λ⁵-Phosphorus-Containing α-Diazo Compounds (PCDCs): a Valuable Tool for Accessing Phosphorus-Functionalized Molecules

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Abstract

The compounds characterized by the presence of a λ⁵-phosphorus functionality at the α-position with respect to the diazo moiety, here referred to as λ⁵-phosphorus-containing α-diazo compounds (PCDCs), represent a vast class of extremely versatile reagents in organic chemistry and are particularly useful in the preparation of phosphonate-, and phosphinoxide-functionalized molecules. Indeed, thanks to the high reactivity of the diazo moiety, PCDCs can be induced to undergo a wide variety of chemical transformations. Among them carbon-hydrogen, as well as heteroatom-hydrogen insertion reactions, cyclopropanation, ylide formation, Wolff rearrangement, and cycloaddition reactions. PCDCs can be easily prepared from readily accessible precursors by a variety of different methods, such as diazotization, Bamford-Stevens-type elimination and diazo transfer reactions. This evidence along with their relative stability and manageability make them appealing tools in organic synthesis. This review aims to demonstrate the ongoing utility of PCDCs in the modern preparation of different classes of phosphorus-containing compounds, phosphonates, in
particular. Furthermore, to address the lack of precedent collective papers, the review also summarises the methods for PCDCs preparation.

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1. Introduction

Phosphorus-containing α-diazo compounds represent a class of derivatives characterized by the presence of a phosphorus functionality at the α-position with respect to the diazo moiety. According to the number of the phosphorus's valence electrons involved in bonds, they can be classified into
λ³- and λ⁵-phosphorus-containing α-diazo compounds. In contrast with the widely studied and synthetically exploited α-diazocarbonyl compounds,¹²,³ phosphorus-containing α-diazo compounds have received comparatively very little attention, and a review completely dedicated to them is still missing in the literature. This review will cover the preparation and the chemistry of λ⁵-phosphorus-containing α-diazo compounds hereinafter referred to as PCDCs. The first recorded synthesis of a PCDC dates back to the work of Horner et al.,⁴ who in 1961 prepared diphenyl α-diazobenzylphosphinoxide (2a). The discovery by Gilbert et al.⁵ that the base-promoted reaction of dimethyl α-diazomethylphosphonate (5a) with aldehydes and aryl ketones could furnish the corresponding homologous alkynes, through the involvement of the intermediate diazoethene, pushed PCDCs into the limelight. Since then, 5a is often referred to as Seyferth-Gilbert reagent, thus honoring also Seyferth, who reported the first preparation of 5a in pure form.⁶ The Ohira-Bestmann modification of this reaction has represented another breakthrough into the PCDC story. Thus, paradoxically, PCDCs became notorious for a reaction in which their phosphorous functionality is lost. However, thanks to the excellent synthetic versatility of the diazo moiety, PCDCs represent useful tools for accessing different phosphorus-functionalized molecules. The phosphonate moiety is the most common functionality present in known PCDCs. Thus, these PCDCs have been extensively used for the preparation of different classes of biologically active phosphonic acid derivatives, often employed in medicinal chemistry due to their increased stability to enzymatic hydrolysis when compared to their corresponding phosphate analogues.⁷,⁸ As an example, α-amino phosphonic acid derivatives are key building blocks in the synthesis of phosphonopeptides, which can act as enzyme inhibitors, antibiotics, plant regulators, and haptens of catalytic antibodies.⁹,¹⁰,¹¹ In the literature, the ability of the phosphonic acid moiety to function as bioisosteric replacement not only for the phosphate,¹²,¹³,⁷,¹⁴ but also for sulfate¹⁵ and carboxylate groups,¹⁶,¹⁷,¹⁸,¹⁹ is well documented. Furthermore, the ability of phosphorous moiety to specifically coordinate with metal-dependent
enzymes explains the presence of a lot of phosphorus-functionalized molecules among enzyme inhibitors.\textsuperscript{20,21,22,23} The use of phosphonic acids in coordination chemistry has been recently reviewed.\textsuperscript{24} Another feature of the organophosphonates, is their ability to be easily converted to other functional groups through the Horner–Wadsworth–Emmons (HWE) reaction.\textsuperscript{25,26}

The huge number of transformations that can occur with PCDCs makes them extremely versatile reactants in the scenario of synthetic chemistry for the preparation of molecules functionalized with a phosphorus-based moiety. Although in general PCDC-based reactions have several advantages, such as mild reaction conditions and the possibility to work with multifunctional substrates, so far the chemistry of PCDCs has been never surveyed, except for an old Regitz’s review,\textsuperscript{27} a short paragraph in a book chapter,\textsuperscript{28} and isolated examples, which are highly dispersed over the literature on diazo-compounds. With the aim to fill this gap, our primary purpose in writing this review is to demonstrate the ongoing utility of DCCPs in the modern preparation of different classes of phosphorus-containing compounds, in particular phosphonates. Furthermore, in view of the lack of precedent collective papers, we also deemed it appropriate to summarize the methods for PCDCs preparation. This review is therefore organized into two main sections. After this brief introduction to the topic in section 1, we start in section 2 with the different methods for preparing PCDCs. In section 3 we describe the vast array of reactions of the PCDCs ordered according to the product obtained. Each section provides relevant introductory information and references, covering the literature published since 1961 until April 2016. Although a considerable part of PCDC chemistry have gotten the inspiration from diazocarbonyl one, we chosen do not cite the corresponding bibliography that can be found by the reader in the references here reported.

2. Synthesis of $\lambda^5$-Phosphorus-Containing $\alpha$-Diazo Compounds
Diazotization reaction, Bamford-Stevens-type elimination, and diazo transfer techniques represent the most popular synthetic methods for accessing PCDCs (Figure 1). The choice of the suitable methodology is strictly dependent on: a) the type of the desired PCDC (terminal or not-terminal diazo function as in A or B, respectively); b) the nature of \( R^1 \) group in the case of \( \alpha \)-substituted PCDCs B; and c) the availability of the required starting material. Thus, \( \alpha \)-diazomethyl-phosphonates and -phosphinodioxides A are prepared either by diazotization of the corresponding primary amines C or by dehydroxylation diazo-transfer reactions, after \textit{in-situ} activation of methylphosphonates D. Diazotization reaction is not a common method for the synthesis of PCDCs B, the only example in the literature being represented by the preparation of diethyl 1-diazo-2,2,2-trifluoroethylphosphonate starting from E. PCDCs B substituted at \( \alpha \)-position with an activating \( R^1 \) group, can be efficiently obtained by direct diazo transfer reaction starting from F. Bamford-Stevens-type elimination of \( \alpha \)-ketophosphonates G is the method of choice when the group \( R^1 \) is not activating enough for direct diazo transfer and/or the precursor \( \alpha \)-ketophosphonate G is easily available. \( \alpha \)-Alkyl- and \( \alpha \)-benzyl-PCDCs B can be also synthesized by oxidation of the corresponding hydrazones H.

Another approach used for the preparation of PCDCs involves modification of an already prepared PCDC with retention of the diazo functionality. Such reactions, which generally involve the substitution of the hydrogen atom of terminal PCDCs by electrophilic reagents, are presented in paragraph 2.5. PCDCs can also act as nucleophiles in a base-promoted aldol-type addition with carbonyl compounds and imines, thus generating \( \alpha \)-functionalized-PCDCs. This particular aspect will be discussed in section 3.8.
2.1. Diazotization

The first PCDC reported in the literature in 1961 is the diphenyl \( \alpha \)-diazobenzylphosphinoxide (2a), which was prepared by Horner et al.\(^4\) by diazotization of diphenyl \( \alpha \)-aminobenzylphosphinoxide (1a) with sodium nitrite in acidic conditions. \( \alpha \)-Diazomethylphosphinoxides 2b and 2c were synthesized few years later by Kreutzkamp et al. following the same methodology (Scheme 1).\(^{29}\)
In 1970, Seyferth\textsuperscript{6,30} reported the preparation of the dimethyl \(\alpha\)-diazomethylphosphonate (5a), which is the most popular among PCDCs. Compound 5a was synthetized by diazotization of dimethyl aminomethylphosphonate acetate salt (4a), which in turn was obtained by hydrazinolysis of dimethyl phthalimidomethylphosphonate (3a) (Scheme 2). Although the diethyl analog of 5a had been already prepared via a different route (see section 2.3.2), this work represents the first example in which a dialkyl diazomethylphosphonate could be obtained in pure form by short-path distillation.

Following this procedure, Regitz et al. prepared diethyl \(\alpha\)-diazomethylphosphonate (5c),\textsuperscript{31} diphenyl \(\alpha\)-diazomethylphosphinoxide (5d), and methyl \(\alpha\)-phenyl-\(\alpha\)-diazomethylphosphinate (5e) in 51\%, 45\% and 16\% yield, respectively.\textsuperscript{32,33} This protocol was also applied by Marinozzi et al.\textsuperscript{34} to the multi-gram scale synthesis of the diisopropyl analog 5b. Recently some dialkyl aminomethylphosphonates became commercial available, thus simplifying this synthetic protocol.

Scheme 2. Syntheses of Dialkyl \(\alpha\)-Diazomethyl-Phosphonates, Phosphinates and \(-\)Phosphinoxides

5a-e

\[
\begin{align*}
3a-e &\xrightarrow{1. \text{N}_2\text{H}_4, \text{MeOH}} 4a-e
\end{align*}
\]

\[
\begin{align*}
4a-e &\xrightarrow{1. \text{NaNO}_2 \text{aq. AcOH}} 5a-e
\end{align*}
\]

\[
\begin{align*}
a: R^1 = R^2 = \text{OMe}, 46\%; & \quad b: R^1 = R^2 = \text{OiPr}, 70\%; & \quad c: R^1 = R^2 = \text{OEt}, 51\%; & \quad d: R^1 = R^2 = \text{Ph}, 45\%; \\
e: R^1 = \text{Ph}, R^2 = \text{OMe}, 16\% \end{align*}
\]
The first fluorinated PCDC was also synthesized by a diazotization reaction (Scheme 3). In particular, the amine 7, obtained in 74% overall yield 3 step procedure from the commercial available trifluoroacetic aldehyde ethylhemiacetal (6), was treated with isopropyl nitrite in neutral conditions to afford 8 in 67% yield. Diethyl 1-diazo-2,2,2-trifluoroethylphosphonate (8) was shown to be a stable and, under reduced-pressure, distillable, light-yellow liquid. Few years later the same authors published another synthesis of 8, which differed from the previous one only in the preparation of the amine 7. Both the procedures proved to be equally efficient and applicable to the multi-gram scale synthesis of 8.

Scheme 3. Synthesis of Diethyl 1-Diazo-2,2,2-trifluoroethylphosphonate (8)

![Scheme 3](image)

2.2. Bamford-Stevens-type Elimination

The Bamford-Stevens reaction, commonly employed to convert carbonyl compounds into diazo derivatives, can also be used for the preparation of PCDCs. α-Ketophosphonates easily form p-toluenesulfonyl hydrazones, which upon treatment with bases, such as sodium carbonate and triethylamine, at room temperature, undergo a remarkably facile Bamford-Stevens-type elimination to give the corresponding PCDCs. Accordingly, α-substituted-α-diazomethylphosphonates 11a-c were prepared by sodium carbonate-induced decomposition of p-toluenesulfonyl hydrazones 10a-c in water (Scheme 4). The compounds were obtained in very high yield after distillation (11a) or crystallization (11b,c).
Scheme 4. Synthesis of α-Substituted Dimethyl α-Diazomethylphosphonates 11a-c

Following an analogous protocol, Gurudata et al. prepared a large series of dimethyl α-aryl-, α-alkyl-, α-cycloalkyl- and α-vinyl-α-diazomethylphosphonates.\textsuperscript{39,40}

The alkaline cleavage of the ρ-toluenesulfonylhydrazones 12a,b allowed them to get the corresponding conjugated 1,3-diene unit-containing α-diazomethylphosphonates 13a,b (Scheme 5).\textsuperscript{41}

Scheme 5. Synthesis of Dimethyl α-Diazo-5-phenyl-2,4-pentadiene phosphonate (13a) and α-Diazo-2,4-hexadiene phosphonate (13b)

By Bamford-Stevens-type elimination, α-diazomethylphoshinic esters 14 were also prepared (Figure 2).\textsuperscript{33}
Figure 2. Examples of α-Diazoethylphosphinic Esters Prepared by Bamford-Stevens-type Elimination

Recently, Cai et al.\textsuperscript{42} employed this methodology for the preparation of a series of natural amino acid-derived PCDCs 17a-e, which were easily obtained from the corresponding \( p \)-toluenesulfonylhydrazone 16a-e by treatment with Et\(_3\)N in dichloromethane (Scheme 6).

Scheme 6. Synthesis of Diethyl β-Phthalimido-β-Substituted-α-Diazoethylphosphonates 17a-e

\[ \text{H}_2\text{N-CO}_2\text{H} \quad \text{15a-e} \quad \rightarrow \quad \text{16a-e} \quad \rightarrow \quad \text{Et}_3\text{N} \quad \text{CH}_2\text{Cl}_2, \text{rt} \quad \rightarrow \quad \text{17a-e} \]

a: R = CH\(_3\), 42%; b: R = CH\(_2\)Ph, 47%; c: R = iPr, 46%; d: R = CH\(_2\)CH(CH\(_3\))\(_2\), 46%; e: R = H, 11% yields calculated from 15

2.3. Diazo Transfer Reactions

As in the case of \( \alpha \)-diazocarbonyl compounds,\textsuperscript{2,1} diazo transfer to the \( \alpha \)-methylene position of a phosphoryl group requires the presence of an azide and a base of appropriate strength to deprotonate the substrate. Thus, on the basis of the substrate acidity, we will consider simple diazo transfer reactions on substrates characterized by the presence of a sufficiently reactive \( \alpha \)-methylene
(2.3.1), or deforminglylationg diazo transfer reactions when a prior substrate activation is necessary (2.3.2).

2.3.1. Simple Diazo Transfer Reactions

The diazo transfer protocol was first applied to the synthesis of PCDCs in 1967 by Petzold and Henning, who prepared PCDCs 19a-e from 18a-e using potassium tert-butoxide and tosyl azide as base and diazo donor reagent, respectively (Scheme 7).

Scheme 7. Synthesis of α-Substituted α-Diazomethyl-phosphonate and Phosphinoxides 19a-e

A year later, Regitz et al. reported another synthesis of 19a and 19b along with PCDCs 20a-g employing different bases for the deprotonation of the substrates: phenyllithium in ether for 19a and 20e, potassium tert-butoxide in benzene for 19b, 20c, 20f and 20g, and just piperidine in the case of 20d (Figure 3). Potassium tert-butoxide in benzene/THF was also used for the preparation of α-diazophosphinic esters 21a-d (Figure 3).
Figure 3. Examples of PCDCs Prepared by Diazo Transfer Reaction

Since Regitz’s reports, diazo transfer reactions have become the standard route for preparing non-terminal PCDCs substituted at α-position with an activating group. A variety of different reagent combinations (base/solvent/azide) have been described. For example, the preparation of the dimethyl analog of 20e was also reported using sodium hydride and methanesulfonyl azide.\(^4\) A particular mention has to be dedicated to the diethyl (1-diazo-2-oxopropyl)phosphonate (20d) that would become, along with its corresponding dimethyl analog, 22 (Bestmann-Ohira reagent, BOR) the most famous PCDC (\textit{vide infra}). The preparation of BOR (22) has been accomplished by reacting dimethyl-2-oxopropylphosphonate, tosyl azide or \(p\)-acetamidobenzenesulfonyl azide, in the presence of NaH, tBuOK or Et\(_3\)N in benzene and THF.\(^5\) The use of polymer-supported tosyl azides has been also reported. Recently, an alternative route for the preparation of α-aryl α-diazoalkylphosphonates was also disclosed (see section 2.5).

In 2011, the preparation of \(^{13}\)C-labelled 20d was also reported (Scheme 8).\(^6\) The diazo transfer step was performed in benzene/THF using sodium hydride as the base and tosyl azide as donor.
Scheme 8. Synthesis of $[^{13}\text{C}_2]\text{-Diethyl (1-Diazo-2-oxopropyl)phosphonate (}^{13}\text{C-20d)}$

Moody et al. used LDA and $p$-nitrobenzenesulfonyl azide in THF at very low temperature for the conversion of benzodiazaphosphole-2-oxide 23 into the first example of a chiral PCDC 24 first obtained in a mixture with the azido-transfer-derived compound 25, and then purified by recrystallisation (Scheme 9).\(^{49}\)

Scheme 9. Synthesis of (3aS,7aS)-2-Diazobenzyl-1,3,3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1H-1,3,2$\lambda^3$-benzodiazaphosphole-2-oxide (24)

Sodium hydride or DBU in THF were instead used for the preparation of $\alpha$-diazo-$\alpha$-(diethoxyphosphoryl)-acetates 27$\text{a, b}$ and -acetamides 27$\text{c-1}$ (Scheme 10).\(^{50}\)
Scheme 10. Synthesis of Diethyl \(\alpha\)-Diazophosphono-Acetates and –Acetamides 27a-1

\[
\begin{align*}
\text{Et}_2\text{O}_3\text{P} & \quad \rightarrow \quad \text{Et}_2\text{O}_3\text{P} \\
26a-1 & \quad \text{TsN}_3, \text{NaH or DBU} \quad \text{THF} \\
& \quad \rightarrow \\
& \quad \text{Et}_2\text{O}_3\text{P} \\
27a-1 & \quad \text{R} \\
a: \text{R} = \text{OnPr}, 81\%; \text{b: R} = \text{OiBu}, 77\
\end{align*}
\]

\[
\begin{align*}
\text{R} = \\
\text{27c, 92\%} & \quad \text{27d, 97\%} & \quad \text{27e, 56\%} & \quad \text{27f, 83\%} & \quad \text{27g, 58\%} \\
\text{27h, 91\%} & \quad \text{27i, 87\%} & \quad \text{27j, 98\%} & \quad \text{27k, 93\%} & \quad \text{27l, 69\%} \\
\end{align*}
\]

PCDCs 28-30 were obtained in excellent yield by treating the corresponding compounds that have an activate methylene group with potassium hydride and TsN\(_3\) in THF (Figure 4).\(^{51}\) However, the same reaction conditions applied to the secondary amides 31a-c led to the corresponding hydroxytriazoles 32a-c, which were converted to the tautomeric PCDCs 33a-c during distillation under reduced pressure (Scheme 11).\(^{51}\)

\[
\begin{align*}
\text{28} & \quad \text{Pr}_2\text{O}_3\text{P} - \text{PO}_3\text{Me}_2 \\
\text{29} & \quad \text{Me}_2\text{NOC} - \text{PO}_3\text{Me}_2 \\
\end{align*}
\]

Figure 4. Examples of PCDCs Obtained by Diazot Transfer Protocol

Scheme 11. Synthesis of Dimethyl \(\alpha\)-Carboxamido-\(\alpha\)-diazomethylphosphonates 33a-c
Collomb et al.\textsuperscript{52} reported the preparation of a series of $\alpha$-diazo-$\beta$-keto-$\delta$-aryl-$\gamma,\delta$-alkenylphosphonates 37a-h in overall yields (from 35a-h) ranging from 38\% to 83\%, using the combination TsN$_3$/K$_2$CO$_3$/CH$_3$CN (Scheme 12). The same reaction conditions were applied by Dayoub et al.\textsuperscript{53} for the synthesis of $\alpha$-diazo-$\beta$-ketoalkylphosphonates 40a-d starting from $\gamma$-lactones 38a-d (Scheme 13).

\textbf{Scheme 12. Synthesis of $\beta$-Keto-$\gamma,\delta$-alkenyl-$\delta$-aryl-$\alpha$-diazenophosphonates 37a-h}

\textbf{Scheme 13. Synthesis of $\beta$-Keto-$\alpha$-diazoalkylphosphonates 40a-d}
Despite the fact that tosyl azide is well known to present some safety issues,\textsuperscript{54} it remains the most used diazo donor for activated methylene compounds on a laboratory scale. However, as a valid alternative, numerous sulfonyl azides have been developed for the synthesis of PCDCs. These azides were reported to be superior to tosyl azide in terms of stability, safety and product purification.\textsuperscript{55,56,57,58,59,47} Among them, trifly azide showed to be essential for the successful transformation of the nitrophosphonate 41 into diethyl [nitro(diazo)methyl] phosphonate (42) (Scheme 14).\textsuperscript{59}

\textbf{Scheme 14. Synthesis of Diethyl [Nitro(diazo)methyl]phosphonate (42)}

\begin{center}
\begin{align*}
\text{O}_2\text{N} & \overset{\text{TfN}_3, \text{ Py}}{\rightleftharpoons} \text{PO}_3\text{Et}_2 & \text{CH}_3\text{CN-hexane} & 63\% \rightarrow \text{O}_2\text{N} \overset{\text{N}_2}{\rightleftharpoons} \text{PO}_3\text{Et}_2 \\
41 & & & 42
\end{align*}
\end{center}

2-Azido-1,3-dimethylimidazolinium chloride (44) represents the only example of a diazo donor, used for the preparation of PCDCs, that does not belong to the sulfonyl azide family. Compound 44, prepared \textit{in-situ} from commercially available chloroimidazolinium chloride (43) and sodium azide in acetonitrile, was reacted with diethyl (2-oxopropyl)phosphonate affording diethyl (1-diazo-2-oxopropyl) phosphonate (20d) in 76% yield (Scheme 15).\textsuperscript{60}
2.3.2. Deformylating Diazotransfer and Related Modifications

While the diazo transfer reaction works well in those cases in which the reaction site is activated by a carbonyl function, it fails when the methylene group is activated exclusively by the phosphoryl group. This limitation was overcome by Regitz et al. who first proposed to further activate the substrate by the insertion of a formyl moiety, which was then lost during the diazo transfer reaction. Following this methodology, they were able to obtain, for the first time, although only as crude material, diethyl α-diazomethylphosphonate (5c) (Scheme 16).

