# $\lambda^5$-Phosphorus-Containing α-Diazo Compounds (PCDCs): a Valuable Tool for Accessing Phosphorus-Functionalized Molecules

Maura Marinozzi,[a,*] Fabrizio Pertusati[b] and Michaela Serpi[b]

[a] *Dipartimento di Scienze Farmaceutiche, Università degli Studi di Perugia, Via del Liceo 1, 06123 Perugia, Italy*

[b] *School of Pharmacy anc Pharmaceutical Sciences, Cardiff University, King Edwad VII avenue, Cardiff CF10 3NB, UK*

**Abstract**

The compounds characterized by the presence of a $\lambda^5$-phosphorus functionality at the α-position with respect to the diazo moiety, here referred to as $\lambda^5$-phosphorus-containing α-diazo compounds (PCDCs), represent a vast class of extremely versatile reagents in organic chemistry and are particulary 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.

**CONTENTS**

## 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

$\lambda^3$- and $\lambda^5$-phosphorus-containing α-diazo compounds. In contrast with the widely studied and synthetically exploited α-diazocarbonyl compounds,[1,2,3] 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 $\lambda^5$-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 sulfate[15] 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.[20,21,22,23] The use of phosphonic acids in coordination chemistry has been recently reviewed.[24] Another feature of the organophosphonates, is their ability to be easily converted to other functional groups through the Horner–Wadsworth–Emmons (HWE) reaction.[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,[27] a short paragraph in a book chapter,[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 literarure 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 α-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 α-substituted PCDCs **B**; and c) the availability of the required starting material. Thus, α-diazomethyl-phosphonates and -phosphinoxides **A** are prepared either by diazotization of the corresponding primary amines **C** or by deformylating diazo-transfer reactions, after *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 α-position with an activating $R^1$ group, can be efficiently obtained by direct diazo transfer reaction starting from **F**. Bamford-Stevens-type elimination of α-ketophosphonates **G** is the method of choice when the group $R^1$ is not activating enough for direct diazo transfer and/or the precursor α-ketophosphonate **G** is easily available. α-Alkyl- and α-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 α-functionalized-PCDCs. This particular aspect will be discussed in section 3.8.

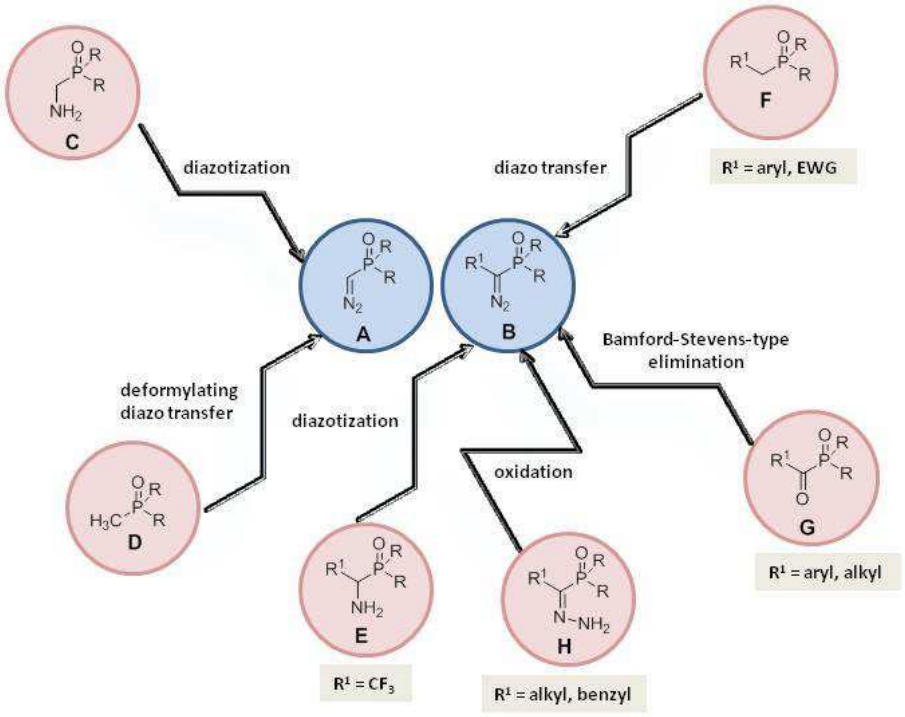
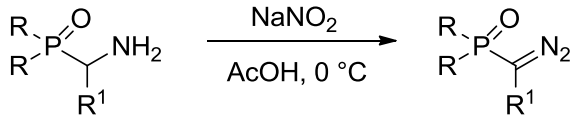



**Figure 1. Common Approaches to PCDCs**

## 2.1. Diazotization

The first PCDC reported in the literature in 1961 is the diphenyl α-diazobenzylphosphinoxide (**2a**), which was prepared by Horner *et al*.[4] by diazotization of diphenyl α-aminobenzylphosphinoxide (**1a**) with sodium nitrite in acidic conditions. α-Diazomethylphosphinoxides **2b** and **2c** were synthesized few years later by Kreutzkamp *et al*. following the same methodology (Scheme 1).[29]

**Scheme 1. Synthesis of α-Diazomethylphosphinoxides 2a-c**

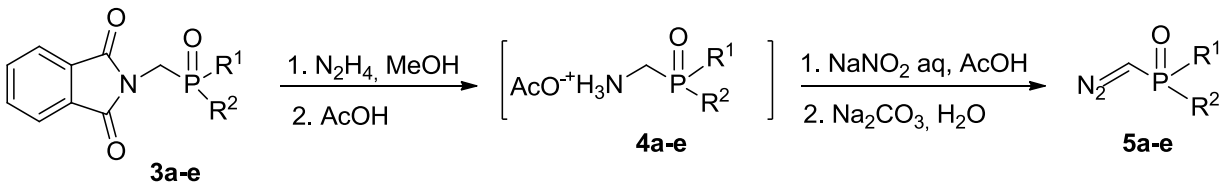



**1a-c** **2a-c**

a: R = $R^1$ = Ph, yield not reported; b: R = Ph, $R^1$ = H, 70%; c: R = $PhCH_2$, $R^1$ = H, 90%

In 1970, Seyferth[6,30] reported the preparation of the dimethyl α-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 α-diazomethylphosphonate (**5c**),[31] diphenyl α-diazomethylphosphinoxide (**5d**), and methyl α-phenyl-α-diazomethylphosphinate (**5e**) in 51%, 45 % and 16% yield, respectively.[32,33] This protocol was also applied by Marinozzi *et al*.[34] to the multigram scale synthesis of the diisopropyl analog **5b**. Recently some dialkyl aminomethylphosphonates became commercial available, thus simplifying this synthetic protocol.

**Scheme 2. Syntheses of Dialkyl α-Diazomethyl-Phosphonates, Phosphinates and –Phosphinoxides 5a-e**

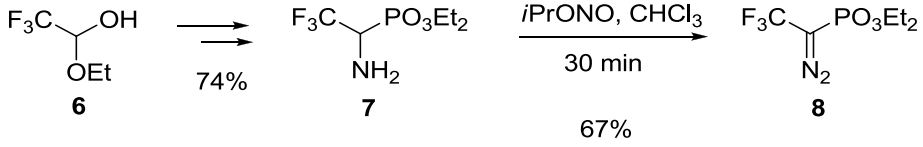



**3a-e** **4a-e** **5a-e**

a: $R^1$ = $R^2$ = OMe, 46%; b: $R^1$ = $R^2$ = O*i*Pr; 70%; c: $R^1$ = $R^2$ = OEt; 51%; d: $R^1$ = $R^2$ = Ph, 45%;
e: $R^1$ = Ph, $R^2$ = OMe, 16%

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.[35] 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**.[36,37] Both the procedures proved to be equally efficient and applicable to the multi-gram scale synthesis of **8**.

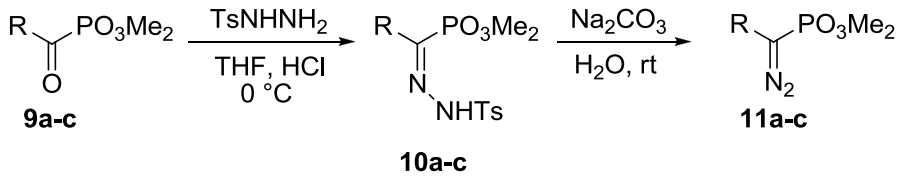
**Scheme 3. Synthesis of Diethyl 1-Diazo-2,2,2-trifluoroethylphosphonate (8)**




**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**).[38,30]

**Scheme 4. Synthesis of α-Substituted Dimethyl α-Diazomethylphosphonates 11a-c**

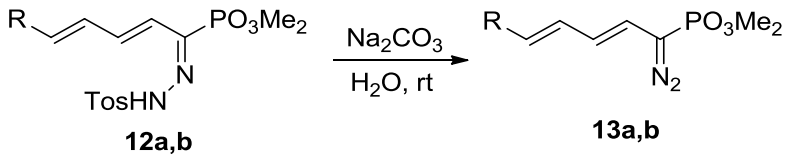



a: R = Me, 55%; b: R = Ph, 93%; c: R = 3,5-$(MeO)_2C_6H_3$, 90%

Following an analogous protocol, Gurudata *et al.* prepared a large series of dimethyl α-aryl-, α-alkyl-, α-cycloalkyl- and α-vinyl-α-diazomethylphosphonates.[39,40]

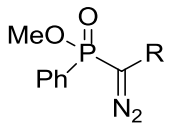
The alkaline cleavage of the *p*-toluenesulfonylhydrazones **12a,b** allowed them to get the corresponding conjugated 1,3-diene unit-containing α-diazomethylphosphonates **13a,b** (Scheme 5).[41]

**Scheme 5. Synthesis of Dimethyl α-Diazo-5-phenyl-2,4-pentadienephosphonate (13a) and α-Diazo-2,4-hexadienephosphonate (13b)**




a: R = Ph, 86%; b: R = Me, 84%

By Bamford-Stevens-type elimination, α-diazomethylphoshinic esters **14** were also prepared (Figure 2).[33]



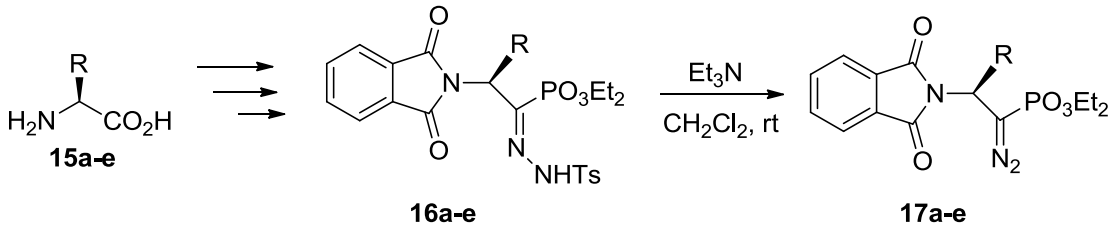

**14**

R = $C_6H_5$, 4-$ClC_6H_4$, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, $CH_3$, $C_6H_5CH_2$, $CH_2$=$CHCH_2$, $(CH_3)_2CCH$

**Figure 2. Examples of α-Diazomethylphoshinic Esters Prepared by Bamford-Stevens-type Elimination**

Recently, Cai *et al*.[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 $Et_3N$ in dichloromethane (Scheme 6).

