occupying only two of the four available valencies on the silicon atom, leaving the remaining two vacancies to ancillary groups. The synthetic utility of multivalent phosphorus, in particular the ability of phosphate triesters to serve as protecting groups, functional handles for transition metal-mediated transformations, and latent leaving groups (Fig. 1) [9–13], provides a compelling argument in favor of the use of phosphate triesters as multifunctional tripodal tethers in the synthesis of bioactive small molecules.

Towards this goal, in 2005, Hanson and coworkers published the first use of phosphate triesters as tripodal tethers for the synthesis of 1,3-skipped polyol-containing bioactive small molecules (Scheme 1) [14]. Inspired by the work of Burke and coworkers with ketal tethers [15, 16], the authors envisioned that the tripodal coupling of a chiral, non-racemic 1,3-*anti*-dienediol [as shown (*S*,*S*)-**1.1**] with phosphorus oxychloride and allyl alkoxide could provide a phosphate triester [as shown (*S*,*S*)-**1.2**] in which three-dimensional conformation could bias the reactivity of each olefin in the once C_2-symmetric dienediol. Symmetry breaking ring-closing metathesis, promoted by $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (Grubbs second generation catalyst, **G-II**) [17] or Hoveyda-Grubbs second generation catalyst (**HG-II**) [18–20], yields the corresponding bicyclo[4.3.1]phosphate (**1.3**) as a single diastereomer. The synthesis of **1.3** was later simplified to a three-step process, whereby dichlorodione **1.4** undergoes enantioselective hydrogenation under Noyori conditions [21] to provide dichlorodiol (*S*,*S*)-**1.2** [22]. Subsequent olefination using $Me_3S^+I^-$ ylide furnishes the desired dienediol [(*S*,*S*)-**1.1**], which, upon treatment with phosphorodiamidite **1.6**, oxidation with *t*BuOOH, and

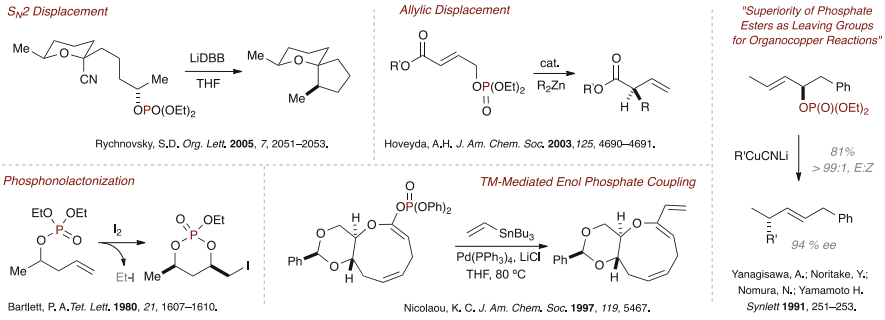
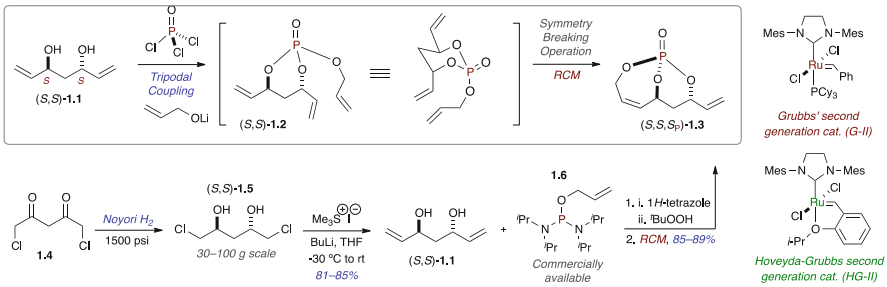


Fig. 1 Representative reactivity profile of phosphates in organic synthesis



Scheme 1 Synthesis of bicyclo[4.3.1]phosphate **1.3**

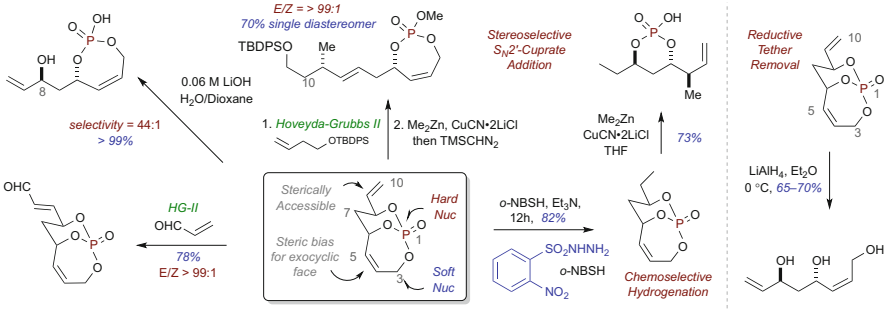


Fig. 2 Synthetic utility of bicyclo[4.3.1]phosphates

diastereoselective RCM with **G-II**, affords bicyclo[4.3.1]phosphate **1.3** in good overall yield.

Since this initial report, efforts have been focused on the establishment of a reactivity profile for this bicyclo[4.3.1]phosphate system so as to fully understand its behavior in a variety of conditions (Fig. 2) [23]. This profile includes a variety of nucleophilic additions, stability in acidic and basic media, reductive tether removal with lithium aluminum hydride ($LiAlH_4$), cross metathesis with a number of olefin cross-partners, chemoselective hydrogenation of the exocyclic olefin utilizing mild diimide reduction conditions [24], and stereoselective S_N2'-cuprate additions to both the original diene-containing bicyclic phosphate and the hydrogenated analog. Several significant features of phosphate tethers continue to emerge from these investigations, including: (1) orthogonal stability, (2) latent leaving group ability which orchestrates selective cleavage pathways within the phosphate tether, (3) inherent stereochemical restraints which dictate regioselective hydrogenation and facile cross metathesis (CM), and (4) stereo- and regioselective cuprate addition into the cyclic allylic phosphate.

