Phosphinate-containing heterocycles: A mini-review

Olivier Berger and Jean-Luc Montchamp*

Abstract
This review provides an overview of recent efforts towards the synthesis of phosphinate heterocycles $R_1R_2P(\text{OR})$. Our laboratory and others’ have been involved in this field and as a result new P–C, P–N, and P–O containing heterocyclic motifs are now available through a variety of methods. While developing rapidly, this area is still in its infancy so that biological testing of the compounds has not yet been conducted and applications are rare. The growing availability of synthetic methods will undoubtedly change this situation in the near future.

Introduction
The preparation of P-heterocycles has been the subject of many studies over the years, and the field has been extensively reviewed [1-8]. Typically, accessing P-heterocycles involves multistep sequences with low overall yields [1-8]. In the past 20 years, significant effort has been devoted to synthetic and reactivity studies of a particular family of organophosphorus compounds: the phosphinates $R_1R_2P(\text{OR})$ [9]. Because the phosphinic acid moiety $\text{P(OR)}$ can mimic carboxylic acids, its incorporation into heterocycles may offer new opportunities for the discovery of biologically active analogs. However, little or no biological data is available at this time. Selected recent synthetic work by us and others is presented below.

Review

Phospholes

Several compounds have been prepared in this series. Keglevich and coworkers realized the synthesis of phosphole derivatives $2a$–$f$ based on the McCormack reaction [10] followed by microwave-assisted esterification of the phosphinic acid using different alcohols in large excess (Scheme 1) [11,12]. Six phospholes $2a$–$f$ were prepared in yields up to 94%.

Montchamp and coworkers have synthesized phospholes $4a,b$ by ring closing metathesis using 2 or 5 mol % of 2nd generation Grubbs’ catalyst (Scheme 2) [13,14]. Two compounds $4a,b$
were prepared in 51% and 62% yields. The same approach was reported earlier by Mioskowski and coworkers [15,16] except the starting phosphinates 3a,b were prepared less efficiently by the sila-Arbuzov reaction of bis(trimethylsiloxy)phosphine (Me₃SiO)₂PH.

Cyclohexyl 2-(biphenyl)-H-phosphinate 7 was cyclized using 2 mol % of Pd(OAc)₂ in refluxing THF to produce another phosphindole 8 in 48% yield (Scheme 4) [18].

Phosphindoles
Montchamp and coworkers have synthesized a few phosphindoles. The first phosphindole 6 was simply obtained in 84% yield by reacting an α,ω-bisphosphonate derivative 5 with n-butyllithium in a phospha-Dieckmann condensation (Scheme 3) [17].

Tanaka and coworkers have synthesized chiral benzopyrano and naphthopyrano-fused helical phosphafluorenes 14a–d from dialkynyl phosphinate 12 and phenol-linked terminal tetrayne 13 at room temperature for only 1 h using a cationic rhodium(I)/(R)-tol-BINAP complex as a catalyst. Four helical phosphafluorenes 14a–d were prepared in yields up to 40% and enantiomeric excesses up to 73% (Scheme 6) [20].

Chen and Duan have synthesized one phosphinoline 17 in 60% yield by the alkyne–arene annulation of ethyl phenyl-H-phosphinate (15) using 2 equivalents of Ag₂O (Scheme 7) [21]. Miura et al. simultaneously reported the same reaction but with 4 equivalents of AgOAc instead, delivering the heterocycle 17 in 53% yield (Scheme 8) [22]. Both reactions used 4 equivalents of Ag(I) as well as an excess of H-phosphinate.

1,3-Oxaphospholes
Cristau and coworkers have achieved the direct synthesis of 1,3-oxaphospholes 20a–f (Scheme 9) by reacting chloroalkylphosphinic or phosphonic chlorides 18 with malonic diester 19 in the

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**Scheme 1:** McCormack synthesis.

**Scheme 2:** Ring-closing metathesis.

**Scheme 3:** Phospha-Dieckmann condensation.

**Scheme 4:** Palladium-catalyzed oxidative arylation.

**Scheme 5:** Tandem cross-coupling/Dieckmann condensation.

**Scheme 6:** Tandem cross-coupling/Dieckmann condensation.

**Scheme 7:** Tandem cross-coupling/Dieckmann condensation.
presence of two equivalents of sodium hydride [23,24]. 1,3-Oxaphospholes 20a–f were obtained in yields up to 70%.