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




a: R = $CH_3$, 42%; b: R = $CH_2Ph$, 47%; c: R = *i*Pr, 46%; d: R = $CH_2CH(CH_3)_2$, 46%; e: R = H, 11%
yields calculated from **15**

**2.3. Diazo Transfer Reactions**

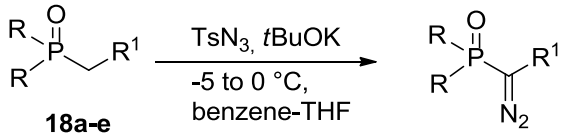
As in the case of α-diazocarbonyl compounds,[2,1] diazo transfer to the α-methylene position of a phosphoryl group requires the presence of an azide and a base of appropriate strength to deprotonate the substrate. Thus, on the basis of the substrate acidity, we will consider simple diazo transfer reactions on substrates characterized by the presence of a sufficiently reactive α-methylene

(2.3.1), or deformylating diazo transfer reactions when a prior substrate activation is necessary (2.3.2).

### 2.3.1. Simple Diazo Transfer Reactions

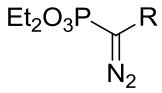
The diazo transfer protocol was first applied to the synthesis of PCDCs in 1967 by Petzold and Henning,[43] who prepared PCDCs **19a-e** from **18a-e** using potassium *tert*-butoxide and tosyl azide as base and diazo donor reagent, respectively (Scheme 7).

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



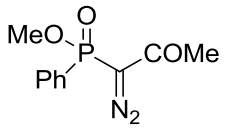

a: R = Ph, $R^1$ = COPh, 65%; b: R = Ph, $R^1$ = $CO_2$Et, 60%; c: R = PhO, $R^1$ = $CO_2$Et, 65%;
d: R = Ph, $R^1$ = $POPh_2$, 14%; e: R = $R^1$ = Ph, 25%

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).[44,45] Potassium *tert*-butoxide in benzene/THF was also used for the preparation of α-diazophoshinic esters **21a-d** (Figure 3).[33]



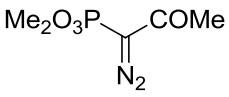
**20a-f**

a: R = Ph, 24%; b: R = 4-$NO_2C_6H_4$, 35%; c: R = 4-$CNC_6H_4$, 60%;
d: R = COMe, 78%; e: R = COPh, 18%; f: R = $PO_3Et_2$, 37%



**21a-d**

a: R = Me, 31%; b: R = Ph, 42%; c: R = 4-$MeC_6H_4$, 44%;
d: R = OMe, 43%



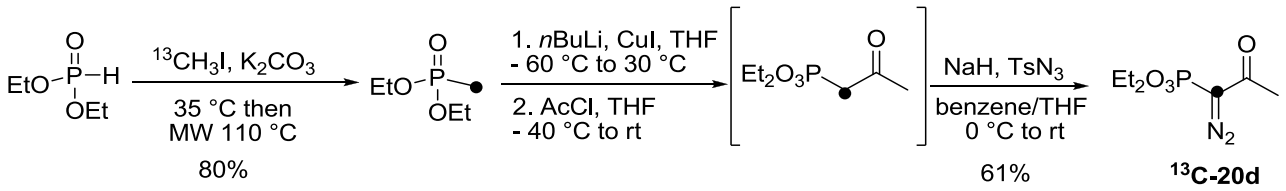
**22**

**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.[46] 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 (*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, *t*BuOK or $Et_3N$ in benzene and THF.[47] The use of polymer-supported tosyl azides has been also reported. Recently, an alternative route for the preparation of α-aryl α-diazomethylphosphonates was also disclosed (see section 2.5).

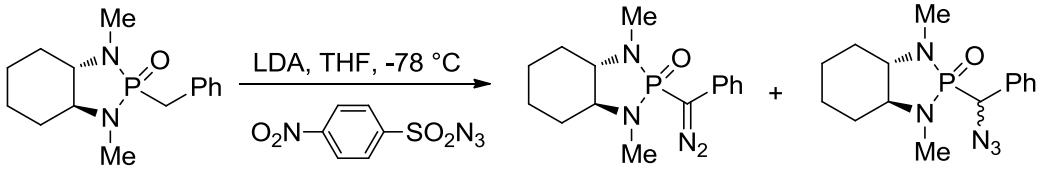
In 2011, the preparation of $^{13}C$-labelled **20d** was also reported (Scheme 8).[48] The diazo transfer step was performed in benzene/THF using sodium hydride as the base and tosyl azide as donor.

**Scheme 8**. **Synthesis of [$^{13}C_2$]-Diethyl (1-Diazo-2-oxopropyl)phosphonate ($^{13}$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]

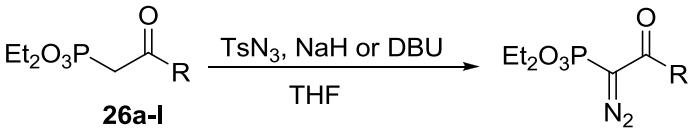
**Scheme 9**. **Synthesis of (3a*S*,7a*S*)-2-Diazobenzyl-1,3,3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1*H*-1,3,2$\lambda^5$-benzodiazaphosphole-2-oxide (24)**




**23** **24,** 31% **25**

Sodium hydride or DBU in THF were instead used for the preparation of α-diazo-α-(diethoxyphosphoryl)-acetates **27a,b** and -acetamides **27c-l** (Scheme 10).[50]

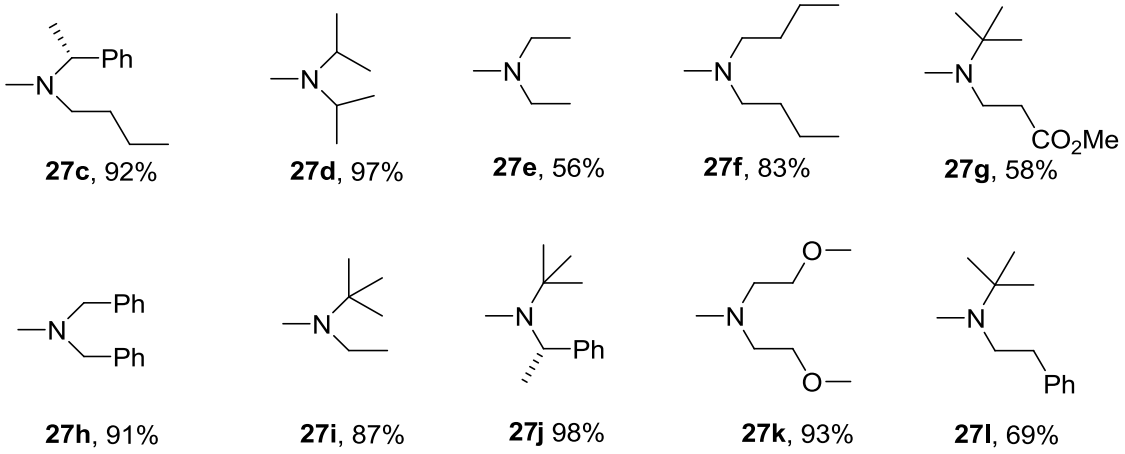
**Scheme 10. Synthesis of Diethyl α-Diazophosphono-Acetates and –Acetamides 27a-l**




**26a-l** **27a-l**

a: R = O*n*Pr, 81%; b: R = O*i*Bu, 77%

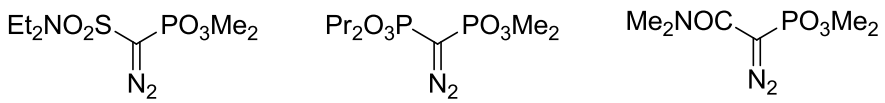
R =




**27c**, 92% **27d**, 97% **27e**, 56% **27f**, 83% **27g**, 58%

**27h**, 91% **27i**, 87% **27j** 98% **27k**, 93% **27l**, 69%

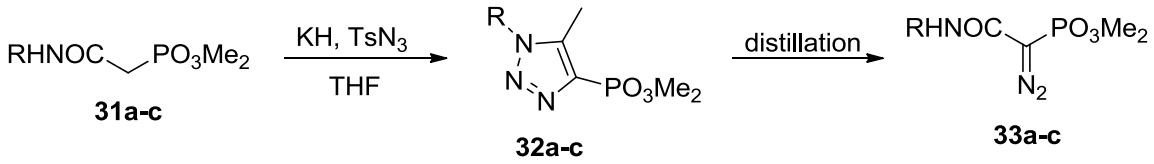
PCDCs **28**-**30** were obtained in excellent yield by treating the corresponding compounds that have an activate methylene group with potassium hydride and $TsN_3$ in THF (Figure 4).[51] However, the same reaction conditions applied to the secondary amides **31a**-**c** led to the corresponding hydroxytriazoles **32a**-**c**, which were converted to the tautomeric PCDCs **33a**-**c** during distillation under reduced pressure (Scheme 11).[51]