Scheme 15. Synthesis of Diethyl (1-Diazo-2-oxopropyl)phosphonate (20d)

Scheme 16. Synthesis of Diethyl α-Diazomethylphosphonate (5c) by Deformylating Diazotransfer Reaction

Following an extension of the Regitz concept, Brown et al. reported a useful synthetic useful diazotransfer/detrifluoroacylating procedure that permitted the preparation of 5a from commercially available starting materials. As depicted in Scheme 17, dimethyl methylphosphonate (45) was temporarily trifluoroacetylated to give the intermediate ketone hydrate 46, which was used without further purification in the following diazo transfer step. The authors indicated p-acetamidobenzenesulfonyl azide (p-ABSA) as the most convenient diazo donor, due to the fact that
the resultant \( p \)-acetamidobenzenesulfonamide by-product can be removed by filtration from the reaction mixture. During the diazo transfer step, loss of trifluoroacetyl group spontaneously occurred leading to the formation of 5a in 50 % overall yield.

**Scheme 17. Synthesis of Dimethyl \( \alpha \)-Diazoethylphosphonate (5a) by Detrifluoroacylating Diazotransfer Reaction**

\[
\begin{align*}
\text{CH}_3\text{PO}_3\text{Me}_2 & \quad 1. \text{nBuLi} \\
45 & \quad 2. \text{CF}_3\text{CO}_2\text{CH}_2\text{CF}_3 \\
\text{THF, -78 °C} & \quad \begin{array}{c}
\text{HO} \\
\text{F}_3\text{C} \\
\text{PO}_3\text{Me}_2
\end{array} \\
\text{46} & \quad \begin{array}{c}
\text{pABSA} \\
\text{MeCN, Et}_3\text{N, 0 °C} \\
50\%
\end{array} \\
\text{N}_2 & \quad \begin{array}{c}
\text{PO}_3\text{Me}_2
\end{array} \\
5a & \quad \text{56% and 94% yield, respectively}
\end{align*}
\]

**2.4. Hydrazone Oxidation**

Nicolle and Moody\(^{63}\) recently reported an alternative preparation of dimethyl \( \alpha \)-diazoethylphosphonate (11a) and diethyl \( \alpha \)-benzyl-\( \alpha \)-diazoethylphosphonate (48b) through oxidation of the corresponding hydrazones by potassium \( N \)-iodo \( p \)-toluene sulfonfylamide (TsNIK). According to this procedure oxidation of the \((E)\)-phosphonate hydrazones 47a,b by 1.1 equivalent of TsNIK in aqueous basic conditions afforded the corresponding PCDCs 11a and 48b in 56% and 94% yield, respectively (Scheme 18). The possibility to obtain high purity products by simple extractive work-up is a substantial advantage of this procedure.

**Scheme 18. Synthesis of PCDCs by Oxidation of Hydrazones**
2.5. Chemical Modifications of PCDCs with Retention of the Diazo Function

Another approach for the synthesis of PCDCs involves the chemical modification of the α-position of a terminal PCDC with retention of the diazo functionality, thus allowing its transformation into a new α-functionalized PCDC.

In 1989, Ohira investigated the base-induced deacylation of BOR (22) as an alternative process for the preparation of 5a. The choice of the base appeared to be crucial for the success of the reaction. Using 0.2 equivalent of potassium carbonate in methanol at 0 °C, 5a was obtained in 90% yield, although in the paper no mention concerning the isolation and the purity of the compound was made (Scheme 19). The possibility to generate 5a in-situ was also described.64

Scheme 19. Synthesis of Dimethyl α-Diazomethylphosphonate (5a) from BOR (22)

Analogously, the base-induced deacylation of 20d, the diethyl analog of 22, performed with sodium phosphate in methanol, allowed obtaining diethyl α-diazomethylphosphonate (5c) in almost quantitative yield after a simple work-up procedure.65
Numerous are the recent examples in which \textbf{22} and \textbf{20d} are employed as \textit{in situ}-precursors of \textbf{5a} and \textbf{5c}, respectively.

More complex modifications of the PCDS involve the substitution of the hydrogen atom by electrophilic reagents, the palladium-catalyzed C-C coupling at the diazo carbon atom or aldol-type C-C coupling of terminal PCDCs with imines.

### 2.5.1. C-C Coupling of Terminal PCDC with Electrophiles

In the '70s Regitz's group published some papers reporting the substitution of the \(\alpha\)-hydrogen of dimethyl \(\alpha\)-diazomethylphosphonate (\textbf{5a}) and diphenyl \(\alpha\)-diazomethylphosphinoxide (\textbf{2b}) by electrophilic reagents.\cite{66,67,68,33} \(\alpha\)-Halo- and \(\alpha\)-alkylated PCDCs were thus prepared via silver or mercury diazo intermediates, as summarized in Table 1.

### Table 1. \(\alpha\)-Substitution Reaction of PCDCs 5a and 2b

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metalation</td>
<td>CH(N(_2))POPh(_2)</td>
<td>HgO, CHCl(_3), r.t.</td>
<td>Hg[CH(N(_2))POPh(_2)] _2</td>
<td>82</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>CH(N(_2))PO(_3)Et(_2)</td>
<td>HgO, CHCl(_3), r.t.</td>
<td>Hg[CH(N(_2))PO(_3)Et(_2)] _2</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
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<td>Et₂O, -5 °C</td>
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<td>Et₂O, -5 °C</td>
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<td>AgC(N₂)POPh₂</td>
<td>Et₂O, -5 °C</td>
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<tr>
<td></td>
<td>AgC(N₂)POPh₂</td>
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22
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<td>Ph₃C(N₂)PO₃Me₂</td>
<td>28</td>
<td>68</td>
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<td>Hg[C(N₂)PO₃Ph₂]₂</td>
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<td>Ph₃C(N₂)PO(CH₆₃)₂</td>
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<td>PhCH₂C(N₂)PO(Ph)OMe</td>
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<td>33</td>
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<td>CH(N₂)PO₃Me₂</td>
<td>CH₃CN, r.t.</td>
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<td>89</td>
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<td>92</td>
<td>66,6,7</td>
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<td>CH(N₂)PO₃Me₂</td>
<td>CH₃CN, r.t.</td>
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<td>CH(N₂)POPh₂</td>
<td>CH₃CN, r.t.</td>
<td></td>
<td>89</td>
<td>66,6,7</td>
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<td>CH(N₂)POPh₂</td>
<td>CH₃CN, r.t.</td>
<td></td>
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Diethyl α-bromo- and α-iodo-α-diazomethylphosphonates (49b,c) were shown to be very unstable and their formation was demonstrated only by trapping them with PPh₃ or methyl vinyl ketone.⁶⁸ Recently Schnaars and Hansen reported the generation of 49b,c, along with that of the corresponding chloro analog 49a, by an efficient deprotonation/electrophilic halogenation sequence from diethyl diazomethylphosphonate (5c) (Scheme 20). Compounds 49a-c were in-situ submitted to cyclopropanation reaction (vedi infra).⁶⁹

**Scheme 20. Synthesis of α-Halo-α-diazomethylphosphonates 49a-c**

The authors later demonstrated that 49a-c could be prepared by nucleophilic halogenations of α-phenyliodonio diazophosphonate triflate 50, in turn obtained by treatment of diethyl diazomethylphosphonate (5c) with diacetoxyiodobenzene and TMSOTf.⁷⁰ In the same paper the conversions of α-phenyliodonio diazophosphonate triflate (50) into α-dimethylsulfonium-α-
diazomethylphosphonate triflate (51) and α-triethylammonium-α-diazomethylphosphonate triflate (52) were described (Scheme 21).70

**Scheme 21. Synthesis of Diethyl α-Dimethylsulphonium-α-diazomethylphosphonate Triflate (51) and α-Triethylammonium-α-diazomethylphosphonate Triflate (52)**

Furthermore, α-benzyl-α-diazomethylphosphonate derivatives were recently prepared in very good yield by the reaction of benzyl bromides 53 with the anion of 5a, generated *in-situ* from BOR (22) (Scheme 22). However, in the case of benzyl bromides bearing electron-withdrawing substituents at the ortho- or para- position, nitrogen elimination occurred furnishing the respective styrylphosphonates 55. This behavior was explained on the basis of the acidity of the benzylic proton, which in these substrates undergo to 1,2-migration.71
Scheme 22. Reaction of Benzyl Bromides 53 with BOR (22)

\[
\begin{align*}
\text{Scheme 22. Reaction of Benzyl Bromides 53 with BOR (22)}
\end{align*}
\]

By using a set of different bromides, dimethyl α-diazoalkylphosphonates 56-58 were also prepared.

Acylation of diethyl α-diazomethylphosphonate (5c) was exploited for the preparation of diethyl 1-diazo-2-oxo-3,3,3-trifluoropropanephosphonate (59), whose preparation did not work under standard diazo transfer conditions starting from the corresponding 2-oxoalkylphosphonate (Scheme 23).72

Scheme 23. Synthesis of Diethyl 1-Diazo-2-oxo-3,3,3-trifluoropropanephosphonate (59)

2.5.2. Palladium-Catalyzed C-C Coupling at the Diazo Carbon Atom

In 2014 two research groups, independently, reported the preparation of α-aryl-α-
diazomethylphosphonates, such as 61a-h, by palladium(0)-catalyzed cross coupling reaction of aryl iodides with BOR (22) or diethyl diazomethylphosphonate (5c). According to Ye’s approach, aryl iodides 60a-h were reacted with BOR (22) under deacylative conditions promoted by potassium carbonate (Scheme 24).\textsuperscript{73} Aryl iodides bearing both electron-donating and electron-withdrawing groups worked well in the reaction to afford the corresponding PCDCs 61a-h in moderate to good yields.

Scheme 24. Synthesis of Dimethyl α-Aryl-α-Diazomethylphosphonates 61a-h

Similarly, Kosokobov \textit{et al.}\textsuperscript{74} performed Pd-catalyzed arylation of diethyl diazomethylphosphonate (5c) (Scheme 25). Screening of several reaction conditions led to the selection of PdCl\(_2\)(PPh\(_3\))\(_4\), acetonitrile and DBU as preferred catalyst, solvent and base respectively. The presence of formic acid as a reducing agent for the generation of Pd(0) species showed to be a crucial parameter. A significant influence of the electronic effect of the substituent at the aromatic ring was observed, with the best yields obtained starting from aryl iodides bearing electron-withdrawing substituents. Good yields were observed with iodobenzene (62a) or arenes containing weak electron-donating groups, whereas 1-iodo-4-methoxybenzene (62h) gave the corresponding PCDC in only 25% yield.

Scheme 25. Synthesis of Dimethyl α-Aryl-α-Diazomethylphosphonates 63a-h
2.5.3. C-C Coupling of Terminal PCDCs with Imines

β-Amino-substituted PCDCs 65a-g were prepared by DBU-catalyzed Mannich-type addition of 5a to N-tosylimines 64a-g (Scheme 26).75

Scheme 26. Mannich-Type Coupling of 5a with N-Tosylimines

An enantioselective version of this reaction, using the axially chiral dicarboxylic acid 68, was also reported (Scheme 27). Highly optical pure diazocompounds 67 were obtained in good to excellent yields.76,77,78

Scheme 27. Asymmetric Synthesis of Mannich-Type Coupling of 5a with N-Boc-Imines
Although the procedure worked with efficiency and good enantioselectivity, the high catalyst loading represented a substantial drawback. Thus, Zhang et al.\textsuperscript{79} proposed chiral phosphoric acids as alternative catalysts in the asymmetric Mannich reaction of $N$-carbamoyl imines \textbf{69} and dialkyl $\alpha$-diazomethylphosphonates \textbf{5}. The paper reported in-depth, reiterative optimization of the reaction conditions concerning the catalyst nature and loading, the alkyl group of the diazo reagent, solvent and temperature (Scheme 28).

Scheme 28. General Synthetic Procedure for the Preparation of Chiral Dimethyl $\beta$-Amino-$\alpha$-diazoalkylphosphonates 70
The binaphtyl phosphate \textbf{71} resulted the best catalyst combining high efficiency in yield and enantioselectivity with a low loading (0.1 mol%). The reaction outcome was also positively influenced by the use of bulkier diazo component. The scope of the reaction was explored starting from a vast array of \textit{N}-carbamoylimines \textbf{69}. When azomethine imines were used as electrophiles the corresponding \textit{β}-hydrazino-PCDCs could be prepared. Hashimoto \textit{et al.} generated azomethine imines \textit{in-situ} by the condensation of \textit{N}-benzylbenzoyl hydrazide \textbf{73} with the aldehydes \textbf{72a-c}. In the presence of dimethyl \textit{α}-diazoethylphosphonate (\textbf{5a}) and a catalytic amount of the axially chiral catalyst \textbf{75}, the \textit{β}-hydrazino-PCDCs \textbf{74a-c} were synthesized with excellent enantioselectivity (Scheme 29).
Scheme 29. Synthesis of Dimethyl β-Hydrazino-α-diazoalklyphosphonates 74a-c

\[
\begin{align*}
\text{RCHO} & + \text{Bn}^+\text{NH,NH.Bz}^+ \rightarrow \text{R}^+\text{NHBz}^+ \\
\text{72a-c} & \quad \text{5a} \quad \text{(R)}-\text{75} (5 \text{ mol%}) \quad \text{PhCF}_3, 4 \text{ Å MS} \\
& \quad 0 \text{ °C}, 20 \text{ h} \\
\text{74a-c} & \\
\end{align*}
\]

a: R = cyclopropyl, 68%, 95% ee; b: R = CH\text{2}\text{CH}_2\text{Ph}, 77%, 95% ee; c: R = Ph, 64%, 90% ee

Finally, exploring the scope of the three-component reaction of 2-aminopyridines, aldehydes and diazo compounds, Gulevich et al. reported the preparation of the PCDCs 76a,b by the Y(OTf)₃-catalyzed reaction of 5c, 2-aminopyridine, and two different aryl aldehydes (Scheme 30).

Scheme 30. Preparation of PCDCs 76a,b by Y(OTf)₃-Catalyzed Three-Component Reaction

\[
\begin{align*}
\text{NH}_2\text{NH-NH} & + \text{R-CHO} + \text{N}_2\text{PO}_3\text{Et}_2 \rightarrow \text{Y(OTf)}_3 (10 \text{ mol%}) \\
\text{76a,b} & \quad 4 \text{ Å MS} \\
& \quad \text{CH}_2\text{Cl}_2, 0 \text{ °C-rt} \\
\end{align*}
\]

a: R = Me, 67%; b: R = Br, 51%

The proposed mechanism (Scheme 31) involves the initial formation of the Y(III)-activated imine A, which underwent the nucleophilic attack by the diazo compound to produce the zwitterionic species.
B/C. Deprotonation of B/C by the pyridine nitrogen produced the final compound upon release of the catalyst and tautomerization. In summary, the process can be considered as a pyridine-assisted addition of the diazo reagent to the imine.

Scheme 31. Proposed Mechanism for the Three-Component Reaction involving 2-Aminopyridine, Aldehyde and Diethyl α-Diazoethylphosphonate

3. Chemistry of λ⁵-Phosphorus-Containing α-Diazo Compounds

The huge number of transformations that can occur with PCDCs makes them extremely versatile reactants. Those reactions proceeding with loss of nitrogen represent the most significant area of interest, although numerous examples involving PCDCs in 1,3-dipolar cycloaddition can also be found. In most cases, the reactive intermediates formed, such as carbenes, carbenoids, ylides or
diazonium cations, are generated from PCDCs by a metal catalyst. Unlike diazocarbonyl compounds, however, the area of enantioselective transformations has been little explored, remaining an open field of research. Due to its size, this section is divided into subsections based on the type of product obtained when PCDCs react with different functional groups. Our goal is to allow the reader to better appreciate and understand the synthetic versatility of PCDCs.

### 3.1. C-H Insertion Reactions

α-Phosphonocyclopentanones, and α-phosphono-substituted γ-lactams and -lactones represent the main products accessible by intramolecular C-H insertion reaction of PCDCs. The reported studies demonstrate, as a key trend, the propensity toward the \textit{trans}-substituted five-membered ring formation. Rhodium(II) salts have so far represented the catalysts of choice for these transformations. The area of asymmetric C-H insertion has not yet been fully explored.

In 1992, Afarinkia \textit{et al.} \cite{Afarinkia1992} reported about the metal-catalyzed decomposition of α-diazo-β-ketophosphonamidates 77a,b furnishing in low yields the corresponding monocyclic 1,2-azaphosphetidines 78a,b as the result of the intramolecular C-H insertion of the carbene intermediates. Both the insertion products were formed diastereoselectively in a ratio of about 10:1 in favour of the (S\textsubscript{p}, R\textsubscript{c}) relative configuration (Scheme 32). When an analogous reaction was performed using α-diazo-β-ketophosphonamidates 79a,b, only the corresponding Wolff rearrangement-derived compounds 80a,b were observed due to the increased strain associated with the bicyclic transition state for the insertion-derived products. This evidence was also confirmed in photolytic conditions (Scheme 33).
Scheme 32. Rh$_2$(OAc)$_4$-Catalyzed Synthesis of 1,2-Azaphetidines 78a,b

![Chemical structure](image1)

$a$: R = $i$Pr, 33%; b: CH$_2$Ph, 16%

Scheme 33. Photolytic or Rh$_2$(OAc)$_4$-Catalyzed Decomposition of α-Diazo-β-ketophosphonamidates 79a,b

![Chemical structure](image2)

$a$: azacycle = piperidine, 50% (hv), 64% (Rh$_2$(OAc)$_4$); b: azacycle = 2-methylpiperidine, 50% (hv), 34% (Rh$_2$(OAc)$_4$)

Mikołajczyk et al. applied rhodium(II) acetate-catalyzed C-H insertion reaction of α-diazo-β-ketophosphonates for the synthesis of trans-3-substituted-2-dimethoxyphosphorylcyclopentan-1-ones, key intermediates for the preparation of naturally occurring cyclopentanoids, such as (±)-sarkomycin (81) and (±)-rosaprostol (82) (Scheme 34 and Scheme 35).$^{83,84}$

Scheme 34. Synthesis of (±)-Sarkomycin (81)

![Chemical structure](image3)

Et$_2$O$_3$P

$\xrightarrow{\text{Rh}_2$(OAc)$_4$, CH$_2$Cl$_2$, 58%}$

(±)-sarkomycin 81
Analogously, 2-phosphonocyclopenten-3-ones 84a-d were obtained starting from ε-tert-butyldimethylsilyloxy-α-diazo-β-ketophosphonates 83a-d, by a concomitant C-H insertion reaction and elimination of the silyloxy group (Scheme 36).\(^8\)

Cyclopentenyl-3-phosphonates 86a-e were prepared in high yields by Rh\(_2\)(OAc)\(_4\)-catalyzed intramolecular C-H insertion reaction from alkyl, benzyl and homoallyl PCDCs 85a-e (Scheme 37).\(^8\) The equilibration of the cis- and trans-diastereoisomeric mixtures 86b,d,e, thus obtained, into the corresponding single trans-isomers could be performed by treatment with DBU.
α-Phosphonolactams 87 and 88 were obtained in high yields by Rh₂(OAc)₄-catalyzed cyclization of α-diazo-α-diethoxyphosphorylacetamides 27c-g, j, l (Scheme 38). Also in this case, the reaction proceeded with a remarkable preference for the formation of five-membered rings with substituents in reciprocal trans-orientation. The huge selection of substrates allowed the study of the effect of the substituent on the cyclization course: electron-donating groups promoted the insertion into the α-methylene as opposed to those electron-withdrawing. The same reactions were also performed in the ionic liquid 3-n-butyl-1-methyl-imidazolinium [bmim][PF₆], as a medium for the immobilisation of the catalyst. High yields, as well as high regio- and stereocontrols were maintained, over 5-6 cycles. The authors later demonstrated that such reactions could be efficiently performed using water and CO₂, as reaction media.
Furthermore Candeias et al.\textsuperscript{91} reported the decomposition of α-diazo-α-diethoxyphosphorylacacetamides induced by photolysis in non-convetional media, such as water or a film. Irradiation of 27m by a mercury vapor high-pressure lamp resulted in the formation of the aromatic substitution product 89 with a higher selectivity than the Rh\textsubscript{2}(OAc)\textsubscript{4}-catalyzed cyclization reaction in which in addition to 89, the β-lactam 87m was also formed (Error! Reference source not found.).