1-Aza-3-phospha-6-oxabicyclo[3.3.0]octanes

The synthesis of chiral bicyclic phosphinates 23a–k by domino hydrophosphinylation/Michael/Michael reaction was realized by Fourgeaud et al. (Scheme 10) [25]. Several 1-oxa-3-aza-6-phosphabicyclo[3.3.0]octanes derivatives 23a–k were obtained in yields around 70% by reacting alenes 21 with imines 22 derived from (R)- or (S)-phenylglycinol, (S)-2-aminobutanol or ethanolamine. Diastereoisomeric ratios were generally close to 50:50. A model for this reaction’s diastereoselectivity was proposed.

Cyclo-PALA

Montchamp and coworkers have achieved the synthesis of 5- and 6-membered rings “cyclo-PALA” analogs which are 1,3-azaphospholidine and 1,4-azaphosphorine derivatives 26, 29 [26].
For the 5-membered ring 26, hydroxymethyl-\(H\)-phosphinic acid (24) underwent a sila-Arbuzov reaction with the bromide 25, the crude mixture was esterified with diphenylidazomethane, cyclized using Mitsunobu conditions and then hydrogenolyzed to produce the five-membered amide 26 in 22% overall yield (Scheme 11).

For the six-membered “cyclo-PALA” 29, isoprenyl-\(H\)-phosphinic acid (27) reacted with the bromide 25 under sila-Arbuzov conditions, the crude phosphinic acid was esterified, using BnBr/Ag\(_2\)O, ozonolyzed and then reduced with sodium borohydride to afford an alcohol intermediate 28. This product was cyclized using Mitsunobu conditions and finally hydrogenolyzed to deliver the 6-membered heterocycle 29 in 12% overall yield (Scheme 12) [26].

In this particular study phosphinates 26 and 29 were tested as inhibitors of aspartate transcarbamoylase (ATCase).
5-Membered 26 was completely inactive, whereas 6-membered 29 showed modest activity ($K_i = 1 \mu M$, 63 times less active than phosphonic acid N-phosphonacetyl-L-aspartate PALA, $K_i = 16 \text{nM}$).

1,3-Azaphosphorines and 1,3-azaphospholidines

Several 1,3-azaphosphorines and 1,3-azaphospholidines were synthesized by Montchamp and coworkers. The reaction of 2-aminoethyl-$H$-phosphinates 30a ($n = 1$) with carbonyl compounds 31 in refluxing butanol or concentrated hydrochloric acid took place smoothly to generate seven 1,3-azaphospholidines 32a–g in yields up to 55% (Scheme 13) [27,28].

The reaction of 3-aminopropyl-$H$-phosphinates 30b with aldehydes 31 in refluxing butanol allowed the formation of eight 1,3-azaphosphorines 32h–o in yields up to 76% (Scheme 13).

Montchamp and coworkers also prepared two other examples of 1,3-azaphosphorines 35a,b ($n = 1$) in yields up to 61% by reacting ethyl-3-chloropropyl-$H$-phosphinate 33 with imines 34 in toluene at reflux (Scheme 14) [29].

1,3-Azaphosphindoles and 1,3-benzazaphosphorines

Several compounds in this series were synthesized by Montchamp and coworkers using two different approaches. The first one is the reaction between an imine 34 and 2-bromo-phenyl-substituted $H$-phosphinate esters 36 in the presence of $\text{Cs}_2\text{CO}_3$, and catalytic Pd(PP$_3$)$_4$ in refluxing toluene to generate the corresponding cyclized products 37a–h in yields up to 76% (Scheme 15) [29].

The second way is the formation of the imine first by reacting an amine 39a,b with an aldehyde 38, then the phosphinate is introduced and the mixture stirred for 24 h at reflux to generate the corresponding $H$-phosphinate esters. Addition of DIPEA and catalytic Pd/dppf in a mixture DMF/DME to the intermediates generated the corresponding cyclized derivatives 40a,b in yields up to 53% (Scheme 16) [18].
For these compounds, the authors were able to separate the different diastereoisomers generated during the reaction by simple column chromatography on silica gel.