**28** **29** **30**

**Figure 4. Examples of PCDCs Obtained by Diazo Transfer Protocol**

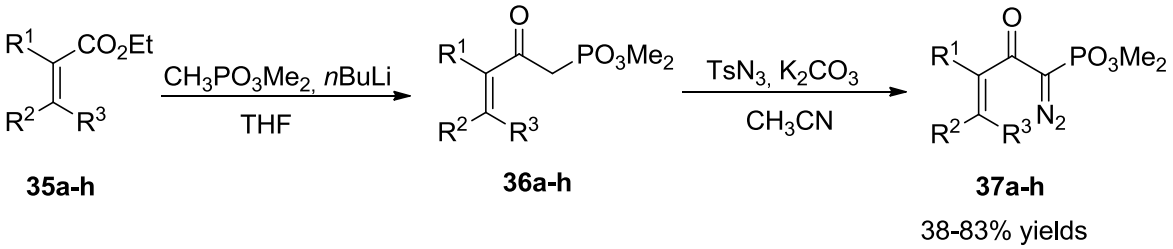
**Scheme 11**. **Synthesis of Dimethyl α-Carboxamido-α-diazomethylphosphonates 33a-c**




a: R = *i*Pr; b: R = c-$C_6H_{11}$; c: R = $CH_2Ph$

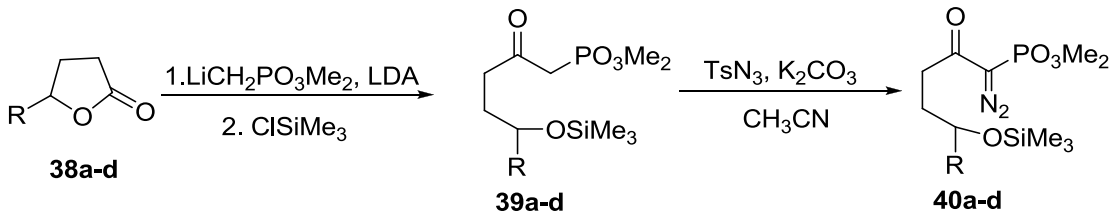
Collomb *et al*.[52] reported the preparation of a series of α-diazo-β-keto-δ-aryl-γ,δ-alkenylphosphonates **37a-h** in overall yields (from **35a-h**) ranging from 38% to 83%, using the combination $TsN_3/K_2CO_3/CH_3CN$ (Scheme 12). The same reaction conditions were applied by Dayoub *et al*.[53] for the synthesis of α-diazo-β-ketoalkylphosphonates **40a-d** starting from γ-lactones **38a-d** (Scheme 13).

**Scheme 12**. **Synthesis of β-Keto-γ,δ-alkenyl-δ-aryl-α-diazophosphonates 37a-h**




a: $R^1$ = $R^2$ = H, $R^3$ = Ph; b: $R^1$ = H, $R^2$ = $R^3$ = Ph; c: $R^1$ = H, $R^2$ = $R^3$ = 4-MeO-$C_6H_4$;
d: $R^1$ = H, $R^2$ = $R^3$ = 4-Cl-$C_6H_4$; e: $R^1$ = H, $R^2$ = Me, $R^3$ = Ph; f: $R^1$ = H, $R^2$ = $CF_3$, $R^3$ = Ph
g: $R^1$ = F, $R^2$ = H, $R^3$ = Ph; h: $R^1$ = H, $R^2$ = $R^3$ = 2,2'-biphenyl

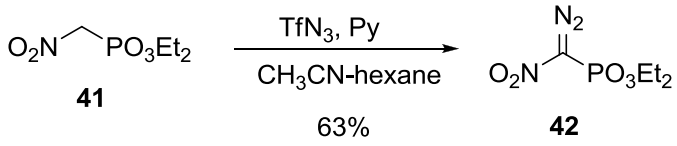
**Scheme 13. Synthesis of β-Keto-α-diazoalkylphosphonates 40a-d**




a: R = H, 63%; b: R = Me, 81%; c: R = Et, 71%; d: R = $C_6H_{13}$, 82%

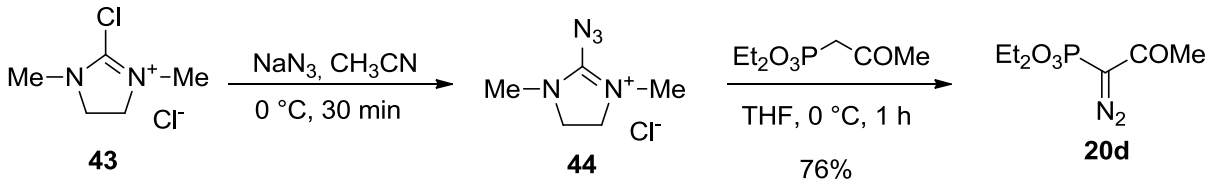
Despite the fact that tosyl azide is well known to present some safety issues,[54] it remains the most used diazo donor for activated methylene compounds on a laboratory scale. However, as a valid alternative, numerous sulfonyl azides have been developed for the synthesis of PCDCs. These azides were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

**Scheme 14. Synthesis of Diethyl [Nitro(diazo)methyl]phosphonate (42)**




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 *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).[60]

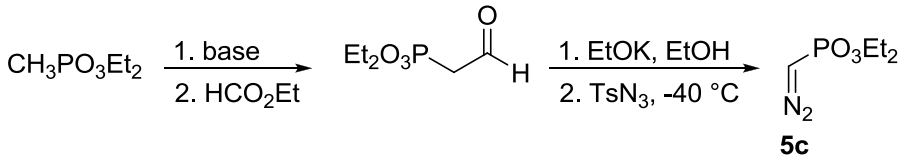
**Scheme 15. Synthesis of Diethyl (1-Diazo-2-oxopropyl)phosphonate (20d)**




### 2.3.2. Deformylating Diazo Transfer 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*.[61] 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).

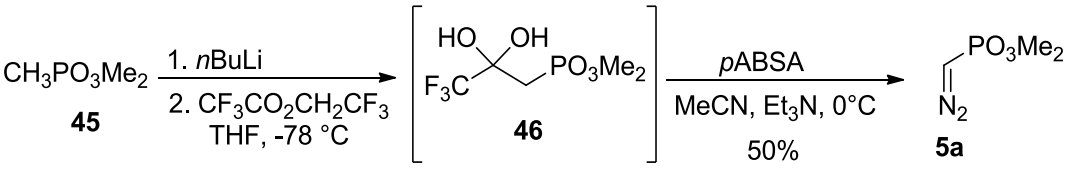
**Scheme 16**. **Synthesis of Diethyl α-Diazomethylphosphonate (5c) by Deformylating Diazo Transfer Reaction**




Following an extension of the Regitz concept, Brown *et al*.[62] 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 methylphoshonate (**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 trifluoroacyl group spontaneously occurred leading to the formation of **5a** in 50 % overall yield.

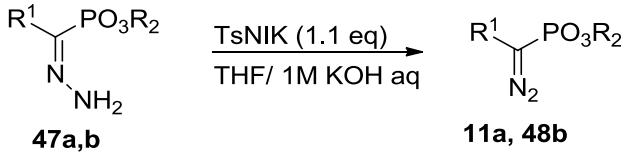
**Scheme 17**. **Synthesis of Dimethyl α-Diazomethylphosphonate (5a) by Detrifluoroacylating Diazo Transfer Reaction**




**2.4. Hydrazone Oxidation**

Nicolle and Moody[63] recently reported an alternative preparation of dimethyl α-diazoethylphosphonate (**11a**) and diethyl α-benzyl-α-diazomethylphosphonate (**48b**) through oxidation of the corresponding hydrazones by potassium *N*-iodo *p*-toluenesulfonylamide (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**




**47a,b** **11a, 48b**

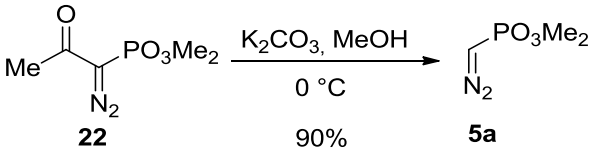
a: R = $R^1$ = Me, 56%; b: R = Et; $R^1$ = $CH_2Ph$, 94%

### 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)**




**22** **5a**

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 **22** and **20d** are employed as *in situ*-precursors of **5a** and **5c**, respectively.

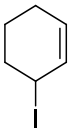
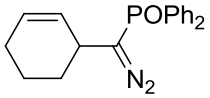
More complex modifications of the PCDS involve the substitution of the hydrogen atom by electrophilic reagents, the palladium-catalyzed C-C coupling at the diazo carbon atom or aldol-type C-C coupling of terminal PCDCs with imines.