Scheme 39. C-H Insertion Reaction vs Aromatic Substitution

After obtaining the same result with different solvents, the authors concluded that the reaction outcome was more dependent on the native substrate conformation rather than to the hydrophobic effect exerted by the water over the diazo substrate. Moreover, the high selectivity toward the formation of compound 89 could be explained by taking into account a preferred aromatic substitution mechanism resulting from the reactive species attack on the electron-rich aromatic ring followed by aromatization. When other α-diazo-α-diethoxyphosphorylacacetamides were subjected to the same reaction conditions the corresponding β- and/or γ-lactams, 87 and 88, were obtained in reasonable
yields and in some cases with good diastereoselectivities. The chemoselectivity observed toward C-H insertions with hydrophobic substrates correlated with their propensity to reorganize in order to decrease the interactions with water, leading to conformations very close to the C-H insertion transition states. On the contrary, using soluble diazo substrates intermolecular water insertion products were obtained in high selectivities and yields.

A first attempt towards an asymmetric version of the reaction using common chiral rhodium(II) catalysts, resulted in only modest to moderate enantioselectivity (up to 40%). Slightly better results were obtained by Slattery and Maguire in the copper-catalyzed C-H insertion of PCDC leading to the formation of the corresponding α-phosphonocyclopentanone derivative (Scheme 40).

Scheme 40. Copper-Catalysed Asymmetric C-H Insertion of Dimethyl (1-Diazo-2-oxo-5-phenylpentyl)phosphonate (90)

Recently, to the rhodium-catalyzed cyclisation of α-diazo-α-phosphorylacetates into the corresponding lactones, first reported by Gois et al., was associated a subsequent HWE olefination step. According to this telescoped reaction sequence the conversion of α-diazo-α-phosphorylacetates 92a-k into the corresponding α-alkylidene-γ-butyrolactones 93a-k was accomplished in good overall yields (Scheme 41).

Scheme 41. One-pot C-H Insertion/Olefination Sequence for the Formation of α-Methylene-γ-
The expanded substrate scope as well as the strengths and limitations of the methodology along with some stereochemical, regiochemical ans stereoelectronic aspects were further reported. An interesting example described in this study was the reaction of the triphenyl-substituted diazo substrate 92l, which under standard C-H insertion conditions, resulted in the formation of trace amount of an unknown product rather than the expected lactone 93l. The same compound was obtained in higher yield by using Rh₂(esp)₂, a bridged robust dirhodium catalyst, superior to a Rh₂(oct)₄ catalyst for chemoselective aromatic C-H insertion reaction. Its structure was assigned as a rapidly equilibrating mixture of the two tautomers 94a/b deriving from the Buchner cyclization reaction (Scheme 42. Buchner Reaction vs C-H Insertion in the Rhodium-catalyzed Decomposition of 92l
\[
\begin{align*}
\text{92I} & \xrightarrow{\text{Rh}_2(\text{oct})_4, \text{CH}_2\text{Cl}_2, 45 \, ^\circ\text{C, 24 h}} \text{93I} \\
\text{Rh}_2(\text{esp})_2 \text{ CH}_2\text{Cl}_2, \text{toluene, 100} \, ^\circ\text{C, 4 h}} & \downarrow \text{94a} \xrightarrow{\text{94b}} \\
\text{94a} & \xleftarrow{\text{50} \, \% \text{ yield}} \text{94b}
\end{align*}
\]
Scheme 42. Buchner Reaction vs C-H Insertion in the Rhodium-catalyzed Decomposition of 92I

The lactone 93m, obtained by this procedure, was then used as the key intermediate for the preparation of (±)-cedarmycins A and B (95a,b), thus demonstrating the applicability of the methodology for natural product synthesis (Scheme 43. Synthesis of (±)-Cedarmycins A and B (95a) and (95b))
Only one example of the intermolecular version of C-H insertion reaction of PCDCs can be found in the literature. In particular Reddy et al.\textsuperscript{96} reported the reaction of PCDC 11b with 1,4-cyclohexadiene in the presence of different chiral rhodium(II) catalysts (Error! Reference source not found.). \textbf{Rh\textsubscript{2}(S-biTISP)}\textsubscript{4} (98), \textbf{Rh\textsubscript{2}(S-PTTL)}\textsubscript{4} (99) and \textbf{Rh\textsubscript{2}(S-PTAD)}\textsubscript{4} (100) showed to give higher asymmetric induction, than the more common dirhodium tetraproline \textbf{Rh\textsubscript{2}(S-DOSP)}\textsubscript{4} (97). By using \textbf{Rh\textsubscript{2}(S-PTAD)}\textsubscript{4} (100) the opposite enantiomer of 96 was preferentially formed.

\textbf{Scheme 43. Synthesis of (±)-Cedarmycins A and B (95a) and (95b)}

\textbf{Scheme 44. Enantioselective Intermolecular C-H Insertion of 11b}
3.2. X-H Insertion Reactions

X-H insertion reactions of diazocarbonyl compounds have been extensively investigated and proven to be of extreme importance in organic synthesis. Analogous transformations with PCDCs did not receive the same attention and the potential of these processes became recognized only recently. Among different X-H insertion reactions, O-H and N-H have been so far the most explored due to the importance of these functional groups in modern organic synthesis. It is possible to have thermal, photochemical, acid- and transition metal-catalyzed reactions (Scheme 45).97

Scheme 45. X-H Insertion Reaction of PCDCS

\[
\begin{align*}
\text{Y} & \text{PO}_3\text{R}_2 \quad \xrightarrow{\Delta \text{ or \ hv} \ \text{or \ catalyst}} \quad \text{Y} \text{PO}_3\text{R}_2 \quad \xrightarrow{\text{X-H}} \quad \text{Y}^+ \text{HPO}_3\text{R}_2
\end{align*}
\]
3.2.1. O-H Insertion Reactions

The decomposition of a PCDC in the presence of hydroxylic compounds (alcohol, phenol or carboxylic acid) results in the formation of a new C-O bond by formal insertion of the carbene into the O-H bond. The thermal decomposition of PCDCs in the presence of alcohol is very rare. However, Regitz and Martin\textsuperscript{98} reported that diazophosphinate \textbf{101} when reacted with aqueous acetone resulted in the hydrolysis of the silyl ester and the concurrent formation of the hydroxyl compound \textbf{102} by O-H insertion into the water (Scheme 46).

\textbf{Scheme 46. Thermal Decomposition of PCDC 101 in the Presence of Water}

\[
\begin{align*}
\text{Ph} & \quad \overset{\text{O}}{\text{P}} \quad \overset{\text{OSiMe}_3}{\text{N}_2} \quad \text{Ph} & \quad \xrightarrow{\text{acetone, H}_2\text{O}} & \quad \text{Ph} & \quad \overset{\text{O}}{\text{P}} \quad \overset{\text{OH}}{\text{OH}} \\
\text{101} & \quad & \text{102, 40\%}
\end{align*}
\]

Regitz\textsuperscript{44} was the first to study the photochemical decomposition of PCDCs in the presence of alcohols. He showed that competition between O-H and C-H insertion might occur in a series of diazophosphine oxides. When the photolysis of \textbf{5d, 19a,b,e} and \textbf{97} in methanol was studied, Regitz observed that the groups on the diazo portion exerted an effect on the product formed. In general, O-H insertion products \textbf{104a-c} were achieved in high yield when R was Ph, CONH\textsubscript{2}, whereas in the case of R = H, COPh or CO\textsubscript{2}Et, the products derived by 1,2-shift rearrangement \textbf{105a-c} proved to be those predominant. The structure-assignment of the products was carried out using IR and NMR analysis.\textsuperscript{99,100}
Later on Tomioka’s group reported additional studies on the photochemistry of α-diazobenzylphosphonates showing that the reactivity of the phosphorylcarbenes, photolytically generated in alcohols, was strongly temperature-dependent. In particular, the photolysis of dimethyl α-diazo-benzylphosphonate (11b) in alcohol at 27 °C gave the O-H insertion product 106 in 70% yield along with a small amount of dimethyl benzylphosphonate 107 (<3%). At much lower temperature (-196 °C) C-H insertion occurred preferentially affording the alcohol 108, as the main product (Scheme 48). The rate of decomposition proved to be very slow at low temperature with total decomposition of 11b achieved in 40 h.
Similar results were obtained when the photolysis of 11b was conducted in ethanol or 2-propanol showing that dramatic and significant increases in the C-H insertion product occurred when the reaction phase was changed from liquid to solid due to the decreased temperature. The dependence of the product distribution on the reaction temperature was explained by the fact that the photolysis in frozen alcohol led to triplet phosphorylcarbene which yielded C-H insertion product; on the contrary singlet carbene was generated at room temperature, which in turn was responsible for the formation of O-H insertion product. In a different report Tomioka et al. proved that the electrophilicity of phosphorylcarbenes was dramatically reduced when the carbene substituents were changed from the phosphonyl ester to its monoanion. Photolysis of dimethyl α-diazobenzylphosphonate (11b) in a mixture of methanol and 2-methylbut-2-ene afforded mainly the mixture of cis- and trans-cyclopropane isomers 111a (81% yield) along with a small amount of dimethyl [methoxy(phenyl)methyl]phosphonate (110) (Scheme 49). When the monosodium salt 109 was irradiated under the same condition, followed by neutralization and esterification with diazomethane, an inverse product distribution was observed, with the O-H insertion product 110 predominantly formed (73% yield) at the expenses of the cyclopropane isomers 111b (16% yield). Since identical results were obtained with the photolysis of other PCDCs the authors ruled out the possibility that inductive, conjugative or steric effects were the cause of the different reactivity.

**Scheme 49. Photolysis of α-Diazobenzylphosphonates: Effect of the Neighbouring Group on the**
The authors explained these results by postulating an interaction between the anion of the phosphonate with the \( p \)-orbital of the singlet carbene.\(^{103}\) This interaction would decrease the tendency of the \( p \)-orbital of the carbene to accept electron from an external substrate such as an alkene and alcohol. The carbene tends to work as nucleophile via the lone pair, which can attack the oxygen while the latter undergoes protonation. This would explain the enhanced reactivity of 109 toward alcohol relative to alkenes. Although Bartlett et al. supported Tomioka’s idea that the phosphonate can interact with the carbenic center, they demonstrated that different results may be achieved depending on the substituent on the carbene center.\(^{104}\) In particular, the irradiation of a methanolic solution of 112 did not give O-H insertion product, but instead gave rise to \( \alpha \)-hydroxyphosphonate 113 along with minor amount of the phosphate 114 (Scheme 50). Strongly electron-withdrawing substituent was able to stabilize greatly the intermediate species leading to different products owing to an anionic character of the carbene rather than to a carbenic one.
All these investigations demonstrate that phosphorylcarbenes can show both electrophilic and nucleophilic characteristic depending on their substituent and on the nature of the reagent with which they react.

Julget and Drahn\textsuperscript{105} reported kinetic investigations on the mechanism of hydrolysis of some PCDCs in dioxane–water with perchloric acid as a catalyst, showing that PCDCs were hydrolyzed in the same way as the cognate $\alpha$-diazocarbonyl compounds with proton transfer as the rate-determining step, followed by rapid decomposition of the diazonium ion. However, no practical use has been made of this synthetic methodology.

The transition metal-catalyzed decomposition of PCDCs, is often the method of choice since it takes place under relatively mild conditions. The reaction is believed to involve a metallo-carbenoid, which retains the reactivity of a “free carbene”.

In analogy with the studies carried out by Regitz on the thermal stabilities of different diazoethanes,\textsuperscript{106} Moody et al. investigated the rate at which different diazo compounds decomposed in the presence of 2-propanol and rhodium catalyst (\textit{Error! Reference source not found.}).\textsuperscript{107} Their findings coincide with Regitz results, showing the PCDCs as the less reactive species. The PCDCs are indeed less nucleophilic for the initial interaction with the vacant coordination site on the rhodium,
which is the first step for the formation of the metallocarbenoid. However, the use of rhodium(II) trifluoroacetamide was shown to improve the reactivity of PCDCs. Higher temperature and prolonged reaction time proved also to be of benefit for the yield.$^{108}$

Table 2. Rhodium-Mediated Insertion Reaction of PCDCs into \textit{i}-PrOH

\[
\begin{align*}
\text{Y} \quad \text{Z} \quad \text{Product} \quad \text{Solvent} \quad \text{Temp.} \quad \text{Catalyst (1 mol\%)} \quad \text{Time (h)} \quad \text{Yield (\%)} \\
1 \quad \text{H} \quad \text{CO}_2\text{Et} \quad \text{115a} \quad \text{CH}_2\text{Cl}_2 \quad \text{rt} \quad \text{Rh}_2(\text{OAc})_4 \quad 0.5 \quad 64 \\
2 \quad \text{Ph} \quad \text{CO}_2\text{Et} \quad \text{115b} \quad \text{CH}_2\text{Cl}_2 \quad \text{rt} \quad \text{Rh}_2(\text{OAc})_4 \quad 0.1 \quad 92 \\
3 \quad \text{PhCH}_2 \quad \text{CO}_2\text{Et} \quad \text{115c} \quad \text{CH}_2\text{Cl}_2 \quad \text{rt} \quad \text{Rh}_2(\text{OAc})_4 \quad 2.0 \quad 32 \\
4 \quad \text{Me}_2\text{NCO} \quad \text{CO}_2\text{Et} \quad \text{115d} \quad \text{CH}_2\text{Cl}_2 \quad \text{rt} \quad \text{Rh}_2(\text{OAc})_4 \quad 32 \quad 66 \\
5 \quad \text{CN} \quad \text{CO}_2\text{Et} \quad \text{115e} \quad \text{CH}_2\text{Cl}_2 \quad \text{rt} \quad \text{Rh}_2(\text{OAc})_4 \quad 3 \quad 86 \\
6 \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \quad \text{115f} \quad \text{CH}_2\text{Cl}_2 \quad \text{rt} \quad \text{Rh}_2(\text{OAc})_4 \quad 125 \quad 66 \\
7 \quad \text{PhSO}_2 \quad \text{CO}_2\text{Et} \quad \text{115g} \quad \text{CH}_2\text{Cl}_2 \quad \text{rt} \quad \text{Rh}_2(\text{OAc})_4 \quad 18 \quad 64 \\
8 \quad \text{Ph}_2\text{PO} \quad \text{CO}_2\text{Et} \quad \text{115h} \quad \text{CH}_2\text{Cl}_2 \quad \text{reflux} \quad \text{Rh}_2(\text{OAc})_4 \quad 1.0 \quad 30 \\
9 \quad \text{Ph}_2\text{PO} \quad \text{CO}_2\text{Et} \quad \text{115i} \quad \text{CH}_2\text{Cl}_2 \quad \text{rt} \quad \text{Rh}_2(\text{tfa}cm)_4 \quad 22.5 \quad 45 \\
10 \quad \text{PO}_3\text{Et}_2 \quad \text{CO}_2\text{Et} \quad \text{115j} \quad \text{CH}_2\text{Cl}_2 \quad \text{reflux} \quad \text{Rh}_2(\text{OAc})_4 \quad 10 \quad 83 \\
11 \quad \text{PhSO}_2 \quad \text{PO}_3\text{Et}_2 \quad \text{115k} \quad \text{CH}_3\text{Ph} \quad 110^\circ\text{C} \quad \text{Rh}_2(\text{OAc})_4 \quad 72 \quad 67 \\
12 \quad \text{PhSO}_2 \quad \text{PO}_3\text{Et}_2 \quad \text{115l} \quad \text{CH}_3\text{Ph} \quad 110^\circ\text{C} \quad \text{Rh}_2(\text{tfa}cm)_4 \quad 2 \quad 79 \\
13 \quad \text{PO}_3\text{Et}_2 \quad \text{PO}_3\text{Et}_2 \quad \text{115m} \quad \text{CH}_3\text{Ph} \quad 110^\circ\text{C} \quad \text{Rh}_2(\text{tfa}cm)_4 \quad 2 \quad 81 \\
\end{align*}
\]

This marked difference in reactivity between $\alpha$-diazo-carbonyls and PCDCs was found to be extremely advantageous when a molecule contains two differently substituted diazo groups, such in
the case of 116. In fact, the more reactive diazo moiety can undergo decomposition in the presence of rhodium(II) acetate giving rise to O-H insertion product 117 leaving the other diazo functionality intact. Then, using a more reactive catalyst, such as rhodium trifluoroacetamide, the second diazo group can be decomposed affording the final compound 118 (Scheme 51).

Scheme 51. Example of Sequential O-H Insertion Reaction of Differently Substituted Diazo Moieties

The first account of O-H insertion of PCDCs catalyzed by rhodium(II) acetate had already been reported by Paquet and Sinay, who described the insertion of trimethyl α-diazophosphonoacetate (119) into the primary alcohol of 1-O-methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (120) and into the secondary alcohol of benzyl 2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-galactopyranoside (122) (Scheme 52).
Subsequently, the rhodium-catalyzed insertion of PCDCs has been founding wide application in the synthesis of chorismic and shikimic acids derivatives. Pawlak et al. reported the reaction of alcohol 124 with PCDC 22, in benzene at reflux in the presence of rhodium catalyst providing the corresponding ethers 125, a precursor of the chorismic acid (Error! Reference source not found.).112 Similarly, rhodium-catalyzed decomposition of PCDCs 126 in the presence of 124 was also used by Wood et al. toward the synthesis of phosphonate analogues of chorismic acid (Error! Reference source not found.).113

Scheme 53. O-H Insertion Reaction of 22 and 126, as Key Steps in the Synthesis of (-)-Chorismic
In the same fashion Alberg and Barlett described the reaction of methyl dibenzyl α-diazophosphonoacetate (128) with the acetonide 129 in the presence of rhodium(III) acetate, as the catalyst, to afford the corresponding O-H insertion product 130, an intermediate toward the synthesis of shikimic acid derivatives 131a,b, inhibitors of 5-enolpyruvylshikimate-3-phosphate synthase (Scheme 54).\textsuperscript{114}

Scheme 54. O-H Insertion Reaction of 128, as a Key Step in the Synthesis of (-)-Shikimic Acid
O-H insertion reactions with PCDCs were also exploited by the Maguire’s group for the synthesis of α-carboxy-phosphononucleosides endowed with potential antiviral and anticancer activities.\textsuperscript{115,116} Thus, rhodium-catalysed O-H insertion reactions of trialkyl diazophosphonoacetate 119 with a series of unprotected or selectively protected nucleosides were investigated. The results obtained on adenosine derivatives, such as 132 showed that O-H insertion cannot be carried out in the presence of unprotected or monoprotected amino group, presumably due to complexation of the catalyst to the nucleobase. Protection of the secondary hydroxy groups at the 2’ and 3’ positions was also required in order to achieve selective reaction at the 5’ position. \(N,N\)-dibenzoyl or \(N,N\)-dibenzyl formamidine protection and isopropylidene or benzoyl, proved to be well tolerated in the reaction conditions (Error! Reference source not found.).

**Scheme 55. Rhodium-Catalysed O-H Insertion Reaction of PCDC 119 with Purine Nucleoside 132**
When the same reaction was assayed on pyrimidine nucleosides, no catalyst poison occurred in the presence of unprotected pyrimidine bases. With NH unprotected uridine 134 as shown in Scheme 56 both compounds 136 and 137 were formed, with N-H insertion being favoured over O-H insertion.

Scheme 56. Rhodium-Catalysed O-H Insertion Reaction of PCDC 135 with Pyrimidine Nucleoside 134

In order to achieve 5’-OH selective insertion in case of uridine derivatives, benzoyl protection can be used for the nitrogen atom. Insertion of diazocompounds 119 and 135 on compounds 138a,b afforded the corresponding phosphononucleosides 139a,b in good yield (Scheme 57).

Scheme 57. Rhodium- Catalysed O-H Insertion Reaction of PCDCs 119 and 135 with Pyrimidine Nucleosides 139a,b

\[ \begin{align*}
&\text{HO-} \quad \text{RO}_2\text{C}\text{P(O)}_2\text{R}_2 \\
\text{138a,b} &\quad \text{+} \quad \text{N}_2 \quad \text{135} \quad \xrightarrow{\text{Rh}_2(\text{ffm})_4 (1 \text{~mol\%})} \quad \text{benzene, reflux, 12 h} \\
&\text{HO-} \quad \text{R}_2\text{O}_2\text{P(O)}_2\text{R}_2 \\
\text{139a,b} &
\end{align*} \]

- a: $R^1 = R^2 = \text{Bz}, R = \text{Me, 60\%;}$ b: $R^1 = \text{Bz}, R^2 = \text{iPr}, R = \text{Et, 55\%}$
Investigations of the competition between the 5’- and 3’-O-H insertions revealed that in thymine derivatives 140a,b the insertion into the primary hydroxy group was preferred. However, since selectivity at the 5’ position was not particularly high, protection at the 3’ position represented an advantage in terms of yield (86% vs 34%) (Scheme 58).

**Scheme 58. Rhodium-Catalysed O-H Insertions Reaction of PCDCs 119 and 135 with Pyrimidine Nucleosides 140a,b: 5’- vs 3’-OH Insertion**

The same authors were able to demonstrate that insertion reactions of 119 worked well also with protected cytosine and 2’-deoxycytosine derivatives 144a,b, affording the insertion products 145a,b in 52% yield (Scheme 59). As expected all the O-H insertion products were reported as an equimolecular mixture of diastereoisomers.