The ongoing investigations involving the use of multivalent phosphate tethers have led to a series of publications and reviews [25, 26] on the application of this methodology to the total and formal syntheses of a number of biologically active

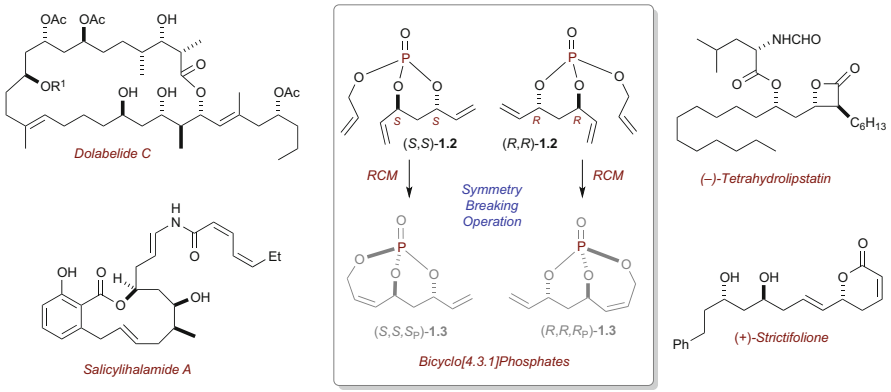
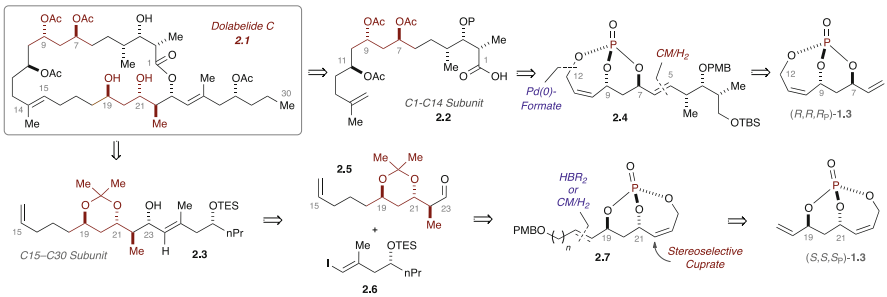


Fig. 3 Targeted natural products synthesized via the use of phosphate tether methodologies

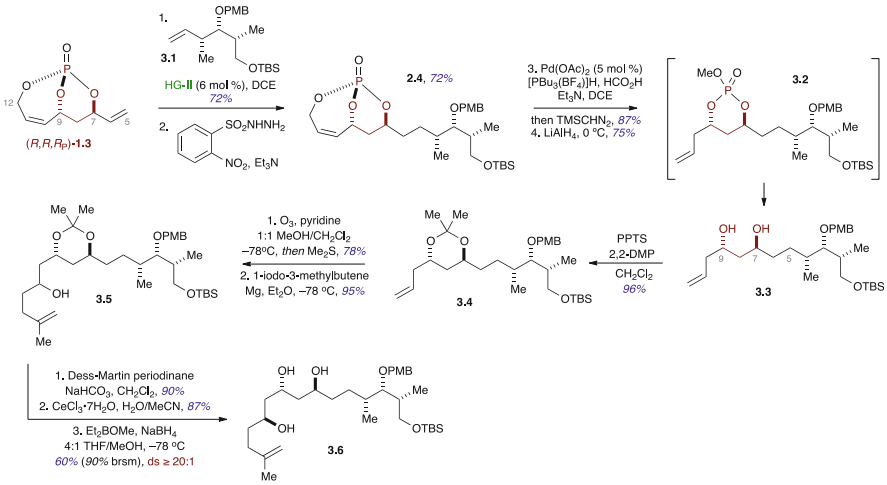
natural products and their analogs, including dolabelide C, salicylihalamide A, (−)-tetrahydrolipstatin, and (+)-strictifolione (Fig. 3). This review highlights these syntheses, as well as certain advances in the development of this methodology which have allowed for the stream-lined synthesis of stereochemically complex polyol-containing intermediates with minimal purification and multiple points of diversification to provide facile routes for library-amenable synthesis.

2 Total Synthesis of Dolabelide C

Dolabelide C (**2.1**) was isolated and characterized by Yamada and coworkers in 1995, from sea hare *Dolabella auricularia*, and was shown to possess potent cytotoxicity against HeLa S_3 cells ($IC_{50} = 1.0$ μg/mL) – a trait it shares with the other members of the dolabelide family (dolabelides A–D (Dolabelides A and B were isolated 2 years prior to the isolation of dolabelides C and D, [27]), Scheme 2) [28]. In 2008, the first two establishments of the northern and southern fragments toward the total synthesis of dolabelide C were published [29, 30], followed by the first complete total synthesis of the 24-membered macrolide in 2011 [31]. Retrosynthetic analysis showed that **2.1** could be obtained through the synthesis and coupling of two major fragments which could be generated from both enantiomers of [4.3.1]-bicyclic phosphate **1.3**: C1–C14 subunit **2.2** and C15–C30 subunit **2.3** (Scheme 2). The eastern portion of **2.2** could be installed via cross-metathesis/chemoselective hydrogenation of (R,R,R_P)-**1.3** with the suitable type II cross partner [32]. Subsequent Pd(0)-formate ring opening of the bicyclic phosphate **2.4** would provide a terminal olefin for further diversification. Subunit **2.3** could be produced via organolithium addition of vinyl iodide **2.6** to aldehyde **2.5**, which could be acquired from a series of transformations utilizing bicyclic phosphate intermediates **2.7** ($n = 0, 3$). In turn, intermediates **2.7** could be provided via a chemoselective hydroboration/oxidation pathway (through the intermediate where