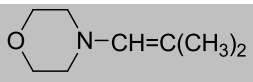
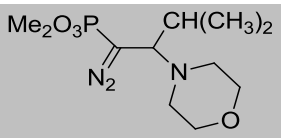
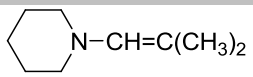
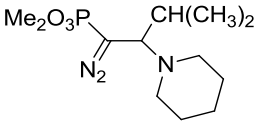
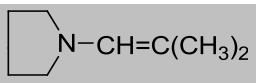
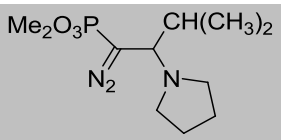
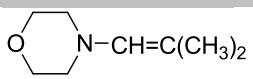
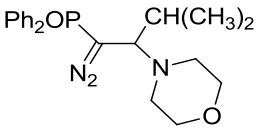
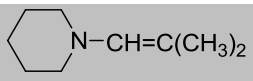
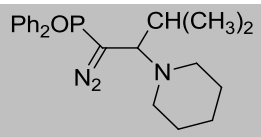
### 2.5.1. C-C Coupling of Terminal PCDC with Electrophiles

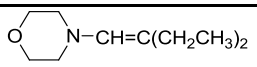
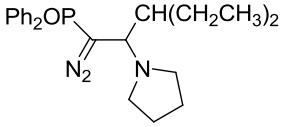
In the '70s Regitz's group published some papers reporting the substitution of the α-hydrogen of dimethyl α-diazomethylphosphonate (**5a**) and diphenyl α-diazomethylphosphinoxide (**2b**) by electrophilic reagents.[66,67,68,33] α-Halo- and α-alkylated PCDCs were thus prepared *via* silver or mercury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

**Table 1**. **α-Substitution Reaction of PCDCs 5a and 2b**

| Reaction | Substrate | Conditions | Product | Yield (%) | Ref |
|---|---|---|---|---|---|
| Metalation | $CH(N_2)POPh_2$ | HgO, $CHCl_3$, r.t. | $Hg[C(N_2)POPh_2]_2$ | 82 | 32 |
| | $CH(N_2)PO_3Et_2$ | HgO, $CHCl_3$, r.t. | $Hg[C(N_2)PO_3Et_2]_2$ | 68 | 32 |
| | $CH(N_2)POPh_2$ | AgO, $CHCl_3$, r.t. | $AgC(N_2)POPh_2$ | 86 | 32 |
| | $CH(N_2)PO_3Et_2$ | AgO, $CHCl_3$, r.t. | $AgC(N_2)PO_3Et_2$ | 90 | 32 |
| | $CH(N_2)PO(Ph)OMe$ | AgO, $CH_2Cl_2$, r.t. | $AgC(N_2)PO(Ph)OMe$ | 43 | 33 |
| | $CH(N_2)PO_3Me_2$ | $Hg(acac)_2$, $CH_2Cl_2$ | $Hg[C(N_2)PO_3Me_2]_2$ | 80 | 30 |
| | $CH(N_2)PO_3Me_2$ | Ag(acac), $CH_2Cl_2$ | $AgC(N_2)PO_3Me_2$ | 95 | 30 |
| | $CH(N_2)PO_3Et_2$ | *n*BuLi, $Et_2O$/THF, 110 °C | $LiC(N_2)PO_3Et_2$ | | 68 |

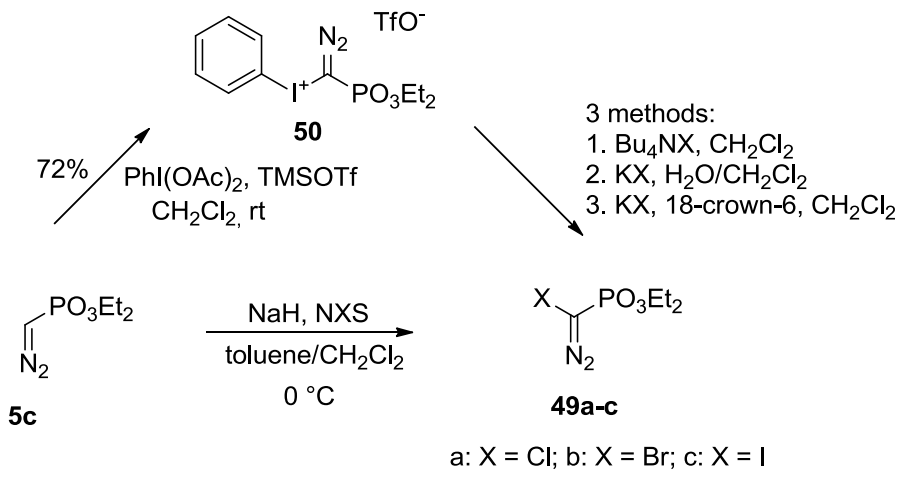
| | | | | | |
|---|---|---|---|---|---|
| **Halogenation** | $AgC(N_2)PO_3Me_2$ | BrCN, $Et_2O$, 0 °C then r.t. | $BrC(N_2)PO_3Me_2$ | 79 | [68] |
| | $AgC(N_2)POPh_2$ | BrCN, $CH_2Cl_2$, -20 °C then -10 °C | $BrC(N_2)POPh_2$ | | [68] |
| | $AgC(N_2)PO_3Me_2$ | $I_2$, $Et_2O$, -10 °C then 0 °C | $IC(N_2)PO_3Me_2$ | | [68] |
| | $AgC(N_2)POPh_2$ | $I_2$, $CH_2Cl_2$, -20 °C | $IC(N_2)POPh_2$ | | [68] |
| | $AgC(N_2)PO_3Me_2$ | allyl iodide, $Et_2O$, 0 °C | $CH_2=CHCH_2C(N_2)PO_3Me_2$ | 62 | [68] |
| | $AgC(N_2)PO_3Me_2$ | $CH_3CH=CHCH_2Br$ | $CH_3CH=CHCH_2C(N_2)PO_3Me_2$ | 48 | [68] |
| | $AgC(N_2)POPh_2$ | allyl iodide or bromide, $Et_2O$, -5 °C | $CH_2=CHCH_2C(N_2)POPh_2$ | 70 | [68] |
| | $AgC(N_2)POPh_2$ | $CH_3CH=CHCH_2I$, $Et_2O$, -5 °C | $CH_3CH=CHCH_2C(N_2)POPh_2$ | 52 | [68] |
| | $AgC(N_2)POPh_2$ | $CH_2=C(CH_3)=CH_2I$, $Et_2O$, -5 °C | $CH_2=C(CH_3)CH_2C(N_2)POPh_2$ | 67 | [68] |
| | $AgC(N_2)POPh_2$ |  $Et_2O$, -5 °C |   | 53 | [68] |
| | $AgC(N_2)POPh_2$ | $PhCH_2I$, $Et_2O$, -5 °C | $C_6H_5CH_2C(N_2)POPh_2$ | 54 | [68] |

| | | | | | |
|---|---|---|---|---|---|
| **Alkylation** | $AgC(N_2)POPh_2$ | 4-$MeC_6H_4CH_2I$, $Et_2O$, -5 °C | 4-$MeC_6H_4CH_2C(N_2)POPh_2$ | 50 | [68] |
| | $Hg[C(N_2)PO_3Me_2]_2$ | $Ph_3CBr$, $CH_2Cl_2$, 0 °C | $Ph_3C(N_2)PO_3Me_2$ | 28 | [68] |
| | $Hg[C(N_2)POPh_2]_2$ | $Ph_3CBr$, $CH_2Cl_2$, 0 °C | $Ph_3C(N_2)PO(C_6H_3)_2$ | 66 | [68] |
| | $AgC(N_2)PO(Ph)OMe$ | $PhCH_2I$, $Et_2O$, - 5 °C | $PhCH_2C(N_2)PO(Ph)OMe$ | 81 | [33] |
| | $AgC(N_2)PO(Ph)OMe$ | allyl iodide, $Et_2O$, - 5 °C | $CH_2=CHCH_2C(N_2)PO(Ph)$ OMe | 59 | [33] |
| | $CH(N_2)PO_3Me_2$ |  $CH_3CN$, r.t. |  | 89 | [66,67] |
| | $CH(N_2)PO_3Me_2$ |  $CH_3CN$, r.t. |  | 92 | [66,67] |
| | $CH(N_2)PO_3Me_2$ |  $CH_3CN$, r.t. |  | 66 | [66, 67] |
| | $CH(N_2)POPh_2$ |  $CH_3CN$, r.t. |  | 89 | [66,67] |
| | $CH(N_2)POPh_2$ |  $CH_3CN$, r.t. |  | 95 | [66,67] |

| | | | | | |
|---|---|---|---|---|---|
| | $CH(N_2)POPh_2$ |  $CH_3CN$, r.t. |  | 97 | 66,67 |

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 $PPh_3$ 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]

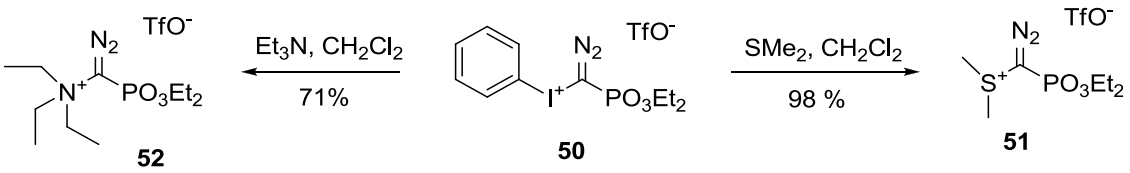
**Scheme 20. Synthesis of α-Halo-α-diazomethylphosphonates 49a-c**




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-

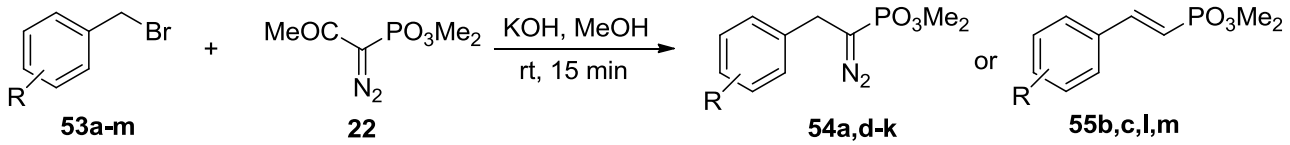
diazomethylphosphonate triflate (**51**) and α-triethylammonium-α-diazomethylphosphonate triflate (**52**) were described (Scheme 21).[70]

**Scheme 21**. **Synthesis of Diethyl α-Dimethylsulfonium-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)**




**53a-m** **22** **54a,d-k** **55b,c,l,m**

a: R = H, 87% (**54**); b: R = 4-$NO_2$, 85% (**55**); c: R = R = 2-$NO_2$, 85% (**55**); d: R = 3-$NO_2$, 80% (**54**); e: R = 4-Me, 78% (**54**); f: R = 3-OMe 79% (**54**); g: R = 2-Br 76% (**54**); h: R = 3-Br 75% (**54**); i: R = 4-F, 78% (**54**); j: R = 2-CN, 86% (**54**); k: R = 4-CN, 83% (**54**); l: R = 2-$NO_2$, 5-Cl, 80% (**55**); m: R = 2-$NO_2$, 5-OMe, 79% (**55**)