**Scheme 59. Metal-Catalysed O-H Insertion Reaction of PCDC 119 with Pyrimidine Nucleosides 144a,b**
Once the methodology was established the same authors applied this approach to the synthesis of different 5’-phosphononucleoside derivatives, in which the carboxylic moiety along with the phosphono group can be envisaged as diphosphate mimic.\textsuperscript{117,118}

O-H insertion reaction with a series of natural amino acids-derived PCDCs 17a-e was recently explored by Cai et al.\textsuperscript{42} Surprisingly, reaction of 17a with benzyl alcohol in the presence of 5 mol\% [Cu(MeCN)\textsubscript{4}]PF\textsubscript{6} as catalyst and 20 mol\% I\textsubscript{2} as additive in dichloromethane at 25 oC did not afford the corresponding O-H insertion product but led to the formation of diethyl (2-(benzylxyloxy)-2(1,3-dioxoisooindolinyl)propyl phosphonate (146) in 50% yield along with (Z)-diethyl(2(1,3-dioxoisooindolin-2-yl)prop-1-en-yl)phosphonate (147), as by product, in 17% yield (Scheme 60).

\textbf{Scheme 60. Combined C-H functionalization/O-H Insertion Reaction}

As plausible reaction mechanism the authors proposed a pathway that it is consistent with a combined C–H functionalization/O–H insertion processes (Scheme 61). They suggested that the metal carbene complex I, initially formed from the PCDC 17 by [Cu(MeCN)\textsubscript{4}]PF\textsubscript{6} and iodine could exist in resonance with the metal-stabilized carbocation II. In II, the β-hydrogen on the phosphonate migrated to the carbon attached to the metal, which was positively charged, to form a tertiary carbocation intermediate III, which after the attack of the relative alcohol gave the intermediate IV. The proton of the hydroxyl group of the alcohol migrated to the carbon attached to the phosphonate, followed by extrusion of Cu(I) catalyst to give the O–H insertion product 146.
When different PCDCs were tested, the authors proved that the ester group at the phosphono moiety (R) had almost no influence, whereas the substituent group at the β-position (R₁) had an impact on the outcome of the reaction. It was indeed found, that bulky substituents impeded the reaction, most probably because they exerted steric hindrance on the carbocation III and that small groups,
such as hydrogen, led only to trace of product due to the lack of stabilization of the carbocation III. As far as the scope of alcohol substrate is concerned, primary, secondary and electron-withdrawing group-substituted benzyl alcohols gave good yield and chemoselectivity, whereas electron-donating group-substituted benzyl and tertiary alcohols showed to be less reactive or unreactive, respectively. This methodology provides straightforward access to tertiary α-alkoxy-substituted β-amino-phosphonates. \( \text{Rh}_2(\text{OAc})_4 \)-catalyzed O-H insertion reaction of α-diazo-β-ketophosphonates was also recently reported in aqueous medium.\(^\text{119}\)

Alkoxyphosphonoacetates, prepared from trialkyl diazophosphonoacetates and the appropriate alcohol under rhodium-catalysis, have proved to be useful synthons in organic synthesis. Several accounts report on their use in a subsequent HWE reaction, as in the case of their application in the preparation of a series of cyclic enol ethers (Scheme 62),\(^\text{120,121}\) as well as in the functionalization of 2,5-disubstituted indoles, endowed with antiglycaemic properties,\(^\text{122,123}\) and acyl indoles derivatives for the treatment of dislipidemia and type 2 diabetes.\(^\text{124}\) Rhodium-catalyzed O-H bond insertion of a PCDC was also a key step in the total synthesis of (+)-xeniolide F (Schemes 63 and Scheme 64).\(^\text{125,126}\)

**Scheme 62. Example of Application of Alkoxyphosphonoacetates in the Preparation of Cyclic Enol Ethers**

\[
\begin{align*}
\text{EtO}_2\text{C} &\text{PO}_3\text{Et}_2 \quad \text{iPrOH, Rh}_2(\text{OAc})_4 \quad \text{51\%} \\
\text{NaH}, \text{THF} \ 0^\circ\text{C} \quad \text{iBuMe}_2\text{SiO}(\text{CH}_2)_n\text{CHO} \\
\text{CSA, toluene reflux} \\
n = 3,4
\end{align*}
\]
Scheme 63. Alkoxyphosphonacetate 136, as a Key Intermediate in the Synthesis of \((-\)-Xeniolide F)
(137)

Scheme 64. Alkoxyphosphonacetate 138, as a Key Intermediate in the Synthesis of Cyclic Allyl Vinyl Ethers 139

In other cases, alkoxyphosphonacetates obtained by O-H insertion reaction, were submitted to Dibal-H reduction and then to Wadsworth-Emmons elimination to give the corresponding \(O\)-alkyl enol ethers.\(^{127}\)
As far as intramolecular version of rhodium-catalyzed O-H insertion reaction is concerned, Davies et al. exploited this strategy on the route to cyclic ethers. In particular, they reported that when heated in boiling benzene in the presence of a catalytic amount of rhodium(II) acetate, α-diazo-β-ketophosphonates 140a,b underwent cyclization by formal intramolecular O-H insertion producing the oxepan-3-ones 141a,b in moderate yield. This synthetic procedure was expanded to the synthesis of other 2-substituted-3-oxepanones and then specifically applied to the synthesis of cis-2,7-disubstituted-oxepane intermediates 142b endowed with the skeleton of the marine natural product isolaurepinnacin (Scheme 65).

Scheme 65. Intramolecular Rhodium-Catalyzed O-H Insertion Reaction of 140a,b

\[
\begin{align*}
140a,b & \xrightarrow{\text{Rh}_2(OAc)_4, \text{benzene, reflux}} 141a,b \\
141a,b & \xrightarrow{\text{NaH, THF, EtCHO}} 142a,b
\end{align*}
\]

a: R = H, 52% (141); b: R = C₆H₁₃, 54% (141)

O-H insertions of PCDCs promoted by rhodium catalyst were also used for the synthesis of optically active 2-phosphoryl-3-oxo-5-alkyl(aryl)tetrahydrofurans 144, which offer a great potential for use in organic synthesis. The compounds exist in rapid equilibrium between cis- and trans-isomers in a 1:1 ratio as confirmed by NMR analyses (Scheme 66).

Scheme 66. Synthesis of Optically Active 2-Phosphoryl-3-oxo-5-alkyl/aryl tetrahydrofurans 144

\[
\begin{align*}
143 & \xrightarrow{\text{Rh}_2(OAc)_4, \text{toluene, reflux}} 144
\end{align*}
\]

R = Me, Et, vinyl, aryl

81-84 % yields
Another elegant example of intramolecular \( \text{Rh}_2(\text{OAc})_4 \)-catalyzed O-H insertion reaction is found in the total synthesis of (±)-maoecrystal V (147), a diterpenoid natural product endowed with a highly complex polycyclic structure.\(^{132}\) Rhodium(II)-promoted decomposition of the \( \alpha \)-diazophosphono ester 145 allowed the formation of the seven-membered ether 146, in quite good yield, as suitable intermediate toward the title compound (Scheme 67).

**Scheme 67. Intramolecular Rhodium-Catalyzed O-H Insertion Reaction of 145, as a Key Step in the Total Synthesis of Maoecrystal V (147)**

The insertion reaction into O-H bond of phenols was first investigated by Cox et al.,\(^{133}\) who reported the reaction of PCDCs 135, 20f and 148 with 4-methoxyphenol in toluene, in the presence of catalytic amount of rhodium(II) acetate, to give the corresponding insertion products 149a,b. Only the PCDC 20f failed to return the expected insertion product 149c even after 7 days at 110 °C (Error! Reference source not found.).

**Scheme 68. Rhodium-Mediated O-H Insertion Reaction of PCDCs 135, 20f and 148 with 4-**
Independently, another group from SmithKline Beecham\textsuperscript{134} reported on O-H insertion of trialkyl diazophosphonoacetates on a variety of substituted phenols. Most of the phenols used gave good to excellent yields (69-86\%), although phenols bearing strong electron-withdrawing groups, or bulky ortho-substituents gave poor results (0-5\% yields). The carbenoid was shown to tolerate also larger bicyclic phenols (Scheme 69).
Scheme 69. Rhodium-Mediated O-H Insertion Reaction of PCDCs 119 and 135 with Phenols

Aller et al.\textsuperscript{135} studied the relative reactivity of the PCDC 119 towards primary, secondary and tertiary alcohols. The results obtained by heating 119 with an equimolar mixture of ethanol, isopropanol and t-butanol in dichloromethane at room temperature with rhodium trifluoroacetamide as catalyst, indicated that ethanol was twice as reactive as t-butanol and isopropanol. Competition experiments proved the relative reactivity of alcohol and phenol in rhodium-mediated insertion reactions.

When 119 was decomposed in boiling toluene in the presence of rhodium(II) acetate and an equivalent amount of isopropanol and 4-methoxyphenol the attack of the carbenoid to the alcohol
proved to be more efficient than to the phenol. Soon after these studies, applications in the synthesis of biologically active compounds appeared in the literature. In particular, the rhodium(II) acetate-catalyzed decompositions of PCDCs \textbf{135} and \textbf{119} with phenol derivatives have been reported to afford useful intermediates toward the synthesis of inhibitors of the 5-enolpyruvoylshikimate-3-phosphate synthase enzyme (EPSP) (Scheme 70).\textsuperscript{136,137}

\textbf{Scheme 70. Applications of PCDCs 135 and 119 in the Synthesis of EPSP Synthase Inhibitors}

![Scheme 70](image)

Investigations on the mechanism of decomposition of PCDCs in the presence of acids were described by Seyferth \textit{et al.}\textsuperscript{38} In particular, they reported on the decomposition of \textbf{11a} either in ethereal acetic acid or benzoic acid. The first acid proved to be very slow in catalyzing the decomposition of \textbf{11a} requiring 15 h for the evolution of nitrogen to be completed, whereas the latter was completely ineffective in decomposing the diazo compound (Error! Reference source not found.).

\textbf{Scheme 71. Metal-Free Decomposition of 11a in the Presence of Acetic Acid}

![Scheme 71](image)
After this first attempt, Nakamura et al.\textsuperscript{138} described the reaction of PCDC 135 with 2-benzoylbenzolic acid in the presence of rhodium(II) acetate in toluene at 80 °C, affording the insertion products 152a-c. The subsequent base-catalyzed reaction gave access to 3,4-disubstituted isocoumarins 153a-c (Scheme 72) and related ring systems such as thieno[3,3-c]pyran derivatives (154) and 2-oxafluoranthene (155) (Scheme 73).\textsuperscript{138}

**Scheme 72. Synthesis of 3,4-Disubstituted Isocoumarins 153a-c**

\[ \text{CO}_2\text{H} \quad \text{EtO}_2\text{C} \quad \text{PO}_3\text{Et}_2 \]

135

\[ \quad \text{N}_2 \quad \text{CO}_2\text{Et} \quad \text{PO}_3\text{Et}_2 \]

152a-c

\[ \quad \text{DBU, toluene, rt} \]

153a-c

a: R = Ph, quantitative (152); b: R = H, quantitative (152); c: R = 3,4,5-(MeO)\textsubscript{3}C\textsubscript{6}H\textsubscript{2}, quantitative (152)

**Scheme 73. Synthesis of Thieno[3,3-c]pyran and 2-Oxafluoranthene Derivatives 154 and 155**

155, 41%

1. Rh\textsubscript{2}(OAc)\textsubscript{4} benzene, 80 °C

2. DBU, toluene, rt

119

1. Rh\textsubscript{2}(OAc)\textsubscript{4} benzene, 80 °C

2. DBU, toluene, rt

154, 80%

Titanyuk et al. reported on O-H and COO-H insertion reactions of PCDC 8 as a novel approach to the synthesis of different α-trifluoromethyl-α-hydroxyphosphoric acid derivatives (Scheme 74. ).\textsuperscript{139}

**Scheme 74. COO-H and O-H Insertion Reaction of PCDC 8**
3.2.2. Asymmetric Catalysis in O-H Insertion Reaction

Intrigued by the possibility to control the stereochemistry of the newly formed tertiary center, Moody et al.\textsuperscript{49} attempted the development of an asymmetric version of O-H insertion reaction using chiral auxiliaries at the phosphonate group, already shown to be effective as chiral auxiliaries in phosphorus chemistry, such as (-)-ephedrine and \textit{trans}-1,2-\textit{bis}(\textit{N}-methylamino)cyclohexane (Scheme 75). Although no products were observed with the diazocompounds bearing the latter auxiliary, the corresponding reaction of ephedrine derivatives \textbf{157} and \textbf{159} with 2-propanol and benzylcarbamate, in the presence of rhodium(II) acetate, led to the formation of the corresponding insertion products \textbf{158} and \textbf{161}, and \textbf{160}, respectively. However, this chiral group was shown to impart poor stereocontrol to the insertion reactions with \textit{de} ranging from 15\% to 32\%. These results were in contrast with those obtained with diazocarbonyls where this chiral auxiliary was able to impart significant asymmetric induction in O-H insertion reaction.\textsuperscript{135}

\textbf{Scheme 75. Rhodium-Catalyzed O-H and N-H Insertion Reactions of Chiral PCDCs 157 and 159}
The first example of asymmetric O-H insertion of PCDCs with alcohols using copper-BOX complexes, as catalysts, was reported by Zhu et al. (Scheme 76).\(^{140}\)

The ligand capable of affording the best chiral induction was the (S\(_a\), S, S\(_a\)) spiro bisoxazoline 162. Several copper salts were effective for the insertion reaction, with CuOTf proved superior for reactivity and enantioselectivity. The additive NaBARF was found to be an essential component of the reaction since in its absence lower yield and poor enantiomeric excess were achieved. The scope of alcohol substrates in the O-H insertion was also investigated showing the applicability of this methodology to various primary alcohols including benzyl alcohol with reaction completed in short time (1-3 h) and affording the products in good yield (69-89%) and good ee (84-91%). Secondary and allylic alcohols required longer reaction times (3-12 h) along with occasionally lower yields (19%) and lower ee (38%) \(\alpha\)-Aryl-PCDCs gave better results than the \(\alpha\)-alkyl ones. This methodology proved to be an efficient approach to access enantiomerically enriched \(\alpha\)-alkoxyphosphonates starting from readily available materials.
3.2.3. N-H Insertion Reactions

The first account on the N-H insertion of carbenoids derived from PCDCs concerns the intramolecular insertion of the diazo moiety into the β-lactam N-H of 163a-d, affording the corresponding carbapenem precursors 164a-d in moderate to good yield (Scheme 77).

The Merck group reported the same reaction leading to identical intermediates 164a,b for the synthesis of different carbapenem analogues.

Scheme 77. Intramolecular N-H Insertion Reaction

\[\text{163a-d} \xrightarrow{\text{R}_{2}(\text{OAc})_{4}, \text{benzene, 80 } ^\circ\text{C, 10 min}}} \text{164a-d}\]

Intramolecular N-H insertion reaction was also exploited for the preparation of cis-5-substituted-pyrrolidine phosphonates 166 starting from the PCDCs 165. The reaction proceeded with high stereoselectivity leading to no more than 13% of the corresponding trans-isomers 167 (Scheme 78).
In 1985, Regitz and Martin reported the decomposition of the t-butylammonium salt of the α-diazo-phosphinate 168 in the presence of t-butyl amine affording the betain 172 in excellent yield (Scheme 79).  

Several years later Haigh published a study on the reactivity of PCDC 135 with aniline showing that N-H insertion was favoured over O-H insertion when phenol was present in the reaction mixture: the N-H insertion derived product 173 was indeed exclusively obtained (Scheme 80).  

The use of 119 in N-H insertion reactions has become a common strategy for the preparation of N-aryl-α-phosphonylglycine derivatives, useful intermediates toward the synthesis of different heterocyclic scaffolds, such as N-aryl indole-2-carboxylates.
In 2003, the first report of N-H insertion reactions of rhodium carbenoids generated by a polymer-supported PCDC was published. Immobilized diethylphosphonoacetate 174, prepared by reaction of a hydroxymethyl polystyrene resin with diethylphosphonoacetic acid, was transformed in the corresponding PCDC 175 with p-dodecylbenzenesulfonyl azide and DBU. The subsequent rhodium-catalyzed decomposition in the presence of a series of haloanilines gave the corresponding N-aryl-α-phosphonylglycines 176a-h, useful intermediates for the preparation of indolecarboxylates (Scheme 81).

**Scheme 81. Solid-phase Synthesis of Indolecarboxylate Derivatives**

This synthetic procedure was subsequently applied to the synthesis of isocumarins via insertion of 175 into the COO-H bond of benzoic acid derivatives.
Aller et al.\textsuperscript{147} assayed N-H insertion of PCDCs as a route to aminophosphonates by the investigation of the rhodium(II) acetate-catalysed decomposition of diazophosphonate 11b with a limited series of primary amides, carbamates and anilines (Scheme 82). The reactions with benzyl and \textit{t}-butyl carbamates gave the corresponding products 177c,\textit{d} in excellent yield, unlike the amides. The reaction with anilines was found to be strongly dependent on the aromatic ring substituent.

\textbf{Scheme 82. N-H Insertion Reaction of 11b as Route to $\alpha$-Aminophosphonates 177a-g}

\[
\begin{align*}
\text{Me}_2\text{O}_3\text{P} & \quad \text{Ph} \\
\text{N}_2 & \quad \text{R-NH}_2 \\
11\text{b} & \quad \text{Rh}_2(\text{OAc})_4 \\
\text{toluene, reflux} & \quad \text{Me}_2\text{O}_3\text{P} & \quad \text{Ph} \\
\text{RHN} & \quad 177\text{a-g}
\end{align*}
\]

\begin{itemize}
\item 177\textit{a}, 13%  
\item 177\textit{b}, 33%  
\item 177\textit{c}, 96%  
\item 177\textit{d}, 88%
\end{itemize}

\begin{itemize}
\item 177\textit{e}, 76%  
\item 177\textit{f}, 16%  
\item 177\textit{g}, 52%
\end{itemize}

In a following report, Ferris et al.\textsuperscript{148} investigated more deeply this synthetic strategy by starting from PCDC 135 (Scheme 83).
The N-H insertion reaction was also exploited for the synthesis of dipeptides of dehydroaminoacids. Thus, by treatment of a series of protected amino acid amides 179a-f with triethyl diazophosphonoacetate (135), under rhodium(II) acetate catalysis, the corresponding N-H insertion products 180a-f were obtained in good yields (Scheme 84). The reaction resulted in complete chemoselectivity with no traces of the product derived by the insertion into the N-H carbamate bond. A full account of this approach was later reported by the same authors.

Scheme 84. N-H Insertion Reaction as a Key Step toward the Synthesis of Dipeptides of
In an effort to elaborate new synthetic routes to anchoring the bisphosphonate moiety into alcohols, phenols, and amines, the metal-catalyzed insertion reaction of PCDC 20f was also developed.\textsuperscript{151,152} Rhodium(II)-catalyzed N-H insertion reaction of BOR (22) with arylcarboxamides was exploited for the synthesis of 2-aryloxazole-4-phosphonates (Scheme 85). In the presence of Rh\textsubscript{2}(OAc)\textsubscript{4}, benzamide gave the corresponding N-H insertion product 181 in 62\% yield. Subsequent cyclodehydration promoted by triphenylphosphine and iodine allowed the formation of 2-phenyl-5-methylloxazole-4-phosphonate (182). It was found that the nature of the ligand of the catalyst plays a crucial role in dictating the diastereoselective outcome of the reaction. When dirhodium tetrakis(heptafluorobutyramide) was employed as the catalyst the corresponding 5-substituted oxazole 183 was indeed formed. This isomeric compound was not obtained by N-H insertion-cyclization route, but rather from O-H insertion of the rhodium carbene intermediate into the carboxamide imino tautomer, followed by cyclodehydration. Analogously, thiazole-5-phosphonates were also efficiently prepared.\textsuperscript{153,154}
After the long dominance by rhodium(II) catalysts, Simonneaux et al. reported the first application of ruthenium catalysis in the N–H insertion reaction of diisopropyl α-diazoethylphosphonate (184) with N-methyl allyl amine. In the presence of a catalytic amount of (TPP)Ru(CO) (185) the phosphonic ester 186 was obtained in reasonable yield (Error! Reference source not found.).

Scheme 86. (TPP)Ru(CO)-Catalyzed N-H Insertion Reaction of Diisopropyl α-Diazoethylphosphonate (184) with N-Methyl Allyl Amine
Later on, the same group reported the effectiveness of TSPPFeCl (186) in catalyzing the N-H insertion reaction of the same PCDC 5b into the amino group of three α-amino acid esters. The reactions, carried out in water/methanol solution, furnished the corresponding products 187a-c in good yields. Noteworthy, the absence of O-H insertion product in the case of tyrosine (Error! Reference source not found.). When this methodology was assayed for N-H insertion in the N terminus of insulin, 20% of insertion compound was isolated using a stoichiometric amount of TSPPFeCl, showing the potential of this approach toward the selective modification of proteins.\textsuperscript{156}
3.2.4. Other X-H Insertion Reactions

An example of insertion reaction of PCDCs into S-H bond was reported by Paul-Roth et al.,\textsuperscript{157} who obtained the methylthio-substituted derivative 189 by the (TPP)Ru(CO)-catalyzed reaction of 5b with 2-propene-1-thiol. The competitive cyclopropanation reaction led to the concomitant formation of the cyclopropyl derivative 190 although as minor component (Scheme 88).
In the wake of their previous works on the catalyzed decomposition of amino acid- derived PCDCs, Cai et al.\textsuperscript{158} recently reported on the trifluoroborane-catalyzed reaction of PCDCs, such as 17a-c, performed in dichloromethane in the presence of an excess of a thiol derivative. As observed in the analogous reaction with alcohols,\textsuperscript{42} a combined C-H functionalization/S-H insertion reaction occurred affording the corresponding products 191a-c along with variable amounts of the β-hydride elimination-derived side-products 192a-c (Scheme 89).