Scheme 2 Retrosynthetic analysis in the total synthesis of dolabelide C



Scheme 3 Synthesis of C1–C14 fragment

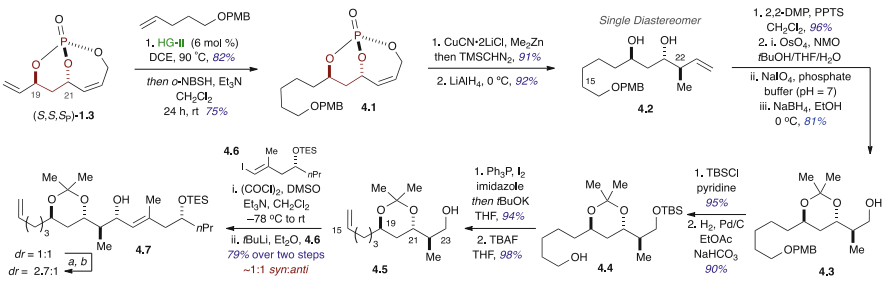
$n = 0$)[1] or a cross-metathesis/chemoselective hydrogenation pathway (through the intermediate where $n = 3$) from the simple [4.3.1]-bicyclic phosphate (S,S,S_P)-**1.3**.

The synthesis of the C1–C14 fragment of dolabelide C commenced with the cross-metathesis of (R,R,R_P)-**1.3** with olefin **3.1** – which was obtained in four steps from the corresponding TBS-protected Roche ester – in the presence of **HG-II** catalyst (6 mol%) in refluxing DCE (Scheme 3) (see footnote 1; [29, 31]). The resultant 1,2-disubstituted olefin was then hydrogenated selectively, in the presence of the internal olefin of the bicyclic phosphate, using mild diimide reduction, which is generated in situ from *o*-nitrobenzene sulfonyl hydrazine [24], affording the

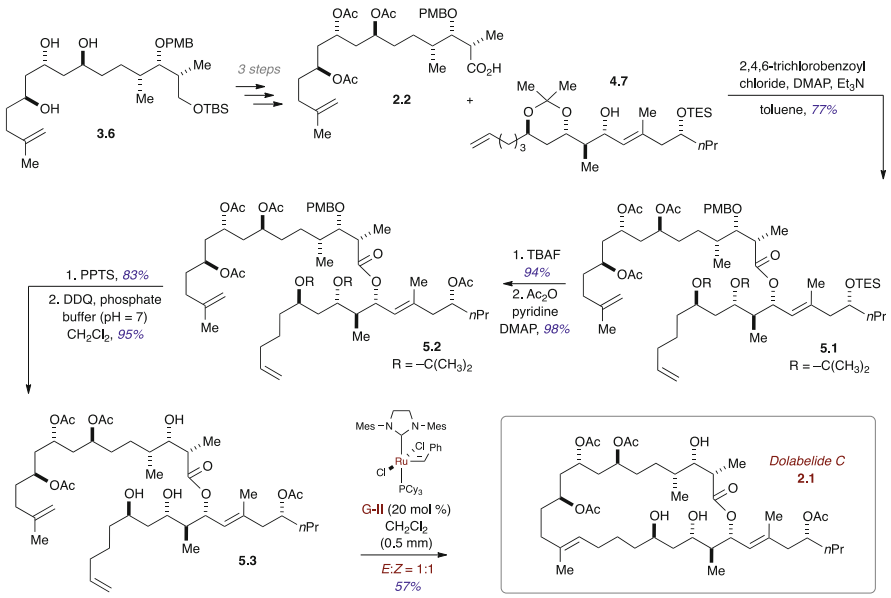
[1] This was the route involved in our first synthetic plans (see [30]); however, in light of the shorter second generation synthesis of this fragment which involves a one-pot, sequential cross-metathesis/hydrogenation, this first route is not addressed in this review.

desired [4.3.1]-bicyclic phosphate **2.4** in 72% yield. Subsequent transposition of the allylic phosphate olefin under Pd(0)-formate conditions, followed by methylation of the free phosphate with TMS-diazomethane, selectively provided intermediate **3.2** containing the desired western terminal olefin – with regioselectivity of the opening arising from orthogonal orbital alignment within the [4.3.1]-bicyclic phosphate precursor [14, 29]. Phosphate removal with $LiAlH_4$ generated diol **3.3**, which, upon treatment with 2,2-dimethoxypropane (2,2-DMP) and pyridinium *p*-toluenesulfonate (PPTS), provided acetal **3.4**, in 75% and 96% yields, respectively. Next, ozonolysis of the terminal olefin to form the terminal aldehyde and Grignard addition with 1-iodo-3-methylbutene yielded a 1:1 diastereomeric mixture of alcohol **3.5**, which was successfully converted to a single diastereomer **3.6** via a three-step sequence involving oxidation of the secondary alcohol, acetonide deprotection with cerium trichloride heptahydrate, and directed *anti*-reduction of the resultant ketone under Evans' conditions (60% yield, 90% based on recovered starting material, ds $\geq$ 20:1) [33].