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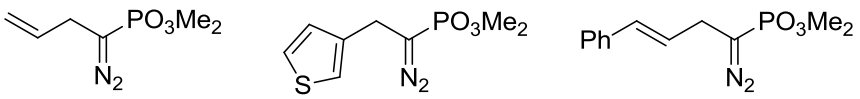
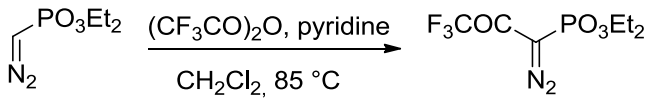



**56,** 76% **57**, 78% **58**, 79%

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)**



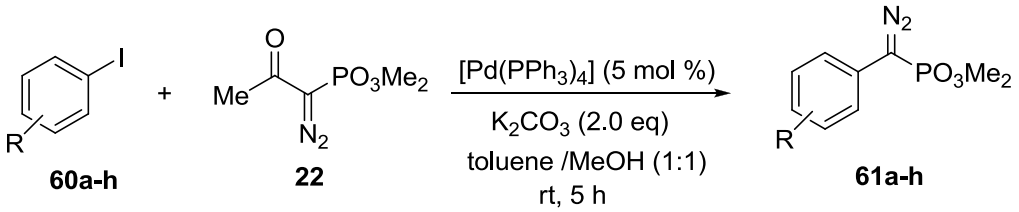

**5c** **59**

### 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).[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.

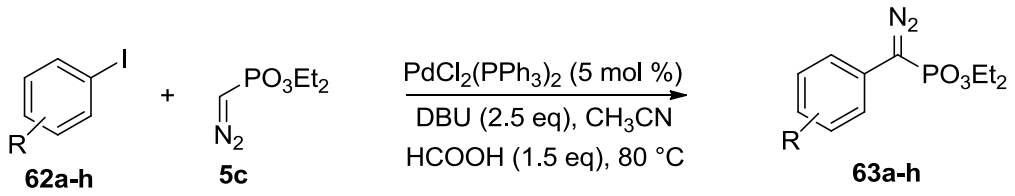
**Scheme 24. Synthesis of Dimethyl α-Aryl-α-Diazomethylphosphonates 61a-h**




a: R = H, 88%; b: R = 4-$CO_2Me$, 92%; c: R = 4-$NO_2$, 88%; d: R = 4-CN; 64%; e: R = 4-F, 50%; f: R = 3,5-diCl, 93%; g: R = 4,5-diMe, 64%; h: R = 3-OMe, 61%

Similarly, Kosokobov *et al*.[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 sybstituent 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-Diazomethylphosponates 63a-h**

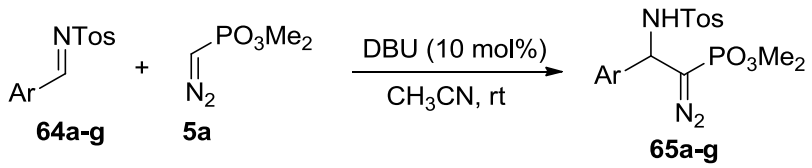



a: R = H, 60%; b: R = 4-$CO_2Me$, 95%; c: R = 3-$CO_2Me$, 75%; d: R = 4-$NO_2$, 94%;
e: R = 3-$NO_2$, 76%; f: R = 2-$NO_2$, 70%; g: R = 3-Me, 66%; h: R = 4-OMe, 25%

### 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]

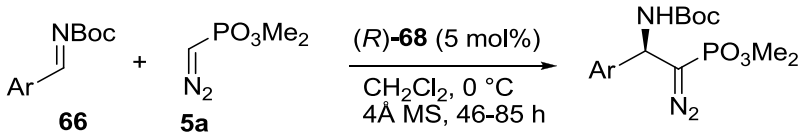
**Scheme 26. Mannich-Type Coupling of 5a with *N*-Tosylimines**

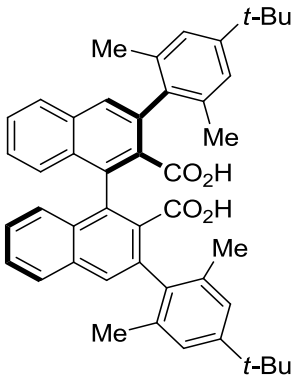



a: Ar = Ph, 75%; b: Ar = 4-$MeC_6H_4$, 68%; c: Ar = 4-$FC_6H_4$, 52%; d: Ar = 4-$ClC_6H_4$, 76%;
e: Ar = 4-$PhC_6H_4$, 54%; f: Ar = 4-$CF_3C_6H_4$, 89%; g: Ar = 2-furyl, 79%

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**

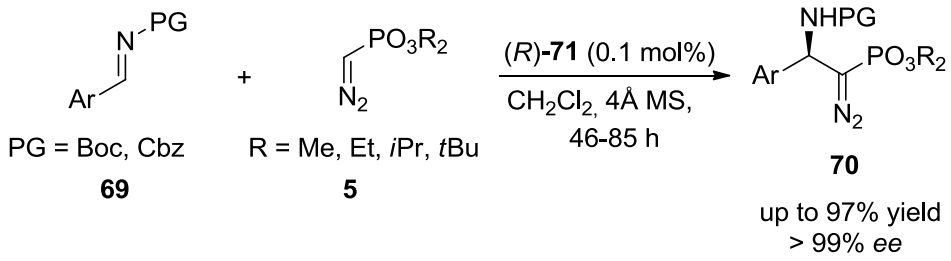


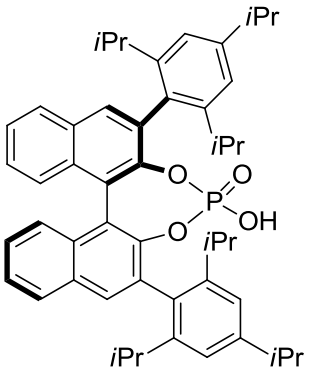




**68**

Although the procedure worked with efficiency and good enantioselectivity, the high catalyst loading represented a substantial drawback. Thus, Zhang *et al*.[79] proposed chiral phosphoric acids as alternative catalysts in the asymmetric Mannich reaction of *N*-carbamoyl imines **69** and dialkyl α-diazomethylphosphonates **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 β-Amino-α-diazoalkylphosphonates 70**

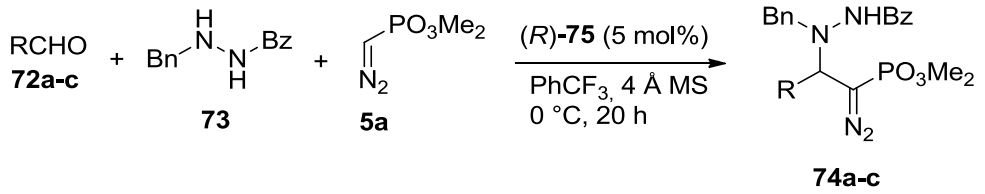


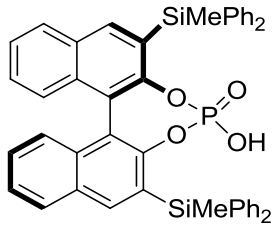

**71**

The binaphtyl phosphate **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 *N*-carbamoylimines **69**. When azomethine imines were used as electrophiles the corresponding β-hydrazino-PCDCs could be prepared. Hashimoto *et al*.[80] generated azomethine imines *in-situ* by the condensation of *N*-benzylbenzoyl hydrazide **73** with the aldehydes **72a-c.** In the presence of dimethyl α-diazomethylphosphonate (**5a**) and a catalytic amount of the axially chiral catalyst **75**, the β-hydrazino-PCDCs **74a-c** were synthesized with excellent enantioselectivity (Scheme 29).

**Scheme 29. Synthesis of Dimethyl β-Hydrazino-α-diazoalkylphosphonates 74a-c**



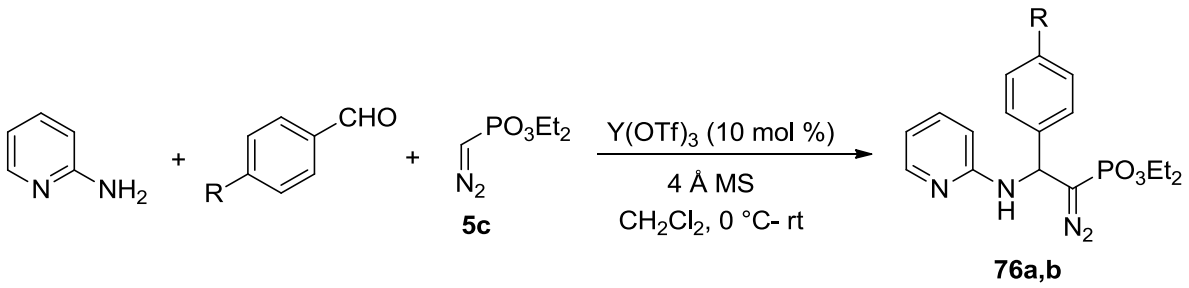

a: R = cyclopropyl, 68%, 95% *ee;* b: R = $CH_2CH_2Ph$, 77%, 95% *ee*; c: R = Ph, 64%, 90% *ee*




**75**

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).[81]