This work represents the first example of the conversion of PCDCs into β-alkyl(aryl)thio-substituted β-aminophosphonates, such as 191a-c, having $N,S$-quaternary centers.
Highly innovative characteristics are present in the paper recently published by Chen et al., who reported the first enantioselective rhodium(I)-catalyzed Si-H insertion of α-diazoesters and PCDCs. The Rh(I)-carbene chemistry has been so far little explored and only recently has demonstrated to exhibit ability in the catalytic asymmetric formation of C-C bonds. Slightly modified conditions (use of a preformed rhodium(I)-diene complex) with respect to the analogous reaction with α-diazoesters were selected for the asymmetric Si-H insertion reaction of PCDCs with triethyl- and arylsilanes (Scheme 90). The expected highly enantioenriched α-silylphosphonates 193a-h were obtained in moderate yields. According to the supposed mechanism of the reaction the absolute configuration at the newly formed stereocenter of 193 was assigned to be S.

Scheme 90. Asymmetric Si-H Insertion Reaction
3.3. Cyclopropanation Reactions

The cyclopropanation of alkene bonds is one of the most investigated area in PCDC chemistry. It does not sound surprising since the cyclopropane ring is an important structural motif in biologically active compounds, as well as a versatile building block being able to be converted into a range of other functionalities. In this type of transformation the use of transition-metal-catalysts, including copper-, rhodium- and ruthenium-catalyst, has represented the method of choice for generating the corresponding reactive species, although some examples employing photochemical-induced nitrogen elimination have to be also cited. High diastereo- and enantio-control have been demonstrated by the use of a number of chiral transition metal complexes, rhodium- and
ruthenium-based catalysts, in particular. However, the possibility to direct the reaction toward the preferential formation of the cis isomer still remains unsuccessful. Moreover there are only few applications of alkene cyclopropanation of substrates other than styrene derivatives.

3.3.1. Intermolecular Alkene Cyclopropanation

Seyferth et al.\textsuperscript{6} reported one of the first examples of cyclopropanation via PCDCs in 1970. The authors found that a solution of 5a in dichloromethane was capable, in the presence of copper powder, of delivering the carbenoid addition to alkenyl derivatives 194a-d leading to the corresponding cyclopropanes 195a-d (Scheme 91).\textsuperscript{6,30} Similarly, \(\alpha\)-diazobenzylphosphonate (11b) gave the corresponding cyclopropanes 196a-c when reacted with an excess of alkenes 194a-c, although with higher yields with respect to 5a. Mechanistically, the authors suggested that the reaction involved the presence of a carbene-Cu(I) complex that reacted with the olefin producing the cyclopropane. Nevertheless, they did not exclude the possibility of other mechanisms, such as 1,3-dipolar cycloaddition, especially in the presence of electron rich olefins, more prone to react via this pathway.\textsuperscript{30} The author did not mention any informations about the diastereoselectivity achieved.

\textbf{Scheme 91. Cyclopropanation Reaction of 5a and 11b with Olefins 194a-c under Copper Powder}
Catalysis

The copper-catalysed cyclopropanation methodology reported by Seyferth, was successively applied by Reid et al. to the synthesis of phosphonate-analogs of the natural insecticidal pyrethrins (Scheme 92). Cyclopropylphosphonate was obtained in 56% yield as a mixture of cis- and trans-isomers, which, without separation of the structural or optical isomers, were than further modified to obtain the desired cyclopropyl phosphonate derivatives.
In order to study the chemical reactivity of alkylidene cyclopropane units, Lewis et al.\textsuperscript{174} re-investigated Seyferth procedure\textsuperscript{6} as synthetic route toward these substrates. To avoid the formation of excessive quantities of carbene-dimerization side products (as observed by Seyferth), the authors initially opted for the use of homogeneous catalyst such as rhodium(II)-acetate and rhodium(II)-pivalate. Although these two catalysts were able to smoothly decompose \textit{5c}, they were rapidly deactivated and the addition of supplementary amounts was necessary. Cu(I) triflate was found to be the best catalyst for this particular case providing that diazophosphonate was added slowly to the mixture of olefin and catalyst. In contrast with Seyferth observations,\textsuperscript{6} only a three-fold excess of olefin was necessary to minimize the formation of diazo-dimerization product. Several olefins were successfully converted into the corresponding cyclopropanes \textit{199a-f}, used then as the starting materials for the subsequent HWE reaction (Scheme 93).
Copper iodide was found to be the best catalyst for the decomposition of diethyl 1-diazo-2,2,2-
trifluoroethylphosphonate (8) in the presence of alkenes to give the corresponding trifluoromethyl-
substituted cyclopropyl phosphonates 200a-d (Scheme 94). The screening of a small series of
different alkenes showed that the reaction worked efficiently with terminal olefins, whereas
cyclohexene gave the corresponding cyclopropane in rather poor yield. Internal trans-olefins, such
as p-methoxyphenyl-β-methylstyrene, stilbene and electron-deficient methyl acrylate did not react
even under more drastic conditions. No further studies were conducted in order to improve the
poor diastereoselectivity of the reaction.

Scheme 93. Copper(I) Triflate-Catalyzed Cyclopropanation of Olefins with 5c.

Scheme 94. Synthesis of Trifluoromethyl Cyclopropyl Phosphonates via Cul-Catalyzed
Rh$_2$(OAc)$_4$ was instead the catalyst used by Dappen et al.$^{176}$ for the synthesis of phosphonooctly cyclopropyl derivatives $202\text{a,b}$, as conformationally constrained analogs of 2-amino-5-phosphonopentanoic acid endowed with competitive antagonist properties at $N$-methyl-$D$-aspartate (NMDA) receptor. In particular, $N$-Cbz-(D)-allylglycine ($201$) was converted into an inseparable mixture of all possible stereoisomers of cyclopropane $202\text{a,b}$ by cyclopropanation with $5\text{a}$. The desired acid derivatives were then obtained after hydrolysis with 6N HCl (Scheme 95).

**Scheme 95. Synthesis of Cyclopropyl Analogues of 2-Amino-5-phosphonopentanoic Acid**

Also chiral rhodium(II) complexes have garnered attention as catalysts for enantioselective cyclopropanation of alkenes by PCDCs. Davies et al.$^{177}$ first reported on the cyclopropanation of alkenes with donor/acceptor PCDCs in the presence of $D_2$-symmetric dirhodium complexes. Despite
Rh$_2$(S-DOSP)$_4$ (97), proved effective in promoting cyclopropanation of styrene with 11b, the poor result in terms of enantioselectivity, forced the authors to investigate the second-generation catalyst Rh$_2$(S-biTISP)$_4$ (98) for this transformation (Scheme 96).

**Scheme 96.** Rh$_2$(S-biTISP)$_4$-Catalyzed Cyclopropanation with Donor/Acceptor-PCDCs

![Scheme](image)

Electron-rich alkenes were essential for efficient cyclopropanation: however, high stereoselectivity was achieved only with aryl alkenes. With a narrow range of aryl- and vinyl-PCDCs all the reactions proceeded in high yield and diastereoselectivity, while the enantioselectivity varied from 68 to 92% ee. As in the analogous reactions with α-diazocarbonyls,\textsuperscript{178} it was found that the diastereoselectivity observed was independent from the size of the phosphonate group, while the enantioselectivity steadily decreases on increasing the phosphonate size.\textsuperscript{179} In the same paper, the Rh$_2$(S-biTISP)$_4$-catalyzed reaction between α-styryl-PCDC 204 and (1E)-buta-1,3-dien-1-ylbenzene was exploited for the construction of the seven-membered carbocycle 205 (Scheme 97). The tandem cyclopropanation/Cope rearrangement proceeded with high diastereoselectivity generating the phosphonate-substituted cycloheptadiene 205 as a single diastereoisomer in 65% ee.
Later on Davies et al. reported \( \text{Rh}_2(S\text{-PTTL})_4 \) (99) and \( \text{Rh}_2(S\text{-PTAD})_4 \) (100) as far superior catalysts than \( \text{Rh}_2(S\text{-biTISP})_4 \) (98), in the cyclopropanation of styrene with dimethyl \( \alpha \)-diazobenzylphosphonate (11b), achieving levels of enantioselectivity of 97% and 99%, respectively.\(^\text{96}\)

In 2014, Adly et al.\(^\text{180}\) studied the effects of lowering the ligand’s symmetry around the rhodium center on the cyclopropanation of styrene. Along with two commercial catalyst \( \text{Rh}_2(S\text{-PTTL})_4 \) (99) and \( \text{Rh}_2(S\text{-NTTL})_4 \) (206a) four new catalysts (206b-e), were evaluated in standard donor-acceptor cyclopropanation reactions using dimethyl \( \alpha \)-diazobenzylphosphonate 11b, as carbene precursor, and styrene. All catalysts were able to give >20:1 \( dr \) in favour of the trans-isomer (Scheme 98). The best performing catalyst was 206a bearing the bulky t-butyl group. The other catalysts gave very poor \( ees \). The scope of the \( \text{Rh}_2(S\text{-1,2-NTTL})_4 \)-catalyzed cyclopropanation reaction was further investigated with respect to the alkene. All reactions proceeded smoothly with cyclopropylphosphonates obtained in high yields (86–93%), good diasteroselectivity (>20:1 \( dr \)), and excellent enantioselectivity (94–99% \( ee \)). Also in this case it was observed that the increased size of the phosphonate moiety was parallel with a decrease in enantioselectivity.
Scheme 98. Rhodium(II)-Catalyzed Enantioselective Cyclopropanation Reaction with 11b

![Scheme 98. Rhodium(II)-Catalyzed Enantioselective Cyclopropanation Reaction with 11b](image)

The intrinsic instability of acceptor/acceptor diazo compounds, such as α-halo-α-diazomethylphosphonates has meant that their applications in cyclopropanation reactions were scarce. To circumvent the decomposition of 49a-c during purification on silica and to minimize the amount of dimerization product, Schnaars et al.\(^{69}\) developed a one-pot, telescoped procedure for the generation of halodiazophosphonates 49a-c and their subsequent in-situ cyclopropanation with a series of styrene derivatives (Scheme 99). Among the several Rh(II)-, as well as other metal-based catalysts tested, Rh\(_2\)(esp)\(_2\) showed to be the most active (0.1 mol% catalyst loading). The method proved to be high-yielding for electron-rich styrene derivatives, meanwhile 1,1-disubstituted- (208h) and electron-deficient double bonds (208d-g) gave lower yields. Remarkably, all products showed high diastereoisomeric ratios in favour of the \textit{trans} isomer.

Scheme 99. Diastereoselective Rh(II)-Catalyzed Cyclopropanation of Styrene Derivatives with α-
Later on, the same research group investigated other methodologies for the preparation of PCDCs 49a-c to submit to in-situ cyclopropanation reaction. However, the obtained results were not better than the precedent ones.\(^7\)

Considering the high potential of acceptor-acceptor cyclopropanes in asymmetric synthesis, Lindsay et al.\(^8\) described in 2013, the first catalytic asymmetric synthesis of cycloprop(eny)lphosphonate derivatives, using \(\alpha\)-cyano-\(\alpha\)-diazomethylphosphonate (209), as the starting material. The choice of cyano group, as the second electron-withdrawing substituent of the diazo reagent, was driven by its steric, as well as electronic properties. The optimization studies, performed with styrene as
model substrate, led first to the identification of Rh$_2$(Adc)$_4$ (210) as the best catalyst in terms of diastereocontrol. Under the optimized conditions, cyclopropane 211a was obtained in 99% isolated yield, with 89:11 de (Scheme 100). The subsequent screening of a series of chiral catalysts allowed the selection of Rh$_2$(S-IBAZ)$_4$ (212), able to give cyclopropane 211a in excellent yield, with high diastereo- and enantioselectivities.

**Scheme 100. Catalytic Asymmetric Synthesis of Cyclopropylphosphonate Derivatives using α-Cyano-**
As far as concern ruthenium catalysts, in 2002 Simonneaux et al. described the use of homochiral porphyrins-ruthenium complexes (184 and 213), generally employed for the asymmetric epoxidation of olefins, in the cyclopropanation of styrene derivatives with diisopropyl α-diazomethylphosphonate (5b).182 Under the experimental conditions already tested in analogous
reactions with ethyl diazoacetate (EDA), the corresponding cyclopropanes 214a-d were obtained in yields ranging from 80 to 95% and trans/cis ratio up to 316, as determinate by GC-MS ( ). The trans/cis ratio was dictated by the nature of the porphyrin ligand with electron-deficient TPFPP catalyst (213) showing to give better stereoselectivities than TPP one with all the substrates except than α-methylstyrene.

Scheme 101. Cyclopropanation of Styrene Derivatives with 5b in the Presence of Ru-Porphyrin Complexes

\[
\begin{align*}
\text{R} = \text{R}^1 &= \text{H}, 90\% \text{ (TPP)}, 12 \text{ trans/cis ratio (TPP)}, 95\% \text{ (TPP)}, 104 \text{ trans/cis ratio (TPFPP)}; \\
b: \text{R} = \text{R}^1 &= \text{OMe}, 95\% \text{ (TPP)}, 47 \text{ trans/cis ratio (TPP)}, 95\% \text{ (TPP)}, 316 \text{ trans/cis ratio (TPFPP)}; \\
c: \text{R} = \text{R}^1 &= \text{CF}_3, 93\% \text{ (TPP)}, 4 \text{ trans/cis ratio (TPP)}, 94\% \text{ (TPP)}, 10 \text{ trans/cis ratio (TPFPP)}; \\
d: \text{R} = \text{R}^1 &= \text{H}, 80\% \text{ (TPP)}, 17 \text{ trans/cis ratio (TPP)}, 90\% \text{ (TPP)}, 1 \text{ trans/cis ratio (TPFPP)}
\end{align*}
\]

With the aim of extending the synthetic application of these catalytic systems, Paul-Roth et al. also investigated the reaction between 5b and dienes.\textsuperscript{157} Trans-1,3-pentadiene was cyclopropanated using 5b in the presence of (TPP)Ru(CO) (184) or (TPFPP)Ru(CO) (213) to give a mixture of the two
corresponding cyclopropyl derivatives 215 and 216 in very good yields. The reaction was not regioselective by using 184, whereas the electron-deficient complex 213, was able to preferentially drive the reaction toward the terminal double bond (Scheme 102).

Scheme 102. Cyclopropanation of 1,3-Pentadiene with 5b in the Presence of (TPP)Ru(CO) or (TPFPP)Ru(CO) Catalysts

In 2004, Simonneaux et al.,183 reported the enantioselective synthesis of cyclopropylphosphonates using, as catalyst, the chiral ruthenium-porphyrin complex (217) ( ). The reactivity of 5b was assessed against a series of styrene derivatives. In all cases the reaction showed to be very efficient leading to the corresponding cyclopropanes in good yield and high trans-diastereoselectivity. Up to 92 % ee was observed within the trans-mixture, whereas the ee for cis-one remained very low.
Scheme 103. Cyclopropanation of Styrene Derivatives with 5b in the Presence of Chiral Ru-Porphyrin Complex 217

In 2005, also Charette group investigated the transition metal-catalysed enantioselective synthesis of cyclopropyl phosphonates\(^\text{184}\). The study began with the identification of the most active catalyst. Among different achiral metal catalysts, rhodium-based systems were found to be the most reactive in the cyclopropanation of styrene (85% yield), along with copper(I) triflate (77%). Although in both cases the diastereoselectivity was very low. The less-reactive ruthenium catalyst (40% yield) provided instead a better grade of diastereocntrol (91:19 \(dr\)). In the presence of the chiral Nishiyama catalyst (219), cyclopropanation of diverse olefins was realized with high diastereoselectivity as well as excellent \(ee\) (up to 97 % for trans isomer) (Figure 5).
Despite the existence of several methodologies for the cyclopropanation of olefins, styrene derivatives in particular, the applications to electro-deficient alkenes, such as α,β-unsaturated carbonyl compounds, still remains rare. Only recently, Chanthamath et al.\textsuperscript{185} reported the stereoselective cyclopropanation of alkenes, including α,β unsaturated carbonyl compounds catalyzed by a Ru(II)-Pheox complex (\textsuperscript{220}) (Scheme 104). After the optimization of the reaction conditions, a series of styryl derivatives were then screened with excellent results in term of yield (72-93%), \textit{trans/cis} ratio (62:38 to 99:1) and \textit{ee} (94-96%). Styrenes bearing either electron-donating- or electron-withdrawing groups were well tolerated. The method however, was unsuitable for internal alkene such as \textit{cis}- and \textit{trans}-2-hexene. Vinylamine derivatives could also be cyclopropanated under the same reaction conditions to afford the corresponding cyclopropanes \textsuperscript{221h-i} in excellent yield and with high distereo- and enantioselectivity. When phenyl acrylate was cyclopropanated under the optimized conditions, the corresponding cyclopropane \textsuperscript{221j} was obtained in 65% yield with excellent \textit{trans/cis} ratio (99:1) and \textit{ee} (98%). Similar results gave α-vinylbenzophenone, whereas, among acrylamides, only cyclopropane \textsuperscript{221l} was obtained in good yield and \textit{ee}.
The utility of this methodology was assessed in the synthesis of cyclopropane 222, as a key intermediate for the preparation of the acyclic nucleoside analogue 223 and the glutamic acid analogue 224 as reported in Error! Reference source not found..
the Synthesis of the Acyclic Nucleoside Analogue (223) and the Glutamic Acid Analogue (224)

Only one example describes the use of organocatalysis in cyclopropanation reaction with PCDCs. Since the thermally-induced cyclopropanation of α-methylacrolein by α-diazobenzylphosphonate (11b) proceeded slowly and with low diastereoselectivity, the use of the two proline-derived catalysts, 225a and 225b, was investigated. Although the reaction time was greatly reduced, the effect on the diastereoccontrol was scarce (Scheme 106).

Scheme 106. Thermal and Organocatalyzed-Cyclopropanation of α-Methylacrolein with 11b

without catalyst: 36h, 72%, 56/44 (trans/cis);
with 225a catalyst: 12h, 54%, 61/39 (trans/cis);
with 225b catalyst: 12h, 74%, 62/38 (trans/cis)
3.3.2. Intramolecular Cyclopropanation

Olefins α-diazo-β-ketophosphonates, such as PCDCs 227a-g, have been successfully subjected to intramolecular cyclopropanation to generate the corresponding three-membered ring derivatives 228a-g, which, due to the presence of the electron-withdrawing phosphonate group, rapidly underwent nucleophilic ring opening to afford a variety of interesting building blocks. (Scheme 107).\textsuperscript{187,38} Cyclopropanes 228a-g were obtained in moderate to good yield by refluxing a cyclohexane solution of the appropriate alkene (0.05-1.0 M) in the presence of copper powder. Interestingly, more common catalysts, such as Rh\textsubscript{2}(OAc)\textsubscript{4}, or Cu(acac)\textsubscript{2} were ineffective in this transformation.

**Scheme 107. Copper-Catalyzed Intramolecular Cyclopropanation of PCDCs 227a-g**

Hanson’s group reported the synthesis of P-heterocyclic compounds via intramolecular cyclopropanation of suitable phosphonate templates. In the first example of this reaction, published
in 1999, PCDCs 229a-d were converted into the corresponding P-heterocycles 230a-d in good yield (88-97%), but moderate diastereoselectivity (Scheme 108). The best cis/trans ratio was obtained with bulky carboxylic esters, such as for compounds 229c,d proving that the level of diastereofacial selectivity was influenced by R group size. In a successive study the same authors reported the successful separation of the trans- and cis-diastereoisomers. The major isomer was transformed, via Curtius rearrangement, into the crystalline carbamate cis-231, then submitted to X-ray crystallography.