The synthesis of the C15–C30 fragment of dolabelide C was initiated using a cross-metathesis/chemoselective hydrogenation pathway which coupled [4.3.1]-bicyclic phosphate (S,S,S_P)-**1.3** and PMB-protected 4-penten-1-ol to provide the corresponding bicyclic phosphate **4.1** in good overall yield (Scheme 4). Stereo- and regioselective S_N2' cuprate addition to the bicyclic phosphate (the regio- and stereoselective nature of this S_N2' cuprate addition can be attributed to both electronic and steric constraints inherent to the [4.3.1]-bicyclic phosphate system; see Scheme 4 in [14]), followed by tether removal with lithium aluminum hydride, afforded the corresponding diol (**4.2**) in 91% and 92% yields, for each respective transformation. Acetonide formation with 2,2-DMP and PPTS, followed by dihydroxylation/reductive cleavage to form a terminal aldehyde which was reduced to the alcohol with sodium borohydride without purification, furnished alcohol **4.3** in excellent overall yield. TBS-protection of the eastern alcohol and PMB-deprotection of the western alcohol generated **4.4**, which was successfully converted to the desired olefin via the formation and elimination of an intermediate iodide followed by TBS-deprotection. Oxidation of the primary alcohol under Swern conditions [34] to the corresponding aldehyde, followed by organolithium



Scheme 4 Synthesis of C15–C30 fragment. (**a**) Dess–Martin periodinane, CH_2Cl_2, 85%; (**b**) $NaBH_4$, MeOH, 0°C, 89%

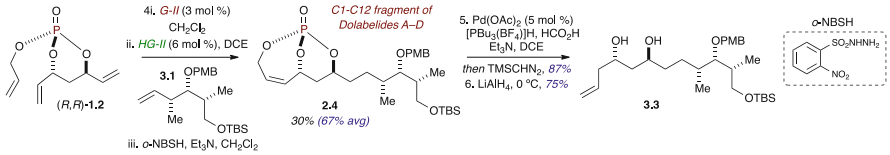


Scheme 5 Endgame of total synthesis of dolabelide C

addition of vinyl iodide **4.6** using *tert*-butyllithium, produced **4.7** in good yield, albeit a 1:1 diastereomeric mixture. This stereoselectivity was increased to nearly 3:1 *syn*:*anti* via oxidation and subsequent reduction with sodium borohydride, allowing for some recovery of material (Scheme 4).

With the syntheses of the C1–C14 and C15–C30 fragments complete, coupling of carboxylic acid **2.2** – obtained in three steps from **3.6** – with secondary alcohol **4.7** under Yamaguchi conditions [35] provided ester **5.1** in 77% yield (Scheme 5). Protecting group interconversion (TES to acetate), followed by acetonide and PMB-deprotection with PPTS and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), furnished the macrocyclization precursor **5.3** in 73% overall yield (over four reactions). Finally, ring-closing metathesis in the presence of the **G-II** catalyst (20 mol%) afforded dolabelide C (**1.1**), along with the undesired *Z*-stereoisomer (1:1 *E*:*Z*), in a 24-step longest linear sequence (LLS) from commercially available starting materials. While the authors were hoping to improve the stereoselectivity of the final macrocyclization by varying catalyst and conditions, efforts proved fruitless, although new and improved methods in reagent-controlled, stereoselective macrocyclic ring-closing metathesis could provide a means of averting loss of precious material in this final step (for recent examples of reagent-controlled *E*-selective metathesis processes, see [36, 37]).

One valuable aspect of tether methodologies, particularly those whose stereochemical influences impart orthogonal reactivity patterns within a functionality-rich system, is the potential to combine multiple steps into a one-pot, single

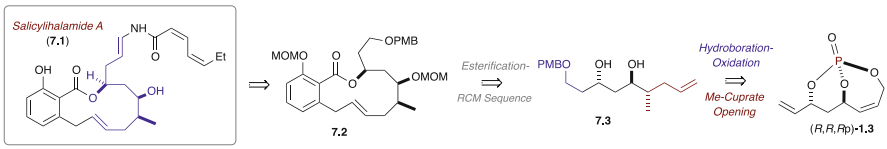


Scheme 6 One-pot, sequential RCM/CM/chemoselective hydrogenation route to C1–C12 of dolabelide C

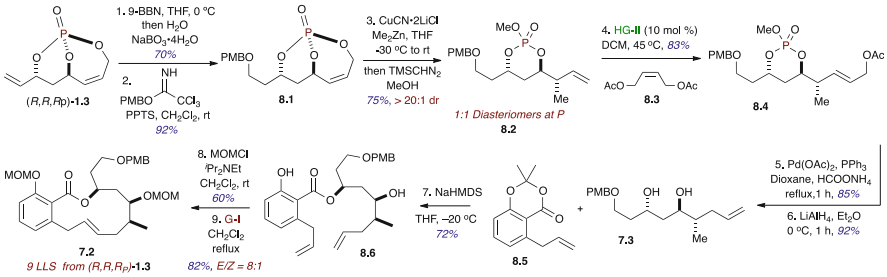
purification sequence which allows for more efficient and streamlined syntheses of complex intermediates. In 2012, Hanson and coworkers published a series of studies on the combination of ring-closing metathesis, cross-metathesis, and chemoselective hydrogenation into a single three-reaction, one-pot sequential sequential process [38]. Within this study, the application of this one-pot, sequential protocol to the C1–C14 fragment of dolabelide C was included (Scheme 6). Exposure of (*R*,*R*)-**1.2** to the **G-II** catalyst (3 mol%), followed by addition of the **HG-II** catalyst (6 mol%) and olefin cross partner, would provide the corresponding di-olefin-containing [4.3.1]-bicyclic phosphate product, which, upon treatment with *o*-NBSH and triethylamine (Et_3N), would afford **2.4** selectively in 30% yield (67% average per reaction). Subsequent allylic phosphate transposition with Pd(0)-formate, methylation of the free phosphate, and tether removal with $LiAlH_4$ would then generate the C1–C14 fragment (*trans* the carboxylic acid) **3.3** in five linear steps from the commercially available starting materials. This protocol would also reduce the LLS of the total synthesis of dolabelide C from 24 LLS to 22 LLS. Further investigations involving other one-pot sequential processes mediated by the phosphate tether could potentially streamline this synthesis – and other syntheses of complex small molecules – moving forward.