**Scheme 30**. **Preparation of PCDCs 76a,b by $Y(OTf)_3$-Catalyzed Three-Component Reaction**

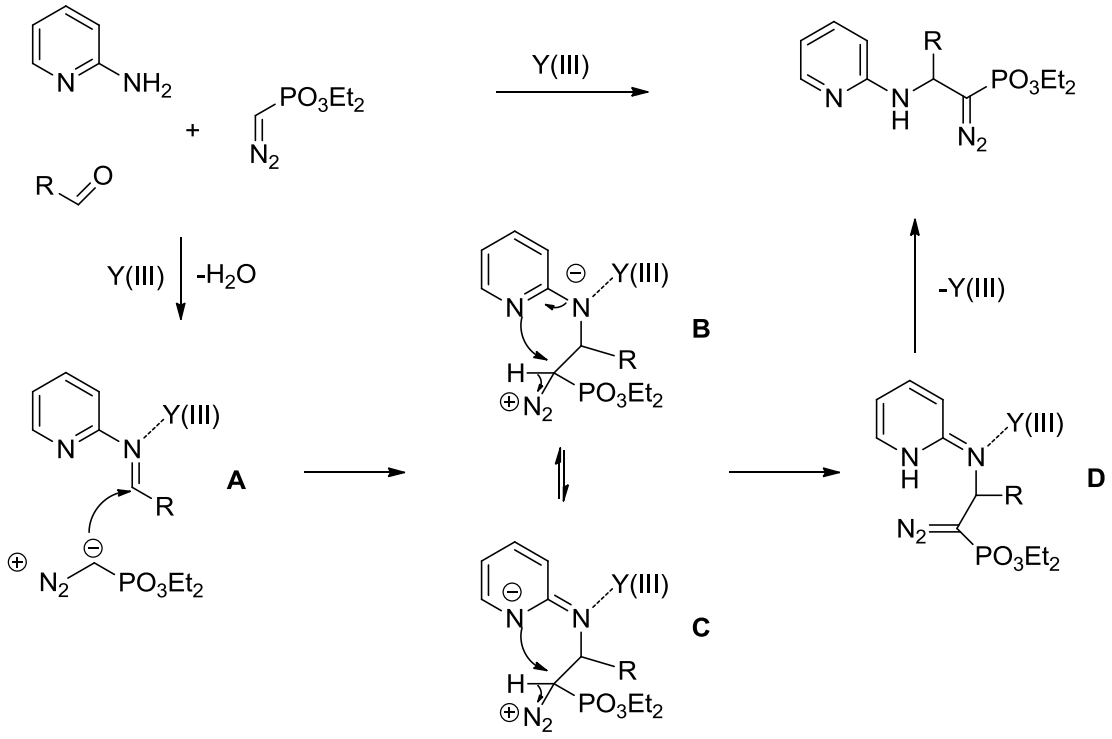



a: R = Me, 67%; b: R = Br, 51%

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-Diazomethylphosponate**




### 3. Chemistry of λ$^5$-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

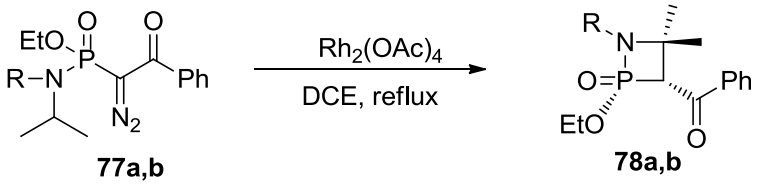
diazonium cations, are generated from PCDCs by a metal catalyst. Unlike diazocarbonyl compounds, however, the area of enantioselective transformations has been little explored, remaining an open field of research. Due to its size, this section is divided into subsections based on of the type of product 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 -lactons 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 *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.

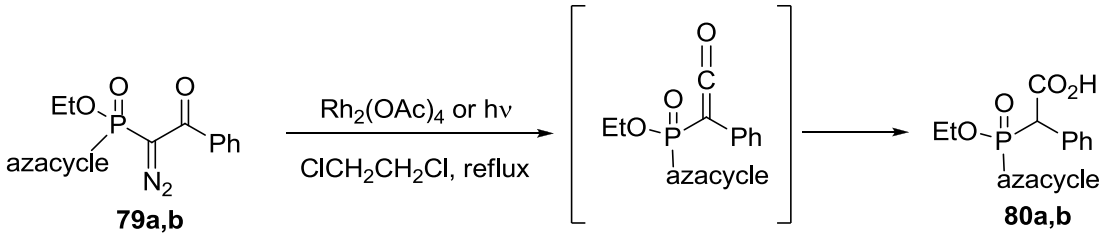
In 1992, Afarinkia *et al*.[82] reported about the metal-catalyzed decomposition of α-diazo-β-ketophosphonamidates **77a,b** furnishing in low yields the corresponding monocyclic 1,2-azaphosphetidines **78a,b** as the result of the intramolecular C-H insertion of the carbene intermediates. Both the insertion products were formed diastereoselectively in a ratio of about 10:1 in favour of the ($S_p$, $R_c$) 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-Azaphosphetidines 78a,b**




a: R = *i*Pr, 33%; b: $CH_2Ph$, 16%

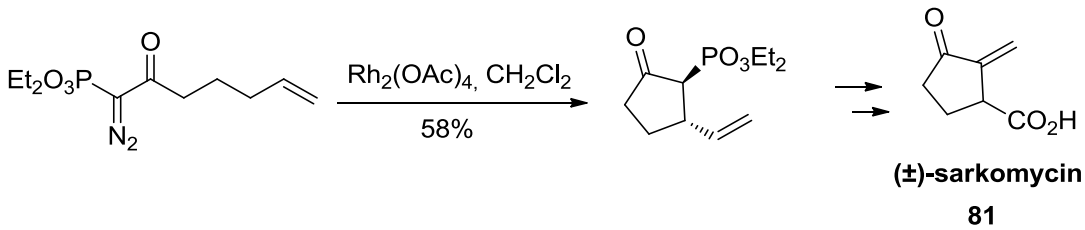
**Scheme 33. Photolytic or $Rh_2(OAc)_4$-Catalyzed Decomposition of α-Diazo-β-ketophosphonamidates 79a,b**



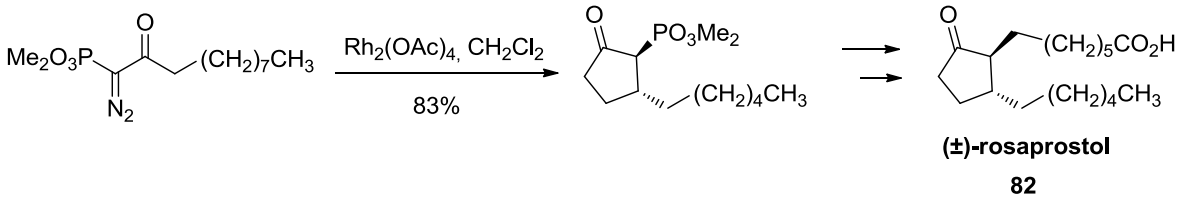

a: azacycle = piperidine, 50% (hν), 64% ($Rh_2(OAc)_4$); b: azacycle = 2-methylpiperidine, 50% (hν), 34% ($Rh_2(OAc)_4$)

Mikołajczyk *et al*. applied rhodium(II) acetate-catalyzed C-H insertion reaction of α-diazo-β-keto-phosphonates for the synthesis of *trans*-3-subtituted-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)**

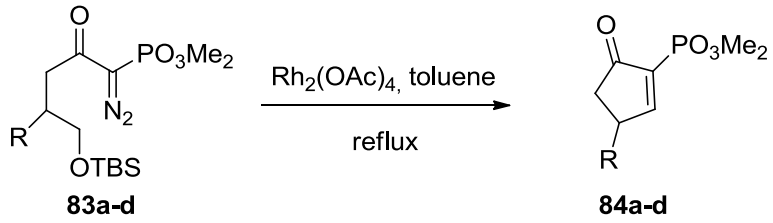


**Scheme 35. Synthesis of (±)-Rosaprostol (82)**




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).[85]

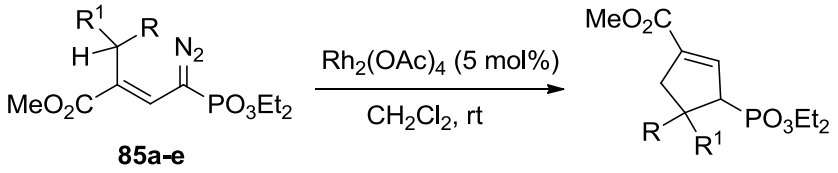
**Scheme 36. Synthesis of 2-Phosphonocyclopenten-3-ones 84a-d**




a: R = TBS, 74%; b: R = Me, 70%; c: R = TBS, 67%; d: R = H, 71%

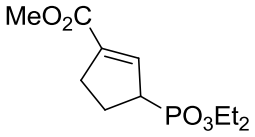
Cyclopentenyl-3-phosphonates **86a-e** were prepared in high yields by $Rh_2(OAc)_4$-catalyzed intramolecular C-H insertion reaction from alkyl, benzyl and homoallyl PCDCs **85a-e** (Scheme 37).[86] The equilibration of the *cis*- and *trans*-diastereoisomeric mixtures **86b**,**d**,**e**, thus obtained, into the corresponding single *trans*-isomers could be performed by treatment with DBU.