Scheme 108. Rh₂(OAc)₄-Catalyzed Intramolecular Cyclopropanation of PCDCs 229a-d

Before obtaining the crystal structure of cis-231, attempts to assign its stereochemistry were made on the basis of ¹H-NMR spectroscopy knowing that, in constrained phosphonate systems, protons inside the “cone” of the phosphonate P=O bond were usually shifted downfield relative to those outside the “cone”. The diastereoselectivity observed in this transformation was rationalized on the basis of the widely accepted Doyle/Davies model. A combination of different effects contribute to the final outcome: a) the relative orientation of the two Rh=C and P=O π-systems (S-cis or S-trans), where opposing dipole interactions would favour the S-trans orientation; b)
electronic stabilization between the reacting olefin and the rhodium carbenoid which dictates the facial orientation (R-cis and S-trans); c) an anomic effect with an axial preference for the P-OR group (S-cis conformation); d) eclipsing effect between the ester group and the olefin (R-cis and S-trans). To further rationalize the stereochemical outcome of the reaction, the authors tried to exert the control of the reacting face of the carbene (re vs. si), (responsible for the control of the enantioselectivity, P-chirality) within the diastereomeric compounds. Two different strategies were then devised: the first based on the chiral auxiliary-substrate control and the second one based on asymmetric reagent control. According to the first approach, different chiral PCDCs were investigated. If with menthol- and 8-phenylmenthol-based PCDCs (232a,b) low diastereoselectivity was observed, with (R)-pantolactone-containing PCDC 232c a great preference for the formation of cis-Rp-233 diastereoisomer was evidenced (Scheme 109).

Scheme 109. Rh2(OAc)4-Catalyzed Intramolecular Cyclopropanation of PCDCs 232a-d

![Scheme 109](image)

**251a:** $R^* = $ menthol, $R_p$-cis-233: $S_p$-cis-233: $S_p$-trans-233: $R_p$-trans-233 = 3.2 : 3.2 : 1.5 : 1.0

**251b:** $R^* = $ 8-phenylmenthol, $R_p$-cis-233: $S_p$-cis-233: $S_p$-trans-233: $R_p$-trans-233 = 4.9 : 4.1 : 1.1 : 1.0

**251c:** $R^* = $ D(-)-pantolactone, $R_p$-cis-233: $S_p$-cis-233: $S_p$-trans-233: $R_p$-trans-233 = 29.1 : 2.8 : 3.6 : 1.0

The D(-)-pantolactone was indeed able to block the si-face of the carbenoid species, thus allowing
preferential access to the re-face of the olefin. The unfavourable interactions occurring between the gem-dimethyl moiety of the chiral auxiliary and the rhodium wall are depicted in the Figure 6. The formation of $R_p$-cis-233, as the major diastereisomer, was also in agreement with a $s$-trans orientation of the rhodium carbenoid and P=O (opposite dipole) and with the preferred facial orientation between the reacting olefin and the rhodium carbenoid, dictated by electronic stabilization.

Figure 6. Steric Clash between gem-Dimethyl Group of the Chiral Auxiliary and the Rhodium Carbenoid

With these results in hand Hanson’s group extended their investigation to the cyclopropanation of bis-methallyl- and bis-crotyl-PCDCs, 234a and 234b (Scheme 110. In the case of 234a, the result obtained was in contrast with the previous observations and the $R_p$-trans-235a was the major isomer formed. This might be due to unfavoured interaction between the terminal methyl group of the crotyl moiety and the rhodium carbenoid. However, the selectivity within the cis series slightly decreased, while trans selectivity increased to some extent when compared to those of the original allyl series.
Diphenyl β-keto-α-diazophosphinoxide 236 turned out to be a key intermediate toward the synthesis of (+)-colletoic acid (Scheme 111).\textsuperscript{194} Thanks to the bulky phosphinoxide motif and the use of chiral copper-BOX complex the intramolecular cyclopropanation resulted in the formation of the bicyclic derivative 237 with 91% ee. Interestingly, the stereoselectivity observed was comparable to that reported for the corresponding α-diazo-β-ketosulfones.\textsuperscript{195}
3.3.3. Cyclopropenation of Alkynes

Donor-acceptor substituted diazo compounds have also been used as carbenoid precursors in the enantioselective synthesis of chiral cyclopropenes using iridium-Salen chiral catalysts.\textsuperscript{196} Although the authors reported the reaction mainly with diazocarbonyl-derived carbenoids, they also screened dimethyl α-diazobenzylphosphonate (11b) for the conversion of terminal alkyne into the corresponding cyclopropenes. Although enantiomeric excesses were inferior to those observed starting from the corresponding α-diazoacetates, the cyclopropenes 239\text{a-c} were obtained in good to excellent yield (Scheme 112).
The other example of cyclopropenation present in the literature involves the diacceptor PCDC 209. Rh$_2$(Adc)$_4$ (210) and the chiral Rh$_2$(S-IBAZ)$_4$ (212) were selected for catalyzing the reaction of a set
of terminal alkynes, thus obtaining cyclopropenylphosphonates 240a-d in good yield and excellent enantioselectivity (Scheme 113). Cyclopropenes substituted by either an aromatic or an aliphatic group were obtained with similar efficiency. Chemoselectivity was also observed between terminal triple bond and endocyclic double bond. In contrast with the results obtained with other acceptor-acceptor diazo compounds, 209 did not react with phenylallene.\textsuperscript{181}

**Scheme 113. Cyclopropenation of Terminal Alkynes with 209**

\[
\begin{align*}
\text{i-Pr}_2\text{O}_3\text{P} & \quad \text{CN} \\
\text{N}_2 & \quad \equiv \quad \text{R} \\
209 & \quad \text{method A: DCE, Rh}_2(\text{Adc})_4 (5 \text{ mol\%}) \\
& \quad \text{method B: toluene, Rh}_2(\text{S-IBAZ})_4 (1 \text{ mol\%}) \\
\text{i-Pr}_2\text{O}_3\text{P} & \quad \text{CN} \\
\text{R} & \quad \text{240a-d}
\end{align*}
\]

**3.4. Reactions with Aromatic Compounds**

The reaction of arenes with photochemically generated phosphorylcarbenes (the Buchner reaction), leading to an equilibrating mixture of the corresponding norcaradiene and cycloheptatriene derivatives was reviewed by Regitz.\textsuperscript{27} Later on Maas et al. reported about the substituent dependence of this equilibrium.\textsuperscript{197}

Recent reactions of PCDCs with aromatic compounds concern exclusively C-H functionalization via electrophilic aromatic substitution mediated by Rh(III) catalysts. Whereas the corresponding reac-
tions of α-diazocarbonyl compounds has been received increased attention in the last years, ¹ papers focused specifically on PCDC applications are still missing; the examples below can be found in general papers regarding diazo derivatives. In some examples, the aromatic substitution reaction is the initiating event for a subsequent annulation.

In the frame of a study predominantly directed to the rhodium(III)-catalyzed reaction of diazocarbonyl compounds with aromatics bearing azacyclic directing groups, the reactivity of 135 was also explored (Scheme 114). The reaction, performed in the presence of [Cp*RhCl]₂ (Cp* = pentamethylcyclopentadiene) and AgSbF₆, allowed the obtainment of the ortho-alkylated derivatives 92a,b in excellent yield.

**Scheme 114. Catalyzed Azacycle-Directed Aromatic C-H Functionalization with 20f**

![Scheme 114 Diagram](image)

The same catalytic system was shown to be able to promote the regioselective alkylation of N(2-pyrimidyl)indoline (242) by PCDC 135 (Scheme 115).

**Scheme 115. Regioselective Rhodium(III)-Catalyzed Alkylation of Indoline 242 with PCDC 135**

![Scheme 115 Diagram](image)
C-H activation mediated by Rh(III) resulted to be the cyclization-initiating event in the annulation reaction of oximes and diazo compounds. In particular BOR (22) was reported to react with the oxime 244 to give the isoquinoline N-oxide 245 in almost quantitative yield (Scheme 116).200

Scheme 116. Rh(III)-Catalyzed Synthesis of Dimethyl Isoquinoline-N-oxide-3-Phosphonate (245)

By using N-OAc amido moiety, as the directing group, Lam et al. prepared the benzolactam 248 by the Rh(III)-catalyzed formal oxidative [4+1] cycloaddition of O-acetyl benzohydroxamic acid 246 with PCDC 247 (Scheme 117).201

Scheme 117. Rh(III)-catalyzed Cycloaddition of O-Acetyl Benzohydroxamic Acid 246 with PCDC 247

In 2009, Marinozzi et al.202 reported the unique example of the reaction between a PCDC and an heteroaromatic compound. The catalyzed-decomposition of diisopropyl α-diazomethylphosphonate (5b) in the presence of furan and 2-substituted furans was studied by comparing Rh₂(OAc)₄ and Cu(OTf), as catalysts. In all the tested conditions, the initially formed cycloadduct 249 or 250 was obtained along with the corresponding ring-opening products 251 (Scheme 118, Table 3). Interestingly, however, the catalyst nature as well as the presence of dichloromethane strongly influenced the product distribution as well as the stereochemistry of the conjugated dienes obtained. A further facet of this study lies in the possibility to obtain a single product for reaction, namely the (E,E)diene-251, by treatment with iodine of each reaction crude.
This aspect was notably in view of the importance of stereodefined conjugated dienes as synthetic intermediates and structural motif of a variety of biological interesting products.

Scheme 118. Metal-Catalyzed Decomposition of 5b in the Presence of Furans

Table 3. Metal-Catalyzed Decomposition of 5b in the Presence of Furans

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (%)</th>
<th>Solvent</th>
<th>R</th>
<th>Yield (%)</th>
<th>Product</th>
<th>Product ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Rh₂(OAc)₄ (5)</td>
<td>neat</td>
<td>H</td>
<td>81</td>
<td>249/(1Z,3Z)-251/(1E,3Z)-251</td>
<td>1:1.2:3.8</td>
</tr>
<tr>
<td>b</td>
<td>Rh₂(OAc)₄ (5)</td>
<td>CH₂Cl₂</td>
<td>H</td>
<td>80</td>
<td>249/(1Z,3E)-251/(1E,3E)-251</td>
<td>1:5.5:17.5</td>
</tr>
<tr>
<td>c</td>
<td>CuOTf (0.05)</td>
<td>neat</td>
<td>H</td>
<td>85</td>
<td>249/(1Z,3Z)-251/(1E,3Z)-251</td>
<td>1:0.2:1.2</td>
</tr>
<tr>
<td>d</td>
<td>CuOTf (1)</td>
<td>CH₂Cl₂</td>
<td>H</td>
<td>80</td>
<td>249/(1Z,3Z)-251/(1E,3Z)-251</td>
<td>1:0.4:1.6</td>
</tr>
<tr>
<td>e</td>
<td>CuOTf (0.05)</td>
<td>neat</td>
<td>Me</td>
<td>68</td>
<td>249/250/(1Z,3Z)-251/(1E,3Z)-251</td>
<td>1.1:1:2.0:5.8</td>
</tr>
<tr>
<td>f</td>
<td>Rh₂(OAc)₄ (5)</td>
<td>neat</td>
<td>Me</td>
<td>89</td>
<td>249/(1Z,3E)-251/(1E,3E)-251</td>
<td>1:3.9:11</td>
</tr>
<tr>
<td>g</td>
<td>CuOTf (1)</td>
<td>CH₂Cl₂</td>
<td>OMe</td>
<td>61</td>
<td>(1Z,3Z)-251/(1E,3Z)-251</td>
<td>1:2</td>
</tr>
</tbody>
</table>

3.5. Ylide Formation and Subsequent Reactions
The possibility to react with heteroatomic species giving the corresponding ylide intermediates, which is one of the most characteristic reactions of diazocarbonyl compounds, has been scarcely exploited in the case of PCDCs. Only four examples, involving sulfonium-, nitrogen- and thiocarbonyl ylide, can be found in the literature.

3.5.1. Sulfonium Ylide

The (TPP)Ru(CO)-catalyzed reaction of diisopropyl α-diazoethylphosphonate (5b) with 2-propene-1-thiol afforded, as the major product the α-methylthio-substituted derivative 252, as consequence of the [2,3]-sigmatropic rearrangement of the intermediate sulphonium ylide (Scheme 119).  

**Scheme 119. (TPP)Ru(CO)-Catalyzed Reaction of 5b with 2-Propene-1-thiol**

\[
\text{CHCl}_3, 40 ^\circ \text{C} \quad \text{Ru(TPP)(CO)} \rightarrow 252
\]

Wang et al. prepared quaternary substituted indolines, such as 255a,b, by coupling of α-vinyl-α-diazophosphonate 85a,b and the thioindole derivative 253 in the presence of rhodium(II) acetate (Scheme 120). As already supposed for the analogous reaction with diazoesters, it could be hypothesized that the reaction proceeded via sulfonium ylide 254a,b and a subsequent [3,3]-sigmatropic rearrangement. With 85b as the substrate along with the expected quaternary substituted indoline 255b, a substantial amount of the cyclopentenyl phosphonate 86a was obtained, as the result of the competitive intramolecular C-H insertion reaction of the starting PCDC.

**Scheme 120. Rh(II)-Catalyzed Coupling of Thioindole 253 and PCDCs 85a,b**
3.5.2. Ammonium Ylide

In the chemistry of diazocarbonyl compounds numerous are the examples of polyfunctional molecules prepared by the reaction of different electrophiles with an ammonium ylide, which was in turn generated from diazo reagents and amines. Having to be the trapping of the ammonium ylide by the external electrophile faster than the charge neutralization by intramolecular [1,2]-proton transfer, several examples of three component (diazo, amine and electrophile) reactions have been recently reported. On the contrary, only one example of reaction of PCDCs involving ammonium ylide can be found in the literature.

In 2012, Zhou et al. investigated the rhodium-catalyzed three-component reaction of dimethyl α-diazobenzylphosphonate 20a (or its para-substituted analogs), 2-bromoanilines and 4-nitrobenzaldehyde to give the mixture of the corresponding syn- and anti-α-amino-β-hydroxyethylphosphonates 256, as exemplified in Scheme 121. Example of Three-Component Reaction of PCDC 20, Anilines and Aromatic Aldehydes
The syn-diastereoisomer was the major component in each case. The screening of a series of rhodium- and copper chiral catalysts were also examined, establishing the optimal conditions as 2 mol% [Rh\(_2\)(S-PTAD)_4] in dichloromethane at 40 °C. The scope of the enantioselective reaction was examined for each component. The mechanistic hypothesis, involves the trapping of the Rh-carbene species A by aniline to afford the metal-bound ammonium ylide intermediate B/C. Subsequent nucleophilic addition of the intermediate to the aldehyde resulted in the formation of the final compound (Scheme 122). The high level of enantiocontrol observed provided evidence that the reaction proceed through a metal-bound stabilized ylide rather than a free ylide.

**Scheme 121. Example of Three-Component Reaction of PCDC 20, Anilines and Aromatic Aldehydes**
3.5.3. Thiocarbonyl Ylide

It is known that the reaction of diazo compounds with thiocarbonyl dipolarophiles leads to 2,4-dihydro-1,3,4-thiadiazoles, which offer a convenient access to reactive thiocarbonyl ylides.\(^2\) Analogously, 5a and 5c when reacted with diphenylmethanethione at low temperature gave 2,5-dihydro-1,3,4-thiadiazole-2-phosphonate 257a,c, which by nitrogen loss afforded the corresponding phosphonylated thiocarbonyl ylides 258a,c, as reactive intermediates (Scheme 123). Their reaction with the dipolarophile, still present in the reaction mixture, furnished the symmetrical 1,3-dithiolanes 259a,c. Two main differences of PCDCs when compared the analogous diazocarbonyl derivatives can be evidenced: their higher reactivity and their complete regioselectivity in the final [2+3]cycloaddition reaction.
The ylide 260 obtained by the reaction of diethyl diazomethylphosphonate 5c and the more reactive 9H-fluoren-9-thione in the absence of any intercepting agent dimerized regio- and stereoselectively to give exclusively 261 in 46% yield. Alternatively, 257 could be trapped by other dipolarophiles, such as the thioketones, S-methyl diisopropyl phosphonodithioformate and tetracyanoethane (Scheme 124).
3.6. Wolff Rearrangement

Since Wolff rearrangement is a specific 1,2-rearrangement of a diazo ketone, a PCDC to be able to undergo this transformation has to be characterized by the presence of a $\beta$-keto-$\alpha$-diazo phosphonate moiety. The rearrangements of PCDCs leading to the formation of the corresponding ketene, as the reactive intermediate, are usually initiated by thermolysis. The majority of the examples reported, describe the intramolecular capture of vinylketenes, generated by Wolff rearrangement, by a carbon nucleophile, resulting in a $6\pi$-electrocyclic benzannulation. In other cases, the capture is achieved by an internal nitrogen nucleophile, thus giving access to azacyclic derivatives.
Thermally induced Wolff rearrangement of a series of α-diazo-β-keto-γ,δ-alkenylphosphonate, such as \(262a\) was reported by Doutheau et al.\(^{206,207}\) The authors first demonstrated that the reaction outcome was not influenced by the double bond geometry of the substrate: cis-\(261a\) and trans-\(261a\), indeed, both furnished the naphthol \(265a\) in similar yield after the same reaction time. This behaviour could be explained according to the mechanism depicted in the Scheme 125: the cis-isomer can give rise to \(265a\) by direct electrocyclisation of the intermediate ketene cis-\(263a\) endowed with the requested stereochemistry. The trans-\(261a\), instead, would first afford the vinyl cyclobutenone \(264a\), which would reopen in either cis-\(263a\) or trans-\(263a\), and finally lead to product \(265a\). A different reactivity was observed in the case of the two geometric isomers of \(262b,c\). If the thermolysis of cis-\(262b,c\) gave the expected phenol \(265b,c\) in good yield, trans-\(262b,c\) were inactive under the same reaction conditions. Otherwise, the latter showed to be reactive in the presence of catalytic amount of rhodium(II) acetate, although the expected phenols \(265b,c\) could be not detected. For proving the formation of the intermediate dienylketenes trans-\(263,bc\) the reaction was repeated in the presence of methanol, thus obtaining the corresponding methyl esters \(266b,c\). These results evidenced that the presence of a methoxy group in vicinal position respect to the carbonyl group as in trans-\(262a\) plays a crucial role in the formation of the cyclobutenone intermediate \(264a\).
Thermolysis of PCDCs 267a-h, bearing a γ,δ-double bond as a part of an isoxazole ring afforded a series of 4-phosphono-5-hydroxy-fused isoxazoles 268a-h (Scheme 126). Since experimental evidences showed that the electrocyclization step was slower than the formation of the ketenes, the reaction was performed by heating a benzene solution of the substrate in a sealed vessel to accelerate the ring closure step.208
The thermal decomposition of PCDCs 269a-j allowed the study of the interaction between the ketene and a tertiary-amino moiety. The reaction outcome was strongly influenced by the nature of the substituent on the amino group. Indeed, PCDCs 269a-d, ortho-substituted by piperidine, pyrrolidine, perhydroazepine or unsaturated five-membered ring, gave the corresponding mesoionic compounds 273a-d derived through the attack of the nitrogen lone pair onto the ketene functionality, along with variable amounts of the stable ylides 272a-d. The decomposition of PCDC 269e yielded as a third component, the indolinone 274 as a result of a Stevens [1,2]shift of the ylide 269e. In the case of the substrate 269f, the ylide was not isolated in favor of its rearrangement-derived tricyclic
products 275 and 276. Otherwise, PCDC 269g bearing an ortho-diethylamino moiety afforded the mesionic compound 273g as the major product together with a small amount of the hydroxyindole 277 resulting by Hofmann elimination of the non-isolated ylide 272g. When the substrate was characterized by the presence on the nitrogen atom of a group endowed with a strong migratory aptitude, neither 272h,i nor 273h,i were isolated obtaining exclusively the indolinones 278h,i and 279h,i (Scheme 127).\textsuperscript{209,210}

Scheme 127. Tandem Wolff Rearrangement—"tert-Amino Effect"

![Scheme 127](image_url)

\textsuperscript{a} R\textsuperscript{1}, R\textsuperscript{2} = \text{-(CH\textsubscript{2})\textsubscript{3}}; \textbf{b}: R\textsuperscript{1}, R\textsuperscript{2} = \text{-(CH\textsubscript{2})\textsubscript{5}}; \textbf{c}: R\textsuperscript{1}, R\textsuperscript{2} = \text{-(CH\textsubscript{2})\textsubscript{3}CH=CH\textsubscript{2}}; \textbf{d}: R\textsuperscript{1}, R\textsuperscript{2} = \text{-(CH\textsubscript{2})\textsubscript{6}}; \\
\textbf{e}: R\textsuperscript{1}, R\textsuperscript{2} = \text{-(CH\textsubscript{2})\textsubscript{2}O(CH\textsubscript{2})\textsubscript{2}}; \textbf{f}: R\textsuperscript{1}, R\textsuperscript{2} = \text{-(CH\textsubscript{2})\textsubscript{2}CH=CH-(CH\textsubscript{2})\textsubscript{2}}; \textbf{g}: R\textsuperscript{1} = R\textsuperscript{2} = \text{Et}; \textbf{h}: R\textsuperscript{1} = \text{Me}, R\textsuperscript{2} = \text{allyl}; \textbf{i}: R\textsuperscript{1} = \text{Me}, R\textsuperscript{2} = \text{benzyl}
Extension of the tandem Wolff rearrangement-"α-cyclization of a tertiary amine" process to heterocyclic α-diazo-β-ketophosphonates allowed to prepare some pyran derivatives fused by pyridine or thiophene rings, but not by a furan ring.