3 Formal Synthesis of (−)-Salicylihalamides A

Salicylihalamide A (**7.1**) was isolated from *Halicona sp*. by Boyd, Erickson, and coworkers in 1997 (Scheme 7) [39, 40]. This marine macrolide was found to exhibit potent cytotoxicity (an average 15 nM GI_{50}) against 60 NCI human tumor cell lines and selective inhibition of H^+-ATPase (V-ATPase), with an IC_{50} value <1.0 nM against bovine brain V-ATPase [41]. In 2011, Hanson and coworkers reported the formal syntheses of salicylihalamides A and B from (R,R,R_P)-bicyclo[4.3.1]phosphate **1.3** (Scheme 7) [42]. The synthetic route involves the construction of the core macrocycle via a late stage esterification of the diol fragment **7.3** followed by an *E*-selective RCM. Diol intermediate **7.3** could likewise be generated from bicyclic phosphate **1.3** via chemoselective hydroboration-oxidation of the exocyclic olefin, followed by a stereoselective S_N2'-methylcuprate addition to open the bicyclic structure.



Scheme 7 Retrosynthetic analysis for salicylihalamide A

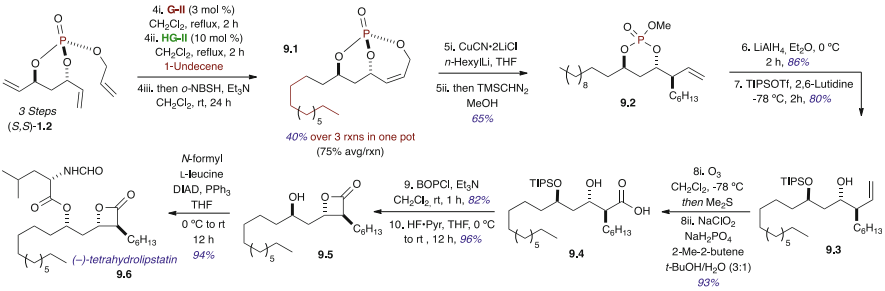


Scheme 8 Synthesis of advanced intermediate **7.2**

Bicyclo(4.3.1)-phosphate (R,R,R_P)-**1.3** was treated with 9-borabicyclo[3.3.1] nonane (9-BBN), followed by oxidation with sodium perborate tetrahydrate ($NaBO_3$•$4H_2O$), to provide the intermediate primary alcohol as the sole product; subsequent PMB-protection furnished the corresponding bicyclic phosphate intermediate **8.1** in good overall yield (Scheme 8). Next, regio- and diastereoselective methylcuprate addition to **8.1**, followed by methylation of the resultant free phosphate, afforded phosphate monocycle **8.2** (75% yield, dr > 20:1) with a terminal olefinic functional handle. Monophosphate **8.2** was then subjected to cross metathesis with (*Z*)-2-butene-1,4-diyl diacetate (**8.3**) to generate monophosphate **8.4** in 83% yield; subsequent regioselective, Pd-catalyzed reductive allylic transposition, followed by phosphate removal with $LiAlH_4$ produced diol **7.3** in excellent overall yield. The targeted diol **7.3** was esterified by treatment with sodium bis (trimethylsilyl)amide (NaHMDS) followed by exposure to **8.5**, affording ester **8.6** as a 3.6:1 (desired:undesired) mixture of regioisomers. Gratifyingly, the other regioisomer was successfully converted back to the starting material **7.3** for further recycling. Finally, MOM-protection of the remaining secondary alcohol, followed by RCM with $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (Grubbs first generation catalyst, G-I), provided macrolactone core **7.2** in 9 longest linear steps (LLS).

4 Total Synthesis of (−)-Tetrahydrolipstatin

(−)-Tetrahydrolipstatin (THL, **9.6**), or, as it is more commonly known, Orlistat®, is a stable, saturated analog of lipstatin (for information on the isolation and biological activity of lipstatin and its analogs, see: [43–47] and references cited therein) which



Scheme 9 Total synthesis of (−)-tetrahydrolipstatin

has been used as an anti-obesity agent but has found renewed interest as a potential anti-cancer agent because of its selective inhibition of thioesterase activity of fatty acid synthase (FAS) in cancer cells (Scheme 9) [48, 49] (see also [50, 51] and references cited therein). In 2010, a concise total synthesis of THL was reported utilizing a phosphate tether-mediated, one-pot sequential, ring-closing metathesis/cross-metathesis/chemoselective hydrogenation protocol to afford the desired bioactive small molecule in nine steps from the readily accessible (*S*,*S*)-dienediol **1.1** [22].

Prepared in three steps from (*S*,*S*)-dienediol **1.1**, phosphate triene (*S*,*S*)-**1.2** was transformed into [4.3.1]-bicyclic phosphate **9.1** via the aforementioned RCM/CM/chemoselective hydrogenation protocol. Treatment with the **G-II** catalyst (3 mol%), followed by the addition of **HG-II** catalyst (10 mol%) and 1-undecene, provided the intermediate diene-containing bicyclic phosphate, which could be converted to **9.1** via selective olefin hydrogenation under mild diimide reduction conditions in 40% yield (75% average per reaction). Subsequent stereoselective S_N2' cuprate addition of *n*-hexyllithium, directed by the concave nature of the bicyclic phosphate **9.1**, followed by methylation of the free phosphate, furnished phosphate-containing **9.2** in 65% yield over two steps. Phosphate removal with $LiAlH_4$ and chemoselective protection of the more sterically accessible alcohol with TIPS-triflate generated olefinic alcohol **9.3** in good yield. Ozonolysis of the terminal C–C double bond to generate a terminal aldehyde, followed by oxidation under Pinnick conditions [52], produced carboxylic acid **9.4** in 93% yield over two steps. β-Lactonization using bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOPCl) and subsequent TIPS-deprotection with HF•pyridine yielded β-lactone **9.5**, which, under exposure to *N*-formyl leucine and Mitsunobu conditions developed by Schneider [53], afforded (−)-tetrahydrolipstatin (**9.6**) in 94% yield.