**Scheme 37. C-H Insertion Reaction of Diethyl α-Diazo-α-Vinylphosphonates 85a-e**

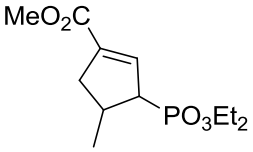



**85a-e** **86a-e**

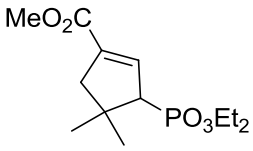
a: R = $R^1$ = H; b: R = Me, $R^1$ = H; c: R = $R^1$ = Me;
d: R = Ph, $R^1$ = H; e: R = vinyl; $R^1$ = H



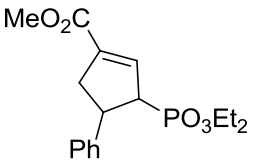

**86a**
67%



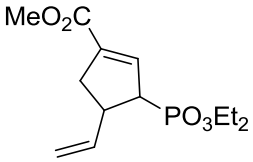

**86b**
89%, 5:1 *dr*




**86c**
87%,



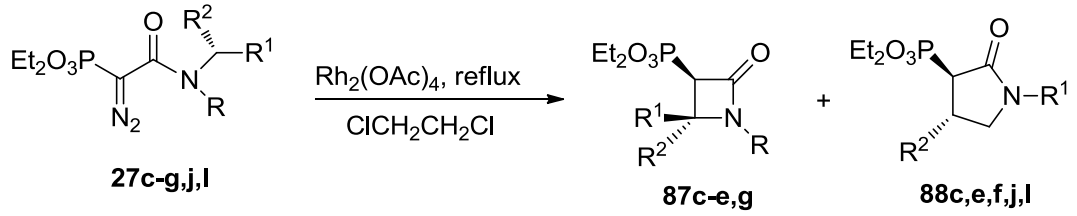

**86d**
78%, 2:1 *dr*




**86e**
82%, 2:1 *dr*

α-Phosphonolactams **87** and **88** were obtained in high yields by $Rh_2(OAc)_4$-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.[50] 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.[87] The authors later demonstrated that such reactions could be efficiently performed using water and $CO_2$, as reaction media.[88,89,90]

**Scheme 38. $Rh_2(OAc)_4$-Catalyzed Cyclization of α-Diazo-α-Diethoxyphosphorylacetamides 27c-g,j,l**

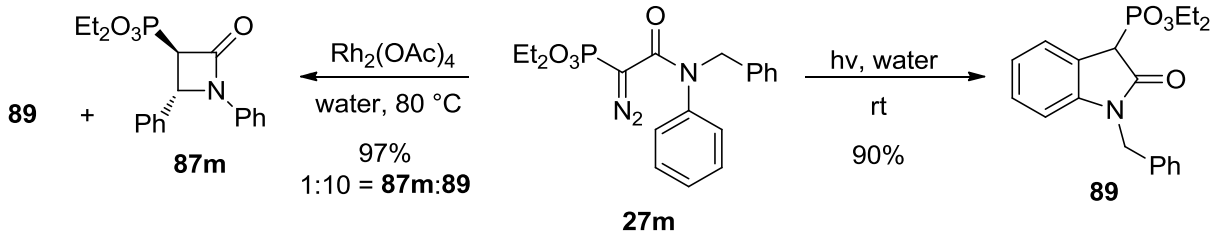



**27c-g,j,l** **87c-e,g** **88c,e,f,j,l**

c: R = *n*Bu, $R^1$ = Ph, $R^2$ = Me, 18% (**87**), $R^1$= CH(Me)Ph, $R^2$= Et, 76% (**88**);
d: R = *i*Pr, $R^1$ = $R^2$ = Me, 88% (**87**); e: R = Et, $R^1$ = H, $R^2$ = Me, 18% (**87**), $R^1$ = Et, $R^1$ = H, 50% (**88**);
f: $R^1$ = *n*Bu, $R^2$ = Et, 87% (**88**); g: R = *t*Bu, $R^1$ = H, $R^2$ = $CH_2CO_2Me$, 94% (**87**); j: $R^1$ = $(CH_2)_2OMe$,
$R^2$ = OMe, 89% (**88**); l: $R^1$ = *t*Bu, $R^2$ = Ph, 81% (**88**)

Furthermore Candeias *et al*.[91] reported the decomposition of α-diazo-α-diethoxyphosphoryla-cetamides 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 $Rh_2(OAc)_4$-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**

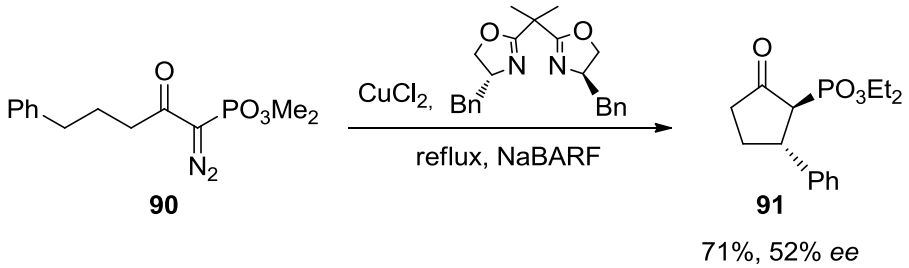



After obtaining the same result with different solvents, the authors concluded that the reaction outcome was more dependent on the native substrate conformation rather than to the hydrophobic effect exerted by the water over the diazo substrate. Moreover, the high selectivity toward the for-mation of 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-diethoxyphosphorylacetamides 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%).[92] Slightly better results were obtained by Slattery and Maguire in the copper-catalyzed C-H insertion of PCDC **90** leading to the formation of the corresponding α-phosphonocyclopentanone derivative **91** (Scheme 40).[93]

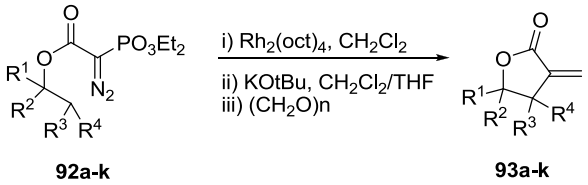
**Scheme 40. Copper-Catalysed Asymmetric C-H Insertion of Dimethyl (1-Diazo-2-oxo-5-phenylpentyl)phosphonate (90)**




Recently, to the rhodium-catalyzed cyclisation of α-diazo-α-phosphorylacetates into the corresponding lactones, first reported by Gois *et al*.,[50] 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).[94]

**Scheme 41. One-pot C-H Insertion/Olefination Sequence for the Formation of α-Methylene-γ-**

**butyrolactones 93a-k**




**92a-k** **93a-k**

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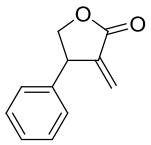
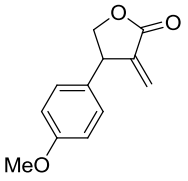
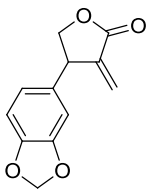