A completely different reactivity was evidenced in the thermolysis of substrates 280a-f characterized by the presence a methylene linker between the nitrogen atom and the aromatic ring: the exclusive formation of 1H-2-benzopyran derivatives 283a-f was, indeed, obtained. The result could be rationalized by a three-step sequence involving: a) Wolff rearrangement with formation of the ketenes 281a-f, b) [1,5]hydride-shift giving access to the iminium enolates 282a-f, followed by c) final ring closure (Scheme 128). The thermolysis of dimethoxymethine-substituted PCDC 284 was also investigated. A different reactivity was in this case observed with 1,3-dimethoxy-4-dimethylphosphono-1H-2-benzopyran (285) obtained as the major product, along with a small amount of the indane derivative 286. Their formation was rationalized according to the mechanism depicted in the Scheme 129.

Scheme 128. Sequential Wolff Rearrangement, [1,5]Hydride-Shift and Cyclization
Scheme 129. Wolff Rearrangement-Initiated Cyclization of PCDC 284

When the Wolff rearrangement was thermally initiated in presence of a metal catalyst, the formation of the ketene showed to be in competition with an aromatic C-H insertion reaction. Thus, α-diazo-β-keto-γ,δ-alkenylphosphonates 287a-h, substituted at δ-position by an aryl group, reacted in refluxing benzene and in the presence of Rh₂(OAc)₄ to afford 288a-h and 289a-h in variable ratios depending on the substitution pattern at the γ,δ-double bond (Scheme 130).
The competition between Wolff rearrangement and C-H insertion reaction was further investigated in the rhodium-catalyzed thermolysis of δ-trialkylsilyloxy-substituted-α-diazo-β-ketophosphonates 290a-d (Scheme 131). Starting from PCDC 290a a hardly separable mixture of α-phosphono-γ-lactone 294a (17%) and 2-phosphonocyclopentenone 296 (37%) was obtained. The formation of the lactone 294a would derive from a Wolff rearrangement of the metallocarbene intermediate 291a to the corresponding ketene 292a, followed by the intramolecular nucleophilic attack of the ether-oxygen. Subsequent migration of the silyl group would give the silyl ketene acetal 293a, which can be further hydrolysed during aqueous work-up. On the contrary 296 would be the result of an intramolecular C5-H insertion reaction of the metallocarbene 291a. Under the same conditions, PCDCS 290b-d gave exclusively the lactones 294b-d, as mixtures of stereoisomers, suggesting that the Wolff rearrangement is the exclusive process when the C5-H bond is less accessible.
A tandem Wolff rearrangement/lactonization process was also exploited for the preparation of α-phosphono-γ-lactones 298a-c, starting from the corresponding δ-hydroxy-α-diazo-β-ketophosphonates 297a-c (Scheme 132). The ketenes, generated under either thermolytic or photolytic conditions, were trapped by the pendant hydroxy groups to give 298a-c in good to moderate yield. The lower yield observed with PCDCs 297a,b are due to competitive O-H intramolecular insertion reactions, which lead to the concomitant formation of the corresponding 3(2H)-furanones 299a,b.212

Alternatively, the insertion-derived compounds 299a,b were the only isolated product in the rhodium(II) acetate-catalyzed thermolysis of 297a,b. Interestingly, under these conditions, PCDC 297c gave still the tandem Wolff rearrangement/lactonization product 298c as the main product, probably due to steric issues which could retard the metallocarbenoid formation. However when Rh₂(tfa)₄, a more reactive, electrophilic rhodium catalyst, was used O-H insertion reaction was favoured affording the expected 3(2H)-furanone 299c in excellent yield. 212
The evidence that rhodium catalyst could promote the Wolff rearrangement of PCDCs, led Collomb and Doutheau to exploit this reaction for generating the vinylketene 301 from the corresponding PCDC 300 (Scheme 133). When exposed to enamine 304, the highly substituted phenol 303 was obtained in 84 % yield, as the result of a [4+2]cycloaddition followed by the elimination of pyrrolidine.213
3.7. 1,2-Hydride Shift Rearrangement

Along with Wolff rearrangement, 1,2-hydride shift (frequently referred to as β-hydride elimination) is the most common type of rearrangement encountered in PCDC chemistry. Although it can represent a competitive side reaction in other transformations involving PCDCs, 1,2-hydride shift rearrangement finds useful application in the synthesis of alkenylphosphonates. In comparison to other methods reported for the preparation of this class of compounds, the synthetic strategy involving PCDC chemistry is characterized by milder reaction conditions, higher yields and the use of easily accessible starting materials. Furthermore, 1,2-hydride shift rearrangement allows the access to trisubstituted alkenylphosphonates, a class of compounds whose synthetic methods are still limited. From the mechanistic point of view, the formation of the alkenylphosphonates derives from the putative metal-bound carbene intermediate within which the 1,2-hydride shift occurs (Scheme 134).

Barluenga et al. observed an unexpected β-hydride elimination during the copper(II)-catalyzed reaction of the vinyl diazophosphonate 305 with iodosylbenzene. Indeed, in contrast with the behaviour of vinylidiazocarbonyl compounds, instead of the expected oxodiazoo derivative 306, dimethyl
(1E)-3-oxoprop-1-enyl phosphonate (307) was obtained, due to an instantaneous β-H elimination within 306 itself (Scheme 135).\(^{214}\)

**Scheme 135. Copper(II)-catalyzed Reaction of Dimethyl α-Vinyl-α-Diazoarylphosphonate (305) with Iodosylbenzene**

\[
\text{Me}_2\text{PO}_3\text{N} = \text{CH} = \overset{\text{Ph}-\text{I}=\text{O}}{\text{Cu(OTf)}_2 (5 \text{ mol\%})} \xrightarrow{\text{CH}_3\text{CN, rt} \atop 68\%} \text{Me}_2\text{PO}_3\text{N} = \text{CH} = \overset{\text{OHC}}{\text{Me}_2\text{PO}_3} \xrightarrow{\text{CH}_3\text{CN, rt} \atop 68\%} \text{Me}_2\text{PO}_3\text{N} = \text{CH} = \overset{\text{OHC}}{\text{Me}_2\text{PO}_3}
\]

By copper powder catalysis the stereoselective conversion of the PCDCs 308 into the corresponding (E)-vinylphosphonates 309 was achieved (Scheme 136).\(^{71}\)

**Scheme 136. Conversion of α-diazoalkylphosphonates 161 into (E)-vinylphosphonates 308**

\[\text{R} = \text{aryl, heteroaryl, benzyl, vinyl}\]

In 2014, Cai *et al.* reported that 1,2-hydride migration and β,γ-dihydrogen shift reaction were competitive processes in the metal-catalyzed decomposition of amino acid-derived PCDCs 17a-e. (Scheme 137).\(^{215}\) The ratio of the three products (310/E-311/Z-311) was correlated with the catalyst employed and the use of iodine as co-catalyst. The product ratio was also influenced by the substrate’s structure with sterically demanding substituents favouring in most cases the β,γ-dihydrogen shift product.

**Scheme 137. 1,2-Hydride Migration vs β,γ-Dihydrogen Shift in the Metal-Catalyzed Decomposition**
The proposed reaction mechanism (Scheme 138) involves the initial formation of the metal carbene intermediate A which undergoes γ-hydrogen migration to afford the carbocation C (path a). Subsequently, the β-hydrogen $H^1$ is picked up by the copper catalyst and subsequent extrusion of the latter gives the final product 310a-e (path a). However, in the intermediate A the β-hydrogen $H^1$ could also migrate to the carbene center to form a carbocation intermediate D, which could be transformed to (Z)-311a-e and (E)-311a-e by 1,2-hydride migration and loss of catalyst (path b).

Scheme 138. Reaction Mechanism of the Metal-Catalyzed Decomposition of PCDCs 17a-e

Following the observation that in the absence of iodine β-aminoenylphosphonates 311a-e are exclusively obtained, the same research group focused on the optimization of the stereoselectivity between (Z) and (E) isomers. The mixture of AgOTf as the catalyst, NaBARF as the
additive, and methyl tert-butyl ether as the solvent was selected as catalytic system for exploring the scope of the reaction in terms of the impact of the substituents at the β-position as well as of the alkyl group at the phosphonate moiety on the (Z) and (E) isomeric ratio (Scheme 139). The authors demonstrated that the steric factors played a fundamental role in affecting the geometric isomerism aptitude in this carbene reaction which always gave a preponderance of the (Z)-stereoisomers.

Indeed, for the migration to occur, the migrating bond needs to be parallel to the $p$ orbital of the carbene carbon in the transitional states, the conformation B should be the disfavored one, because of steric hindrance between the phosphonate and $R_1^\text{t}$ groups. Thus, the β-hydrogen migration probably occurs via transition state A, which leads to the observed major Z-isomer. The ability of the catalyst to coordinate both phosphonate and phthalimide groups in the transition state A (and not in B) reinforces the explanation about the reaction course (Figure 7).

Scheme 139. AgOTf-Catalyzed β-Hydrogen Migration of PCDCs
Figure 7. Conformations Leading to the β-Hydrogen Migration

1,2-Hydride shift rearrangement is the last event in the palladium-mediated coupling reaction between α-aryl-α-diazomethylphosphonates 312 and benzyl or allyl halides leading to (E)-trisubstituted alkenylphosphonates 313 (Scheme 140).\textsuperscript{218}

Scheme 140. Synthesis of Alkenylphosphonates 312 through Palladium Carbene Coupling and 1,2-
Hydride Shift Rearrangement

The competition between 1,2-hydride and 1,2-aryl shift in the decomposition of β-pheny-β-(N-tosyl)amino-α-diazoethylphosphonates 65a was studied in details by Zhao et al.\textsuperscript{75} According to the catalytic system employed (transition metal catalyst, Lewis acid or TsOH) different product distribution were observed: the 1,2-aryl shift derived-products 315 predominated in all cases, however the 

\[ E:Z \] ratio varied under the different catalytic conditions. Most catalysts gave poor stereoselectivity, with the exception of TsOH, which afforded exclusively the Z-isomer 315, stabilized by the intramolecular hydrogen bonding (Scheme 141).

Scheme 141. Decomposition of 65a: 1,2-Hydride- vs 1,2-Aryl Shift

3.8. Reactions with Aldehydes and Ketones

The ability of PCDCs to act as nucleophiles in a base-promoted aldol-type addition with carbonyl compounds has been recognized very early. As far back as 1972, Regitz et al. reported the reaction
of dimethyl diazomethylphosphonate (5a) and diphenyl diazomethylphosphinoxide (2a) with a series of cyclic α-dicarbonyl derivatives furnishing the corresponding β-hydroxy-α-diazophosphono derivatives 316a-o (Scheme 142). Under anhydrous acidic conditions the diazoaldols 316a-o gave the corresponding ring-enlarged products 317a-o through the intermediate carbocations.

Scheme 142. Synthesis of β-Hydroxy-PCDCs 316a-o and the Corresponding Ring-Enlarged Products 317a-o

Shortly after, the application of this reaction to a series of aldehydes was reported (Scheme 143).

Scheme 143. Synthesis of β-Hydroxy-PCDCs 318

R¹ = alkyl, aryl, heteroaryl
Decomposition of the diazoaldols 318a-g, prepared as described above, in the presence of ethereal hydrochloric acid, afforded the corresponding (2-hydroxyvinyl)diphenylphosphinoxides 320b-g, as a consequence of migration of the R group in the carbocation intermediates 319b-g (Scheme 144). Otherwise, the diazoaldol 318a afforded, 1-(diphenylphosphoryl)acetone (322a) by a preferential H-migration pathway. By photolysis and copper-catalyzed thermolysis of 318b-g both R and hydride migrations were instead observed, obtaining mixtures of the corresponding 320b-g and 322b-g through the intermediates carbenes 321b-g.

Scheme 144. Decomposition of β-Hydroxy-α-diazo phosphinoxides 318a-g under acidic condition, photolysis and metal catalysis.

a: R = Me; b: R = 4-MeC₆H₄; c: R = Ph; d: R = 4-CNC₆H₄; e: R = 2-napthyl; f: R = 2-thienyl; g: R = CH=C-Ph
The decomposition in the presence of a Lewis acid was also explored. Thus, the treatment of the diazoaldols 318a-i with BF$_3$.Et$_2$O afforded the corresponding ethynylidiphenylphosphinoxides 325a-i in 45-71% yield. The mechanism of the reaction involves the initial formation of the betaines 323a-i, which by BF$_3$OH anion elimination, gave the vinyl diazonium salts 324a-i. Subsequent elimination of dinitrogen and proton led to the final alkynes 325a-i (Scheme 145).

Scheme 145. Boron Trifluoride Etherate-Catalyzed Decomposition of β-Hydroxy-α-diazophosphonoxides 318a-i

The nucleophilic addition of dimethyl α-diazomethylphosphonate (5a) to a series of 3-iminoisatin derivative 326 was recently reported by Wen et al.,$^{222}$ who exploited this reaction for the preparation of 3-amino-4-phosphono-2-quinolinones 328 (Scheme 146). The screening of various bases in different reaction conditions resulted in the selection of potassium carbonate in toluene as optimal system for the formation of the intermediates 327. The subsequent regioselective ring expansion reaction was then investigated under different acidic conditions, revealing salicylic acid as the most efficient catalyst. The reaction was finally conducted in telescoped conditions with excellent efficiency.

Scheme 146. Telescoped Synthesis of Multifunctionalized 3-Amino-4-dimethylphosphono-2-
3.9. Cycloaddition Reactions

As evidenced in the earlier section dedicated to cyclopropanation reactions, PCDCs are able to participate in cycloaddition reactions. However, there is another mode of cycloaddition in which PCDCs can act as 1,3-dipoles with either retention or loss of nitrogen moiety. The first possibility is the most common situation and involves the addition either to carbon-carbon double bond of activated or strained alkenes or to carbon-nitrogen double bond of imines. PCDCs can also react with the latter with loss of diazo nitrogen moiety giving the corresponding aziridines. Other examples of 1,3-dipolar cycloadditions with nitrogen losing will be reported at the end of this section.

3.9.1. Involving carbon-carbon double bond

The ability of PCDCs to act, in the absence of a catalyst, as 1,3-dipoles in [3+2] cycloaddition reactions has been recognized since their origins. In purely thermal conditions, diphenyl α-diazomethylphosphinoxide (2a) reacted with methyl vinyl ketone or dimethyl maleate to give the corresponding phospono-1-pyrazolines 329 and 330 (Figure 8), both isolated in 70 % yield, after crystallization of the crude from methanol.\textsuperscript{29}
Figure 8. Phosphono-1-Pyrazolines 329 and 330, obtained by Reaction of 2a with Methyl Vinyl Ketone or Dimethyl Maleate

Under the same thermal conditions, dimethyl α-diazoethylphosphonate (11a) and dimethyl α-diazobenzylphosphonate (11b) reacted with a series of activated dipolarophiles affording the corresponding phosphono-2-pyrazolines 331a,b-334a,b (Figure 9).\(^{38}\)

Figure 9. Phosphono-1-Pyrazolines 331-334, obtained by Reaction of PCDCs 11a and 11b with Different Dipolarophiles

Whereas no spectroscopic evidence supporting the structural assignment was provided by Kreutzkamp et al.,\(^{29}\) so that the correctness of the structural assignment cannot be assessed, IR and \(^1\)H NMR spectroscopic data for compounds 331-334 were reported.\(^{38}\) In 1968 Regitz et al.\(^{45}\) reported the synthesis of phosphono-2-pyrazolines by cycloaddition of diethyl diazobenzylphosphonate (20a) and its 4-nitro analog 20b with methyl vinyl ketone. In this case IR data supported the structural assignment.

By the early 70s, Callot et al. published a series of papers focused on the steric and electronic requirements of the cycloaddition between PCDCs and strained olefins, such as norbornene and norbornadiene. In all cases addition resulted in the exclusive formation of exo-1-pyrazolines. However, a different steric course of the reaction was observed when norbornene was reacted with either dimethyl α-diazoethylphosphonate (11a) or α-diazobenzylphosphonate (11b) in CH\(_2\)Cl\(_2\) at -50
°C. Indeed, syn- and anti-1-pyrazolines, 335a and 336, were formed using 11a, whereas the reaction of 11b resulted in the exclusive formation of anti-pyrazoline 335b (Figure 10).223 The same outcome was observed with norbornadiene.223

Figure 10. 3-Phosphono-1-pyrazolines from the Reaction of PCDCs 11a and 11b with Norbornene

\[ \text{335a,b} \]

\[ \text{336} \]

a: R = Me, 81% (335), 19% (336); b: R = Ph, 92% (335)

The authors confirmed this evidence in a more comprehensive publication reporting the study of the addition of fourteen different alkyl- and aryl-α-diazomethylphosphonates to norbornadiene.40 The anti/syn ratio, as reported in Figure 11, clearly indicated that in the case of α-alkyl-substituted diazomethylphosphonates the steric factors are those dominating in the cycloaddition. On the contrary, in the case of α-aromatic substituted PCDCs, electronic factors seem to play a major role. Under more drastic reaction conditions, 11b reacted with norbornadiene to give the corresponding exo-double phosphonopyrazolines.224 It is noteworthy that the configuration of the formed pyrazolines was determined by a detailed analysis of the $^1$H NMR spectra taking advantage from the reported vicinal $^{31}$P-C-C-$^1$H coupling constants and the stereospecific vicinal homoallylic $^5$J$_{PH}$ coupling constants.225 Up to the present Benezra’s papers still remain of substantial value in the poor scenario of spectroscopic data on phosphorus-containing compounds.
Figure 11. Steric Course of the Cycloaddition Reaction of PCDCs with Norbornadiene

![Steric Course Diagram](image)

Theis and coll.\(^{41}\) studied the competitiveness of the diene moiety and the diazo function of PCDCS 13a,b towards different cycloaddition partners. Dimethyl 1-diazo-5-phenyl-2,4-pentadienephosphonate (13a) or 1-diazo-5-methyl-2,4-pentadienephosphonate (13b) reacted with 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione (337) in dichloromethane at room temperature to give the corresponding Diels-Alder products 338a,b as confirmed by a detailed spectroscopic analysis (Scheme 147). The ability of 337 to act as a strong dienophile along with the electron-withdrawing properties of the phosphoryl group lay at the basis of the specificity of this reaction.

Scheme 147. Diels-Alder Reaction of PCDCs 13a,b with Dienophile 337

![Scheme 147](image)

A different outcome was observed for the reaction of 13a,b with dimethyl acetylenedicarboxylate (339), which gave exclusively the 1,3-dipolar cycloaddition products 342a,b. The authors postulated that the final compounds derived from the initial formation of the intermediate 3H-pyrazoles 340a,b, followed by a [1,5]-sigmatropic shift of the phosphoryl group. However, the isolation of
347a,b was not possible due most probably to solvolysis of the N/PO bond rapidly occurring in the presence of traces of water (Scheme 148). In the case of ω-phenyl substituted PCDC 13a, 3H-pyrazole 340 resulted so stable as to be isolated in 66% yield by stopping the reaction after 24 h.

Scheme 148. Cycloaddition Reactions of PCDCs 13a,b with Dimethyl Acetylendicarboxylate (339)

The diene/dienophile dual character of these PCDCs was evidenced by Theis et al., who by heating 13b in benzene obtained the pyrazole 344 deriving from the intramolecular [1,5]ring closure and subsequent H-shift (Scheme 149). Theis’s paper represents another valuable source of spectroscopic data.

Scheme 149. Intramolecular Cycloaddition of PCDC 13b

Under basic conditions, BOR (22) undergoes 1,3-dipolar cycloaddition reactions with double bonds conjugated with nitro, carbonyl, and nitrile groups thus affording the corresponding differently substituted phosphonopyrazoles. This research topic has been very prosperous and has
been recently reviewed. For this reason, only the work published after 2012 will be described here.

Kumar et al. exploited the dual reactivity of BOR (22) in a one-pot, telescoped transformation of aldehydes into phosphonopyrazoles. The synthetic protocol involves an initial step in which BOR (22) reacts with an aldehyde in the presence of an excess of Cs$_2$CO$_3$ in ethanol to generate a terminal acetylene. Then, another batch of 22, a strong base, such as KOH, and the catalyst copper(I) iodide were added with the aim to promote the cycloaddition step (Scheme 150). Under these optimized conditions a series of aryl- and heteroaryl-aldehydes were successfully converted into the corresponding phosphonopyrazoles in yields ranging from 50 to 80%. Although this work represents the first example of BOR (22) and alkynes, as partners in cycloaddition reaction, the reactivity of PCDCs towards triple bonds was already known, as mentioned above.

**Scheme 150. One-pot, Telescoped Transformation of Aldehydes into 3-Phosphonopyrazoles**

Later on Pramanik et al. extensively investigated the reactivity of 22 with a variety of ynones, as dipolarophiles, obtaining 3-carbonylpyrazole-3-phosphonates (Scheme 151). In this case, KOH in methanol proved to be the best base/solvent combination for this reaction. The substrate scope of the reaction was explored with aryl, heteroaryl or alkyl groups in the carbonyl part and either electron-donating, electron-withdrawing substituted-phenyls or TMS moiety in the aryl part. In all cases excellent yield for the corresponding phosphonopyrazoles was observed.
The use of the dipolarophile 348, as the starting material, allowed the evaluation of the relative reactivity of double vs triple bond. Under the optimized reaction conditions, the cycloaddition reaction with 22 afforded the phosphonopyrazole 350 as the sole reaction product (Scheme 152).