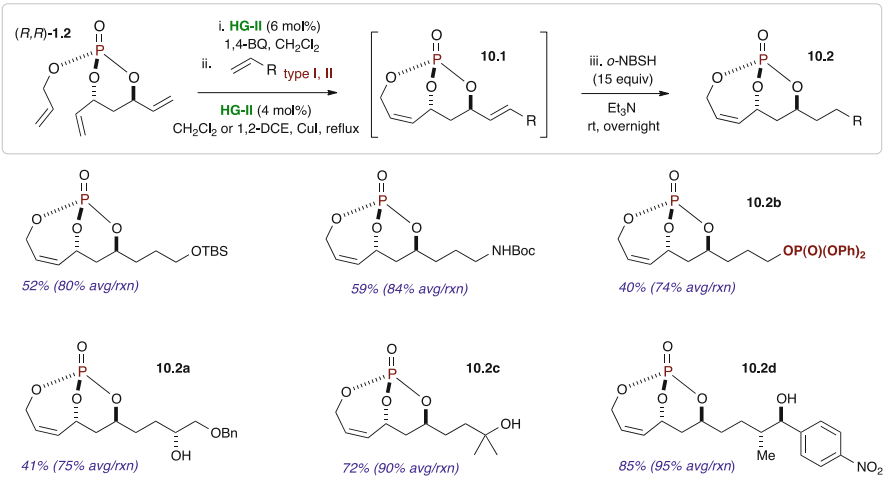
5 Phosphate Tether-Mediated One-Pot, Sequential Processes to Functionalized Polyols

In 2012, Hanson and coworkers developed a three-reaction, one-pot sequential methodology involving RCM, CM, and chemoselective hydrogenation, without intermediate isolation, to facilitate the efficient synthesis of complex and diverse polyol fragments [38]. In this protocol, phosphate triene [as shown (*R*,*R*)-**1.2**] would be treated with catalytic HG-II (6 mol%), in the presence of 1,4-benzoquinone additive, to facilitate a diastereotopic ring-closing metathesis reaction (Scheme 10). Upon completion of the RCM, the solvent (CH_2Cl_2) was evaporated, and CH_2Cl_2 or 1,2-dichloroethane, an olefin cross-partner, and additional catalyst were added to the crude reaction mixture to promote cross-metathesis with the terminal olefin of the resultant bicyclic phosphate and provide substituted intermediates **10.1**.[2] After the completion of CM, chemoselective diimide reduction (utilizing *o*-NBSH) was performed to generate hydrogenated CM bicyclic phosphates **10.2** in good to excellent overall yield (40%–85%, 74%–95% average per reaction). The observed chemoselectivity presumably arises from the deactivated nature of the endocyclic olefin, as well as steric constraints within the bicyclic structure – characteristics innate to the phosphate tether which allow for a certain amount of orthogonal reactivity between the two olefins. The terminal olefin of the initial intermediate bicyclic phosphate, which shows nearly type III [32] olefin behavior in CM reaction, readily undergoes cross-metathesis with a variety of type I and type II olefin cross partners, including those containing free alcohols (**10.2a**), electron-withdrawing groups (**10.2b**), and steric bulk (**10.2c**). In addition, stereochemically-rich cross-partners could allow for the facile synthesis of more complex bicyclic phosphate intermediates (**10.2d**, as well as the application to C1–C14 of dolabelide C), which could prove useful in the simple and efficient synthesis of polyol-containing bioactive small molecules.

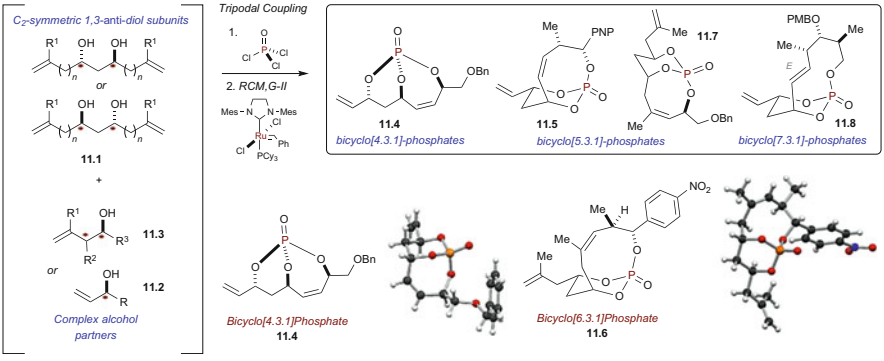
In 2013, Hanson and coworkers reported a detailed study to investigate the effect of ring-size, stereochemistry, and substitution in the context of RCM reactions to provide bicyclo[*n*.3.1]phosphate tether systems (Scheme 11) [54]. In this study, a series of phosphate tethered trienes were synthesized via the tripodal coupling of different 1,3-*anti* diene diols (**11.1**), allylic (**11.2**) and homoallylic alcohol partners (**11.3**) with phosphorus oxychloride ($P(O)Cl_3$). Various bicyclo[*n*.3.1]phosphates (**11.4**–**11.8**) were obtained in good to moderate yields, highlighting the potential of phosphate tethers to mediate the coupling of stereochemically rich alcohols. For seven- to nine-membered ring systems, exclusive *Z*-selectivity was observed (**11.4**–**11.7**), while the ten-membered ring formations were highly *E*-selective (**11.8**).