1,4-Azaphosphorines

In this series, only a few examples have been reported in the literature. One derivative has been prepared by Manthey and coworkers in 50% yield as a precursor to a dihydroorotase inhibitor (Scheme 17) [30].

In this example, the amino acid 41 was first cyclized using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (42) at pH 5.6 followed by protection of the carboxylic acid and phosphinic acid moieties by diphenylmethyl group using a slight excess of diphenyldiazomethane. The two diastereoisomers obtained were readily separable by column chromatography.

Another example has been synthesized in 45% yield by Montchamp and coworkers (Scheme 18) [14].

To prepare the required phosphinate 45 a double allylation of H$_3$PO$_2$ was performed using 2 equivalents of cinnamyl alcohol 44 in the presence of 2 mol % of Pd/Xanthpos followed by an esterification using benzyl bromide. Ozonolysis, and reductive amination using excess benzylamine in the presence of sodium cyanoborohydride completed the synthesis.

Phosphorines

Two phosphorines 47a,b were obtained by Montchamp and coworkers via the cyclization of 5-bromopentyl-\(H\)-phosphinate esters 46a,b in the presence of LiHMDS in 71% and 74% yields for the butyl and ethyl esters respectively (Scheme 19) [28,31].

Another phosphorine 49 was obtained by Montchamp and coworkers in 57% yield via the cyclization through conjugate addition of ethyl 7-(ethoxy-\(H\)-phosphinoyl)-3-methyl-2-heptenooate (48) in the presence of potassium tert-butoxide (Scheme 20) [28].

A phosphorin[3',4':4,5]furo[2,3-d]-1,3-dioxole 51 was synthesized in 36% yield by Tattersall and coworkers by realizing a double Arbuzov-type reaction between bis(trimethylsilyloxy)phosphine and the dibromide 50 followed by the esterification of the phosphinic acid using diazomethane (Scheme 21)
During this work, they obtained 11 different compounds in yields up to 100% and diastereomeric excesses up to 86%. The starting phosphinates 52a–k were prepared using classical chemistry involving Grignard addition to EtOP(O)Cl₂.

**Phenoxaphosphine**

Scheme 23 shows the synthesis of one phenoxaphosphine 56 in 55% yield by Li and coworkers via the reaction between diethyl 2-oxocyclohexylphosphonate (54) and benzene generated from 2-(trimethylsilyl)phenyl triflate (55) and cesium fluoride [35].

**1,4,2-Oxazaphosphinane**

This series of compounds is only represented by few examples all generated through methodology developed by Pirat and coworkers. Scheme 24 shows the synthesis of a H-phosphinate intermediate 59 in 65% yield via the reaction between the imine 57 of the racemic 1,2-diphenylethanolamine with benzaldehyde and methyl phosphinate (58) followed by the cyclization through a base catalyzed transesterification [23,36].

This versatile intermediate 59 was reacted with aldehydes, imines, olefins and aryl bromides or aryl iodides to generate a wide range of phosphinates.

The same authors have also prepared another H-phosphinate intermediate 61 in 71% yield (Scheme 25) [37].

This oxazaphosphinane 61 was synthesized in two steps at room temperature, first, by a nucleophilic attack of methyl hypophosphite on oxazolidine 60 followed by an intramolecular cyclization, this time without base catalyzed transesterification. The authors explained this difference of reactivity by the
Thorpe–Ingold effect [38]. Indeed, the presence of four methyl groups allows the hydroxy function to be spatially closer to the reactive phosphinite, facilitating the intramolecular cyclization of this product.

Conclusion
Phosphinate heterocycles are becoming routine products in the literature. Classical approaches such as the McCormack reaction of conjugated dienes, the sila-Arbusov reaction of bis(trimethylsiloxy)phosphine with dihalides, etc. continue to be useful. However, novel approaches in both the preparation of acyclic precursors and the reactions to achieve their heterocyclization, have led to more efficient synthesis and broader structural diversity. While, like with any other P-heterocycles the phosphinites can be employed for the synthesis of novel phosphorus-containing compounds, their potential for the discovery of novel biologically active motifs is tantalizing.

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