Scheme 152. Cycloaddition Reaction of BOR (22) with Ynone 348

BOR cycloaddition occurred exclusively at the double bond, whereas Michael addition of the methoxide ion is the preferred reaction on the triple bond.

Continuing along this path, Ahmad et al.235 proposed a domino process involving the reaction of α,β-unsaturated aldehydes with an excess of BOR (22) in the presence of KOH in methanol, for obtaining in one-step and very short reaction time the corresponding 4-sustituted-5-vinyl-3-phosphonopyrazoles 206 (Scheme 153). The reaction showed broad tolerance in the substituent pattern on the aldehyde. The proposed mechanism, as outlined in Scheme 154, involved the formation of pyrazoline carboxaldehyde 354, as the key intermediate. The authors assumed that diazomethyl anion 352, generated by methanolysis of BOR (22), added to the aldehyde affording pyrazoline carboxaldehyde...
The latter would then react with another molecule of 22, for generating the transient pyrazoline alkyne 355. The final compound would form from 355 by 1,3-hydrogen shift and subsequent aromatization.

Scheme 153. Synthesis of 5-Vinyl-3-Phosphonopyrazoles 351 by Domino Reaction of α,β-unsaturated aldehydes and BOR (22)

Scheme 154. Proposed Mechanism of the Domino Reaction of α,β-Unsaturated Aldehydes and BOR (22)

The potential synthetic application of this methodology was explored by synthesizing 358, a phosphorus-containing analog of the alkaloid whitasomnine. In particular, the phosphonopyrazole 357, obtained from 3-methoxycinnamaldehyde, was first N-allylated and then treated with Grubbs-II catalyst to afford 358 in 85% yield (Scheme 155).

Scheme 155. Synthesis of Fused Phosphonopyrazole 358
The utility of BOR (22) in cycloadditions was later extended to vinyl sulfones 359a-d, used as cycloaddition partners, for the preparation of the highly functionalized pyrazoles 360a-d (Scheme 156).236

Scheme 156. Synthesis of Phosphonopyrazoles 360a-d via Cycloaddition of BOR (22) to Vinyl Sulfonyle Carboxylates 359a-d

In 2015, Shelke et al. reported the one-pot construction of 3,3'-spirophosphonopyrazole-oxindole skeleton via base-mediated cycloaddition between diethyl 1-diazo-2-oxopropylylphosphonate (20d) and substituted methyleneindolinones 361 (Scheme 157).237

Scheme 157.1,3-Cycloaddition Reaction between Methyleneindolinones 361 and PCDC 20d
The assistance of air oxygen was necessary for obtaining the desired product: indeed, the corresponding phosphonopyrazoles were not formed carrying out the reaction in inert atmosphere. As confirmed by X-ray crystallography, the reaction proceeded with excellent regioselectivity with the carbon atom of the dipole adding exclusively to the carbon bearing the ester group, although the double bond was doubly activated. The scope of the reaction was further expanded by developing a multicomponent reaction sequence based on the domino Wittig reaction/cycloaddition. Thus, isatin derivatives 363a-d, phosphonium ylide 364 and 5a were reacted under the optimized reaction conditions to afford in good yields the tricyclic products 365a-d (Scheme 158).

Scheme 158. Sequential Multicomponent Reaction of Isatin, Phosphonium Ylide and 5a

![Diagram](image)

a: R = H, 82%; b: R = Cl, 79%; c: R = F, 75%; d: R = Br, 77%

The application of PCDCs such as BOR (22), has been widely explored for the preparation of phosphonopyrazoles. On the contrary, the possibility of achieving phosphonopyrazolines by the reaction of PCDCs with activated alkenes found fewer examples in the literature. In addition to the three papers from the '60s,29,45,38 discussed at the beginning of this section, Verma et al.230 reported that, the cycloaddition of BOR (22) to trisubstituted enones, such as 366a-f, could be “interrupted” at the pyrazolines stage (Table 4). Under the established reaction conditions (KOH in MeOH; method A) the yields of the pyrazolines 367a-f were moderate with the reaction remaining incomplete in some case. Alternative reaction conditions (K₂CO₃ in EtOH; method B) led to a substantial yield improvement. In all cases the resulting phosphonopyrazolines 367a-f were formed as a single diastereoisomer.
A more general method for the synthesis of functionalized phosphonopyrazolines was recently reported by Marinozzi et al. The procedure involves the microwave-assisted cycloaddition of diisopropyl diazomethylphosphonate (5b) to electron deficient alkenes, such as α,β-unsaturated nitriles 368a-d (Scheme 159) and esters 370a-i (Scheme 160), solventless. With electron-donating group-substituted dipolarophiles, such as 368b,c and 370b-e, a slight excess of 5b was necessary.
The 1,3-dipolar cycloaddition proceeded with complete regiocontrol, with the carbon atom of the
dipole attacking the beta carbon of the dipolarophile, with the exception of ethyl 4-oxo-4-phenyl-
but-2-enoate (370i), characterized by the presence of two different electron-withdrawing substitu-
ents, from which two regioisomeric phosphonopyrazolines 371i and 372i were obtained. A peculi-
arity of this work relies on the use of diazomethylphosphonate 5b instead of its precursor BOR (22).

With 5b basic conditions can be avoided, allowing the use of base-sensitive dipolarophiles, and ful-
filling completely the condition of atom economy. In addition to that, the dipolarophiles 370b-d
could be efficiently converted into the corresponding phosphonopyrazoles 373b-d by one-pot, two-
step protocol (cycloaddition and aromatic oxidation) as depicted in Scheme 161. The paper reported
X-ray diffraction and a detailed spectroscopic analysis as supports for the structural assignment of the products in terms of regioisomery, stereoisomery and tautomery.

**Scheme 161. One-pot, Two-step Conversion of α,β-Unsaturated Esters 370b-d into Phosphonopyrazoles 373b-d**

![Reaction Scheme](image)

b: R = Me, 85%; c: R = Et, 82%; d: R = Ph, 72%

In 2015, the first example of organocatalytic enantioselective 1,3-cycloaddition with a PCDC was reported. In particular Du et al. demonstrated that the reaction of dimethyl α-diazomethylphosphonate (5a) with a series of isatylidene malononitriles 374, in the presence of the cinchona alkaloid-derived catalyst 376, afforded the corresponding chiral spiro-phosphonopyrazolineoxindoles 375 in high yield and excellent enantioselectivity (Scheme 162). A great deal of work was devoted in optimizing the reaction conditions. The choice of the solvent, in particular, showed to play a crucial role in the reaction outcome in terms of yield (by contributing to the stability of the product during the prolonged reaction time), as well as of enantioselectivity (by modifying the preferred conformation of the catalyst in solution). The synthetic potentiality of this reaction was further expanded by the development of a convergent, three-component reaction based on a domino Knoevenagel condensation/1,3-dipolar cycloaddition sequence (Scheme 163). Compared with the two-component reaction, this strategy maintained the enantioselectivity level, albeit a slight yield decrease was observed. The very prolonged reaction times (4-9 days) at a low temperature (-60 °C) remain a limitation of this protocol.

**Scheme 162. Organocatalytic Enantioselective 1,3-Cycloaddition between 5a and Isatylidene**
The cycloaddition of diethyl diazomethylphosphonate (5c) to a carbon-nitrogen double bond was first reported by Bartnik et al., who exploited this reaction for the preparation of Δ²-1,2,3-triazolinyl-4-phosphonates 380a-d and aziridinyl-2-phosphonates 382a-d. Prolonged reaction of 5c with benzylidene-\(N\)-methylamine (379a) in methanol afforded (1-methyl-5-phenyl-4,5-dihydro-1H-[1,2,3]triazol-4-yl)phosphonic acid diethyl ester (380a) in 77% yield, as single diastereoisomer.
The trans disposition of the substituents was assigned according to the high value of the coupling constant between protons at C-4 and C-5. Similar results were obtained starting from the substrates 379b-d. All the attempts to prepare 1-aryl-1,2,3-triazoline or phosphonoaziridine by thermolysis or photolysis of the corresponding 1,2,3-triazolidine failed. The aziridines 382a-d were instead obtained in good yield by the unending reaction (15 days at room temperature) of 5c with the triaryl-1,3,5-triazines 381a-d used as precursors of the corresponding N-arylenamines (Scheme 164).

Scheme 164. Synthesis of Δ²-1,2,3-Triazolinyl-4-phosphonates 380a-d, and Aziridinyl-2-phosphonates 382a-d

In January 2016, Ahamad et al.\textsuperscript{240} published a paper reporting the first application of BOR (22) in the synthesis of phosphono-triazolines and -triazoles by a domino multicomponent reaction involving aldehydes and amines (Scheme 165). The authors showed that reacting an aldehyde, a primary...
amine, and BOR (22), in methanol at room temperature the corresponding trans-1,4,5-trisubstituted 1,2,3-triazoline 383 are obtained as almost exclusive single diastereoisomer.

Scheme 165. Synthesis of Dimethyl 1,2,3-Triazoline-4-phosphonates 383

The reaction’s outcome demonstrated that the Schiff base formation and the subsequent cycloaddition were faster than the unwanted aldehyde homologation. The reaction showed to be very broad in terms of both amine and aldehyde. During the evaluation of the reaction scope it was discovered that when starting from aromatic instead of aliphatic amines, spontaneous air oxidations of the initially formed triazolines occur affording phosphono-1,2,3-triazoles 384 (Scheme 166). However, due to the lower basicity of aromatic amines the addition of K₂CO₃, was necessary to get the products in reasonable yields. The generality of this strategy was also explored.

Scheme 166. Synthesis of Dimethyl 1,2,3-Triazole-4-phosphonates 384

Pellicciari et al.²⁴¹ prepared 3-substituted aziridine-2-phosphonates cis-386a-d and trans-386a-d by Lewis-acid catalyzed reaction of diisopropyl α-diazomethylphosphonate (5b) and N-benzylidene anilines 385a-d (Scheme 167). Optimization of the reaction conditions, performed on N-benzylidene
aniline (385a) as model substrate, showed zinc trifluoromethansulfonate as the best catalyst in terms of yield. The use of indium trifluoromethanesulfonate [In(OTf)₃] resulted in lower, but still acceptable yield and complete diastereoselectivity, with the cis-isomer 386a exclusively obtained. By selecting In(OTf)₃ as the catalyst of choice, the authors studied reaction of a series of 4-substituted N-(benzylidene)-1,1-diphenylmethanamines 385b-d.

**Scheme 167. Synthesis of cis- and trans-3-Substituted-Aziridine-2-Phosphonates 386a-d**

![Scheme 167](image)

- a: R = Ph, R¹ = H, cis only, 40%; b: R = CHPh₂, R¹ = H, 4/1 cis/trans only, 58% (cis), 19% (trans);
- c: R = CHPh₂, R¹ = Me, 4/1 cis/trans, 40% (cis), 16% (trans); d: R = CHPh₂, R¹ = AcO, 4/1 cis/trans, 68% (cis), 18% (trans);
- e: R = CHPh₂, R¹ = Cl, 6/1 cis/trans, 79% (cis), 12% (trans); f: R = CHPh₂, R¹ = CF₃, 2/1 cis/trans, 54% (cis), 28% (trans); g: R = CHPh₂, R¹ = NO₂, 2/1 cis/trans, 53% (cis), 27% (trans)

Phosphonoaziridine cis-386d was used as starting material for the preparation of [1-amino-2-(4-hydroxyphenyl)ethyl]phosphonic acid hydrochloride (387), the phosphonic acid analog of tyrosine (Scheme 168).

**Scheme 168. Synthesis of [1-Amino-2-(4-hydroxyphenyl)ethyl]phosphonic Acid Hydrochloride (±)-387**

![Scheme 168](image)

The synthesis of 3-acylaziridine-2-phosphonates was recently realized via ruthenium-catalyzed three-component reaction involving dimethyl α-diazoethylphosphonate (5a), a nitrosoarene and
an alkyne (Scheme 169). The optimization of the reaction conditions, already performed in analogous reactions with diazocarbonyl reagents, had evidenced [Ru(p-Cl-TPP)CO] \((H_2-p-Cl-TPP = mesotetrakis(4-chlorophenyl)porphyrin)\) as the best catalyst in terms of yield and diastereoselectivity. A series of 3-acylaziridine-2-phosphonates 388a-i were obtained in good to high yield, except when ethynyl(trimethyl)silane was used as starting material. Excellent diastereoselectivity in favor of the \textit{trans} isomer was always observed. The mechanistic hypothesis as reported by the authors is depicted in the Scheme 170: the nitrene intermediate \textbf{II}, generated by the trapping of ruthenium-carbene complex \textbf{I} by nitrosoarene, undergoes 1,3-dipolar cycloaddition with alkyne to give isoxazoline \textbf{III}, which rapidly rearranges to the corresponding aziridine 388.

**Scheme 169. Synthesis of 3-Acylaziridine-2-Phosphonates 388a-i by Multicomponent Reaction**

![Scheme 169](image)

\(\text{R} = \text{H}, \text{R}^1 = \text{C}(\text{CH}_3)_2\text{OH}, 98\%\), 91:9 \(\text{dr}\); b: \(\text{R} = \text{H}, \text{R}^1 = \text{CH}_2\text{OH}, 95\%\), 90:10 \(\text{dr}\); c: \(\text{R} = \text{H}, \text{R}^1 = \text{CH}_2\text{Cl}, 87\%\), 92:8 \(\text{dr}\); d: \(\text{R} = \text{H}, \text{R}^1 = \text{CH}_3\text{Br}, 85\%\), 92:9 \(\text{dr}\); e: \(\text{R} = \text{H}, \text{R}^1 = \text{Si}(\text{CH}_3)_3, 45\%\), >99:1 \(\text{dr}\); f: \(\text{R} = \text{H}, \text{R}^1 = (\text{CH}_3)_2\text{CH}_3, 77\%\), >99:1 \(\text{dr}\); g: \(\text{R} = \text{H}, \text{R}^1 = \text{C}_2\text{H}_5, 78\%\), >99:1 \(\text{dr}\); h: \(\text{R} = \text{Cl}, \text{R}^1 = \text{C}(\text{CH}_3)_2\text{OH}, 85\%\), 90:10 \(\text{dr}\);

\(i: \text{R} = \text{CH}_3, \text{R}^1 = \text{C}(\text{CH}_3)_2\text{OH}, 94\%\), 90:10 \(\text{dr}\)

**Scheme 170. Proposed Mechanism of the Three-Component Reaction of Dimethyl \(\alpha\)-Diazomethylphosphonate (5a), Nitrosoarene and Alkyne**

![Scheme 170](image)
3.9.3. Other 1,3-Dipolar Cycloaddition Involving Loss of the Diazo Nitrogen Moiety

Carbenoids derived from the metal-catalyzed decomposition of α-acyl-α-diazomethylphosphonates add to multiple bonds with participation of both carbenic carbon and carbonyl oxygen to generate five-membered, phosphonate-substituted-heterocycles. In this cycloaddition mode loss of the nitrogen moiety occurs.

According to Gong’s paper diethyl 1-diazo-2-oxoalkylphosphonates 20d,e and 59 reacted with a series of alkyl vinyl ethers in the presence of rhodium(II) acetate to afford the corresponding 3-phosphoryl-2,3-dihydrofurans 389a-g in very good yield apart in the cases of 389d,e (Scheme 171), which were formed less efficiently most probably due to electronic and steric effects of the phenyl group on the carbonyl moiety in the corresponding starting material 20e.

Scheme 171. Synthesis of Diethyl 2,5-Disustituted-2,3-dihydrofuran-3-phosphonates 389a-g
In similar fashion, PCDCs 20d-f and 390 reacted with aromatic nitriles giving 5-substituted-2-aryl-1,3-oxazol-4-phosphonates 391a-g (Scheme 172). The reactions of 20e resulted also in this case in lower yields, whereas 390 showed to be unreactive. Aliphatic nitriles proved to be not suitable substrates for this type of reactions.243

Scheme 172. Synthesis of Diethyl 2,5-Disubstituted-1,3-Oxazol-4-Phosphonates 391a-g

As part of a work devoted to the synthesis of functionalized pyrrole derivatives by the gold-catalyzed reaction of nitriles with alkenyldiazo compounds, Lonzi et al. reported the synthesis of diethyl (2-phenyl-1H-pyrrol-3-yl)phosphonate (392), (Scheme 173).244
Scheme 173. Synthesis of Diethyl (2-Phenyl-1H-pyrrol-3-yl)phosphonate (392).

The result of the [3+2]cycloaddition was rationalized according to the mechanistic proposal depicted in the Scheme 174. The gold alkenyl carbenoid A, initially formed by the reaction of the α-vinyl-α-diazomethylphosphonate with the catalyst, can be better described as an allyl gold cation B. The latter undergoes the regioselective nucleophilic attack of the nitrile to afford the intermediate C, which by cyclization furnishes D. Final tautomerization gives the pyrrole 392.

Scheme 174. Proposed Mechanism for the Au(I)-Catalyzed Synthesis of Pyrrole Derivative 392

4. Concluding Remarks

More than half century has passed since the first mention of a PCDC was reported. Within this time two PCDCs, dimethyl α-diazomethylphosphonate (Seyferth-Gilbert reagent) and dimethyl 1-diazo-
2-oxopropylphosphonate (Bestmann-Ohira reagent), in particular, have become a valuable tool for preparing a vast array of different phosphonate-functionalized molecules, thanks to the quite exceptional flexibility of the diazo moiety. The past 10 years have been the most productive in the use of PCDC chemistry and new applications, such as those in metal-catalyzed cross-coupling reactions, have been emerged besides the most common ones, insertion reactions, cyclopropanation and Wolff rearrangement. Several recent examples have been shown their involvement in multicomponent, domino- or telescoped reactions. Nowadays the availability of different methods for their straightforward preparation from easily accessible starting materials has certainly contributed to their increased use in organic synthesis. Although PCDC chemistry had made great strides, it has received very little attention if compared to that of α-diazocarbonyl compounds. As an example, enantioselective PCDC reactions still represent an almost unexplored research field that might be highly rewarding. In our opinion the lacking of collective papers dedicated to the chemistry of PCDCs has been partially contributed to relegate PCDCs to specialized niches. We are hopeful that this review could provide a practical framework to facilitate the emergence of PCDC in the modern preparation of different classes of phosphorus-containing compounds, which found numerous biological and pharmaceutical applications.

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The Authors declare no competing financial interest

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**Fabrizio Pertusati** received his MSc in Chemistry in 1999 from the University of Turin and his Ph.D. in asymmetric Organic Chemistry in 2005 at the Cardiff University. After postdoctoral experiences at Emory University with Professor Fredric Menger (surfactant chemistry) and in the laboratories of Nobel Laureate, Professor George Olah at the Loker Hydrocarbon Institute (fluorine and boron chemistry), he is now a Life Science Research Network Wales post-doctoral fellow at the School of Pharmacy of Cardiff University. His current research involves the development of a diastereoselective synthesis of phosphoroamidate prodrugs of nucleoside analogues. His research interests include the discovery of novel antiviral, anticancer, and neurodegenerative diseases-related agents based on rational drug design.

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ABBREVIATIONS

acac       acetylacetonate
BARF       tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
biTISP     (2S,2'S),(5R,5'R)-5,5'-(1,3-phenylene)bis(1-(2,4,6-triisopropylbenzenesulfonyl)
           prolinate
Bn         benzyl
Boc        (tert-butyloxy)carbonyl
BOR        Bestmann-Ohira reagent
BOX        bisoxazoline
Bz         benzoyl
Cbz        carboxybenzyl
Cp         pentamethyl cyclopentadiene
CPME  cyclopentyl, methyl ether
CSA  chlorosulfonic acid
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DCE  1,2-dichloroethane
de  diastereomeric excess
DIBAL-H diisobutylaluminium hydride
dr  diastereomer ratio
DOSP dodecylbenzenesulfonyl prolinate
EDA  ethyl diazoacetate
ee  enantiomeric excess
esp  $\alpha, \alpha, \alpha', \alpha'$-tetramethyl-1,3-benzenedipropionate
GC-MS  gas chromatography- mass spectrometry
hfba  heptfluorobutyramide
IR  infrared (spectroscopy)
HWE  Horner-Wadsworth-Emmons
EWG  electron-withdrawing group
LDA  lithium diisopropylamide
MOM  methoxymethyl
MTBE  methyl, tert-butyl ether
NaBArF sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
NMR  nuclear magnetic resonance (spectroscopy)
NTTL  $N$-(1,8-naphthaloyl)-tert-leucinate
oct  octanoate
$p$-ABSA  $p$-acetamidobenzensulfonyl azide
PCDC  phosphorous-containing α-diazo compounds
piv  pivalate
PG  protective group
PMB  p-methoxybenzyl
PTAD  1-adamantyl-N-phthalimidoacetate
PTTL  N-phthaloyl-tert-leucinate
rt  room temperature
TBAF  tetrabutyl ammonium fluoride
TBS  tert-butyldimethylsilyl
THF  tetrahydrofuran
Tf  trifluoromethanesulfonyl
TMSOTf  trimethylsilyl trifluoromethanesulfonate
TPFPP  tetra(pentafluorophenyl) porphyrin
TPP  tetraphenylporphyrin
Ts  4-toluenesulfonyl
TsNIK  N-ido-p-toluenesulfonamide

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