More importantly, with respect to the eight-membered ring formation, the allylic methyl substitution played a significant role in dictating which of the diastereomeric trienes **SM 5.9** would participate in RCM (Scheme 12). When treated with

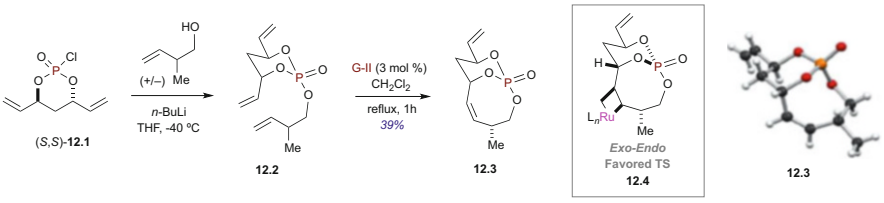
[2] It was observed that the inclusion of CuI, as well as freeze-degas-thawed solvents, increased the yield of cross-metathesis, as well as contributed to an overall cleaner reaction as observed by TLC.



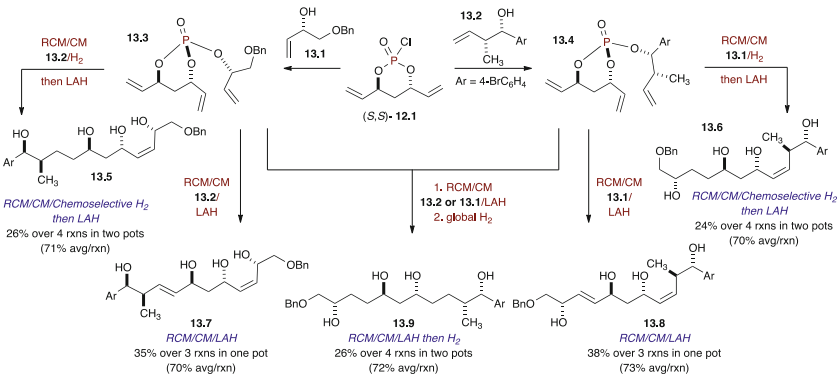
Scheme 10 RCM/CM/chemoselective hydrogenation protocols to functionalized bicyclic phosphates



Scheme 11 Detailed study of the effects of substitution, ring size, and stereochemical complexity on the formation of bicyclic phosphates



Scheme 12 Double diastereotopic differentiation via kinetic resolution by RCM



Scheme 13 General reaction conditions: RCM – HG-II (3 mol%), 1,2-DCE/CH_2Cl_2, 2 h; CM – HG-II (3 mol%), CH_2Cl_2, CM partner (3–5 equiv.); LAH reduction – $LiAlH_4$ (2–4 equiv.), THF, 0°C, 2 h; chemoselective H_2 – *o*-NBSH (12 equiv.), CH_2Cl_2, Et_3N, overnight; global H_2 – *o*-NBSH (20 equiv.), CH_2Cl_2, Et_3N, overnight

G-II, the 1:1 mixture of diastereomeric trienes **12.2** provided bicyclic phosphate **12.3** as a single diastereomer, along with diastereomerically enriched unreacted starting material. Product formation was rationalized according to the favored transition state **12.4**, in which the RuL_n-metallocyclobutane and adjacent methyl group were *trans* to each other, with the larger of the two (the metallocyclobutane) exocyclic with respect to the newly formed bicyclic phosphate. This double diastereotopic differentiation via kinetic resolution by RCM could prove useful in the selective synthesis of stereochemically rich polyol-containing intermediates but also currently presents a limitation and a challenge to the scope of molecules which can be acquired via this specific protocol. Taken collectively, the RCM study demonstrated the utility of phosphate tether in synthesizing complex systems with high diastereoselectivity and also facilitated our understanding of the underlying factors governing RCM for such complex systems.

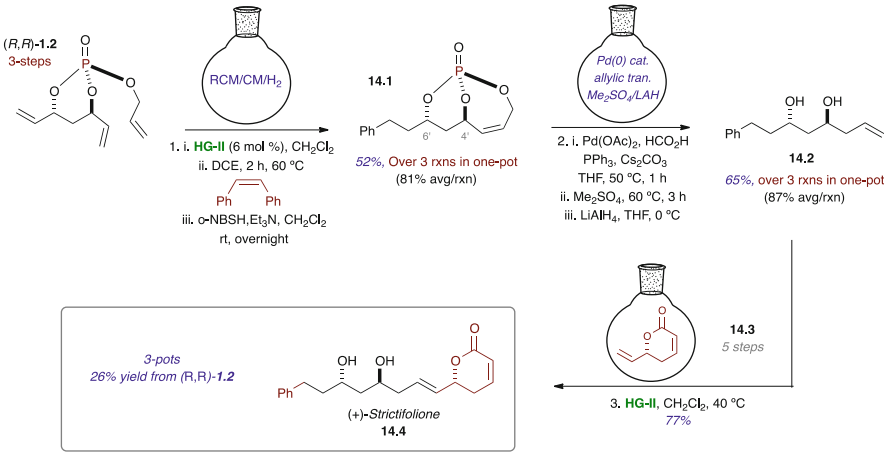
Building upon the previous two studies described above, in 2014, Hanson and coworkers united the idea of coupling stereochemically rich fragments with one-pot, sequential processes to synthesize a variety of polyol scaffolds by phosphate tether-mediated one/two-pot sequential methods (Scheme 13) [55]. The strategy relies on the order of addition of the alcohol partners for tripodal coupling and the cross metathesis steps, thereby generating scaffolds bearing differentiated olefinic ends. Thus, pseudo-C_2-symmetric monophosphate (*S*,*S*)-**12.1** was coupled separately with allylic alcohol **13.1** and homoallylic alcohol **13.2**, yielding two different trienes, **13.3** and **13.4**, respectively. Triene **13.3** was subjected to RCM and subsequent CM with homoallylic alcohol **13.2**, followed by chemoselective hydrogenation in the presence of *o*-NBSH (*ortho*-nitrobenzenesulfonylhydrazide), produced bicyclic phosphate intermediate (not shown in the scheme). Upon tether removal of the resulting bicyclic phosphate intermediate, polyol **13.5** was obtained in an overall yield of 26% over four reactions performed in a two-pot sequence (71% avg/rxn). Similarly, triene **13.4** was subjected to the same two-pot protocol to

furnish polyol **13.6** in an overall yield of 24% over four reactions performed in a two-pot sequence (70% avg/rxn).

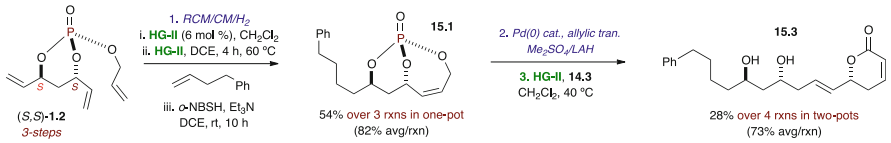
Next, triene **13.3** was subjected to RCM, CM with homoallylic alcohol **13.2**, and subsequent tether removal with LAH to produce polyol **13.7**, bearing both (*Z*)- and (*E*)-configured olefins, in an overall yield of 35% over three reactions (70% avg/rxn) in a one-pot sequence. Following a similar one-pot protocol, polyol **13.8** was generated from triene **13.4** in an overall yield of 35% over three reactions (70% avg/rxn). Starting from triene **13.4**, a one-pot sequential RCM/CM/LAH and global hydrogenation, in the presence of excess *o*-NBSH, furnished polyol **13.9** in an overall yield of 26% in two pots over four reactions (72% avg/rxn). The same polyol **13.9** was obtained from triene **13.3** following similar reaction sequences. Importantly, this study highlighted that stereochemically enriched polyol scaffolds bearing both (*Z*)- and (*E*)-olefinic geometries – which would otherwise be difficult to produce via (Z)- and (E)-selective CM of 1,3-*anti* diol subunits with olefinic partners – can be generated via phosphate tether-mediated one-/two-pot reaction protocols which minimize the time and effort spent on individual purification steps.

6 Total Synthesis of (+)-Strictifolione

In 2013, Hanson and co-workers reported a library-amenable, "pot-economical" synthetic approach utilizing two consecutive, phosphate tether-mediated, one-pot sequential processes and a cross metathesis reaction to afford two antifungal natural products, (+)-strictifolione (**14.4**, Scheme 14) and (6*R*)-6[(*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2*H*-2-pyrone (**15.3**, Scheme 15), in good yield



Scheme 14 Total synthesis of (+)-strictifolione via *P*-tether mediated, one-pot sequential protocols



Scheme 15 Total synthesis of **15.3** via *P*-tether mediated, one-pot sequential protocols

with minimal purification [56]. Exposure of phosphate triene (*R*,*R*)-**1.2** to one-pot, sequential RCM/CM/chemoselective hydrogenation conditions, similar to those described above [38], with olefin cross-partner *cis*-stilbene, provided bicyclic phosphate **14.1** in 52% overall yield (81% avg/rxn). Subsequent allylic transposition under Pd(0)-formate conditions, in situ methylation of the resultant free phosphate with dimethylsulfate [Me_2SO_4], and phosphate tether removal with $LiAlH_4$ furnished differentiated diol **14.2** in a single, high yielding purification step (65% overall yield, 87% avg/rxn). Finally, cross-metathesis of diol **14.3** with lactone **14.4**, prepared in five steps according to via the Jacobsen protocol [57–59], afforded (+)-strictifolione (**14.4**) in 77% yield and excellent *E*-selectivity. This three-pot concise route generated the desired natural product in 26% overall yield from (*R*,*R*)-**1.2** and provides an efficient, scalable, and library-amenable approach to strictifolione, as the protocol allows for easy diversification of the western and eastern portions of the molecule through simple modification of cross-metathesis cross partners.

Similarly, the total synthesis of (6*R*)-6[(*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2*H*-2-pyrone (**15.3**) was accomplished following the three-pot protocol utilized in the total synthesis of (+)-strictifolione. Exposure of phosphate triene (*S*,*S*)-**1.2** to RCM/CM/chemoselective hydrogenation conditions with olefin cross-partner phenyl-but-1-ene provided bicyclic phosphate **15.1** in 54% overall yield (82% avg/rxn). Next, one-pot Pd-catalyzed allylic transposition, in situ methylation of the resultant free phosphate, and reductive removal of the phosphate tether, followed by cross metathesis with **14.3**, afforded the desired natural product (**15.3**) and good overall yield. Notably, this streamlined modular approach takes full advantage of orthogonal protecting- and leaving-group properties innate to the phosphate tether to eliminate the protecting group manipulations which – though often unavoidable – decrease the atom economy and simplicity of a straightforward synthesis.

7 Conclusions

The use of multivalent phosphate tethers, which couple both simple and complex alcohol fragments, has proven to be a valuable tool in the synthesis of stereochemically rich, polyol-containing bioactive small molecules. Moreover, the ability of the phosphate tether to mediate multiple orthogonal reaction

sequences in a single purification step highlights its synthetic utility in the streamlining of routes toward both simple and complex intermediates, while providing facile means for the synthesis of analog libraries. Hopefully, as the understanding of these orthogonal reactivity patterns innate to the phosphate tether deepens, the potential of this method to simplify the synthesis of complex natural products and their analogs will incite other researchers to view these tethers as profitable complements to more established silicon counterparts.

Acknowledgment The authors would like to thank the National Institute of General Medical Sciences (NIH R01 GM077309) and the State of Kansas for their generous support of our program.

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