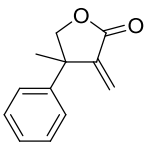
**93a,** 74%



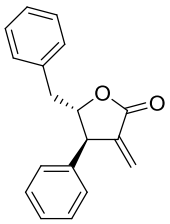
**93b,** 65%



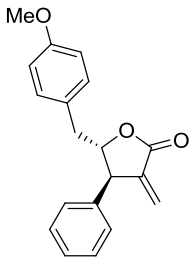
**93c,** 64%



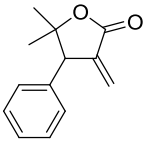
**93d,** 59%



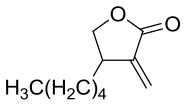
**93e,** 84%



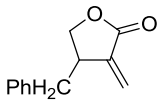
**93f,** 84%



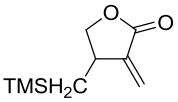
**93g,** 89%



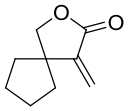
**93h,** 89%



**93i,** 62%

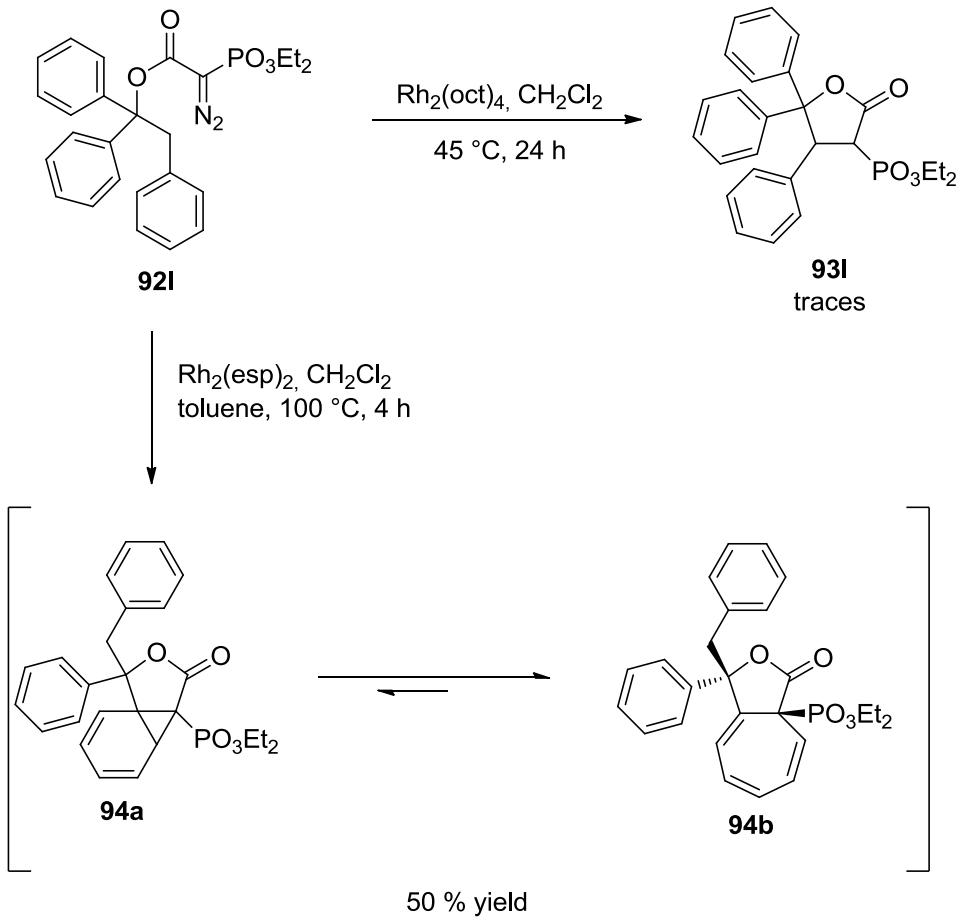


**93j,** 62%



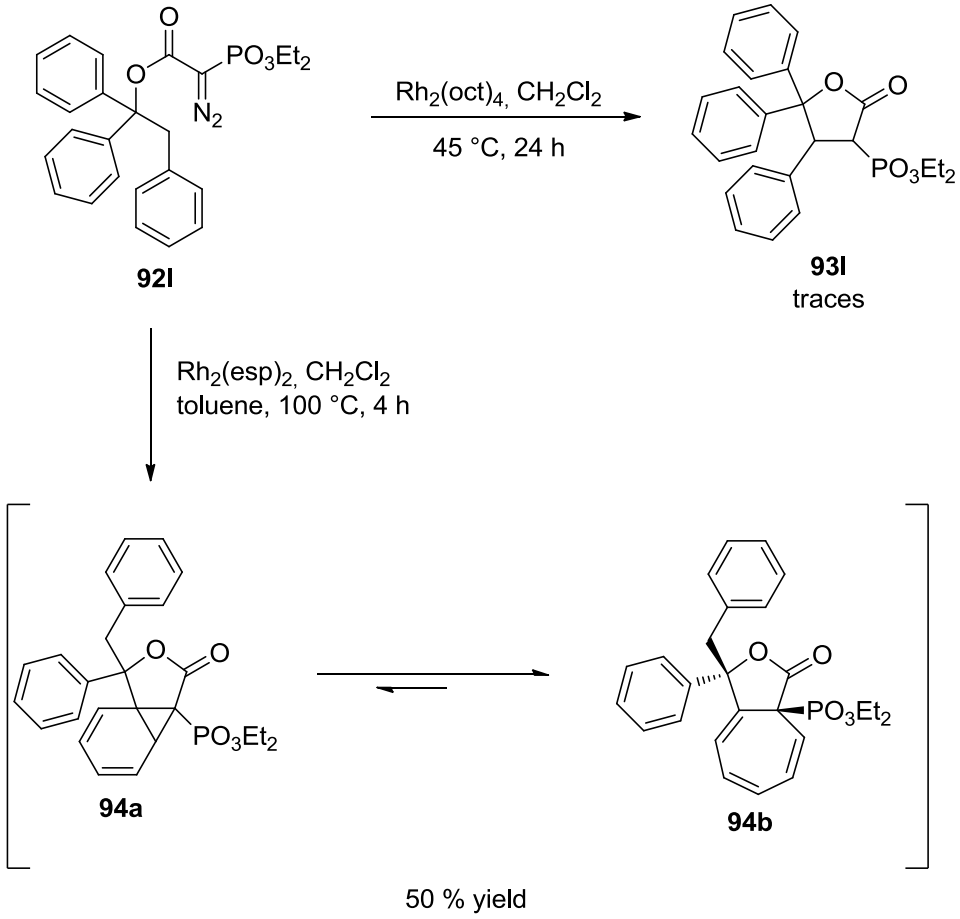
**93k,** 79%

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.[95] 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 $Rh_2(esp)_2$, a bridged robust dirhodium catalyst, superior to a $Rh_2(oct)_4$ 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

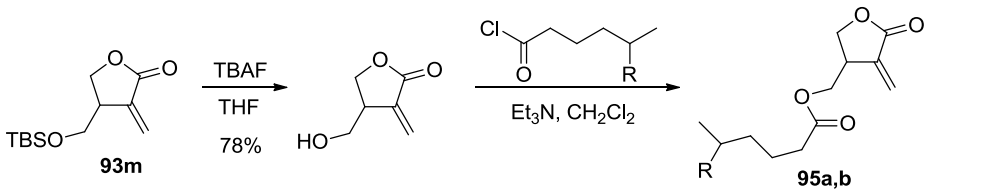

O
O
PO3Et2
N2
Rh2(oct)4, CH2Cl2
45 °C, 24 h
O
O
PO3Et2
92l
93l
traces
Rh2(esp)2, CH2Cl2
toluene, 100 °C, 4 h
O
O
PO3Et2
94a
94b
50 % yield

).[95]

**Scheme 42. Buchner Reaction *vs* C-H Insertion in the Rhodium-catalyzed Decomposition of 92l**

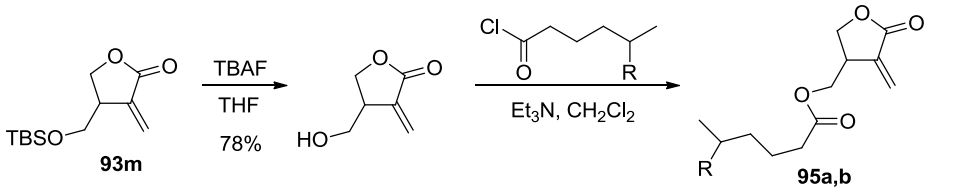



The lactone **93m**, obtained by this procedure, was then used as the key intermediate for the preparation of (±)-cedarmycins A and B (**95a,b**), thus demonstrating the applicability of the methodology for natural product synthesis (Scheme 43. Synthesis of (±)-Cedarmycins A and B (95a) and (95b)




a: R Me, 85%; b: R = H, 57% ).[95]

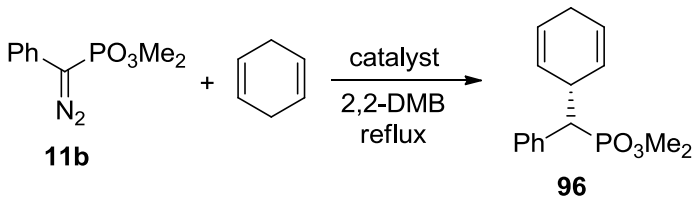
**Scheme 43. Synthesis of (±)-Cedarmycins A and B (95a) and (95b)**



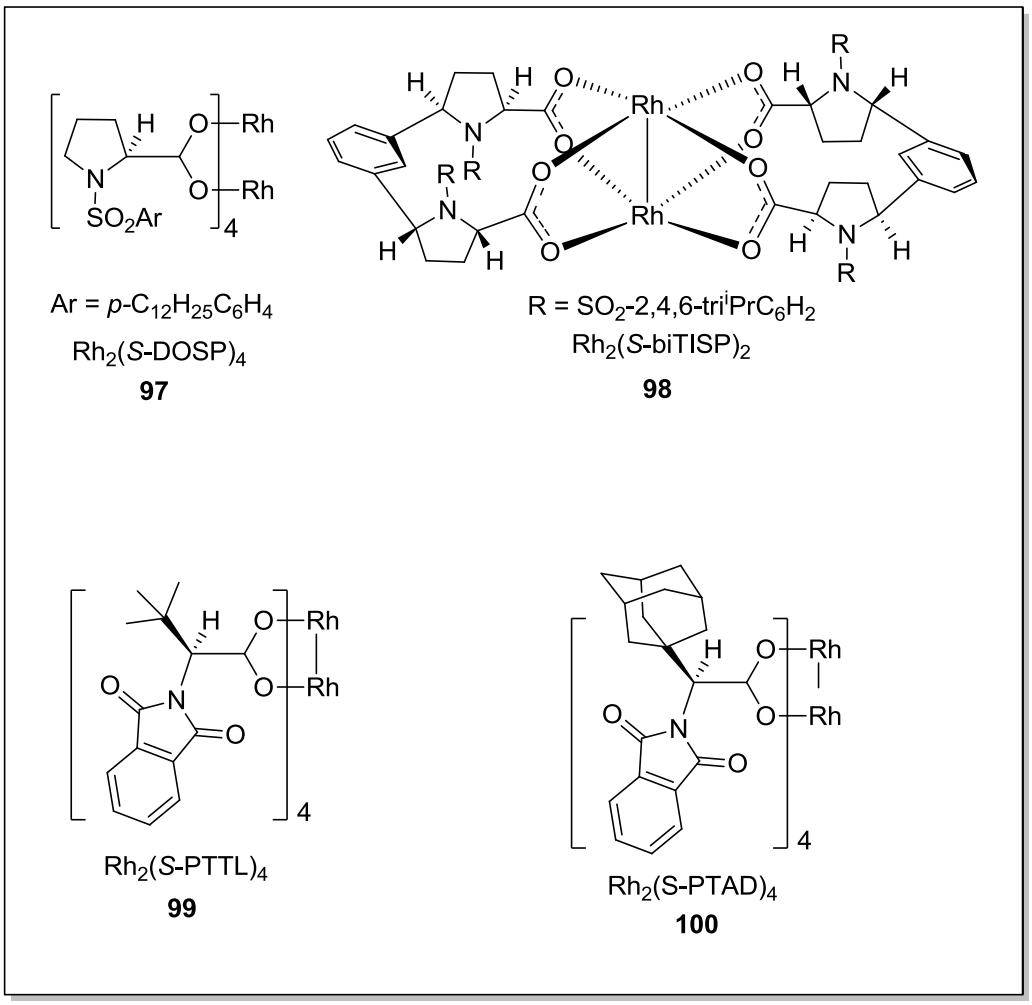

a: R Me, 85%; b: R = H, 57%

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*. [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.**). $Rh_2$(*S*-biTISP)$_4$ (**98**), $Rh_2$(*S*-PTTL)$_4$ (**99**) and $Rh_2$(*S*-PTAD)$_4$ (**100**) showed to give higher asymmetric induction, than the more common dirhodium tetraprolinate $Rh_2$(*S*-DOSP)$_4$ (**97**). By using $Rh_2$(*S*-PTAD)$_4$ (**100**) the opposite enantiomer of **96** was preferentially formed.

**Scheme 44. Enantioselective Intermolecular C-H Insertion of 11b**



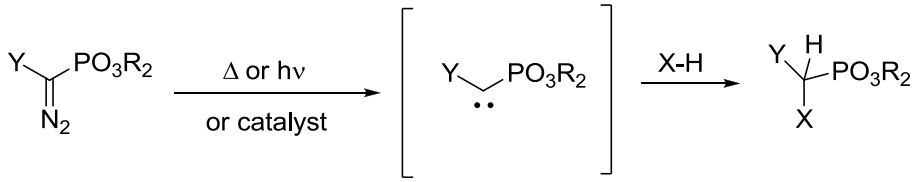

$Rh_2$(S-DOSP)$_4$, 62% yield, 41% ee
$Rh_2$(S-biTISP)$_4$, 57% yield, 72% ee
$Rh_2$(S-PTTL)$_4$, 67% yield, 89% ee
$Rh_2$(S-PTAD)$_4$, 83% yield, 92% ee




### 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]

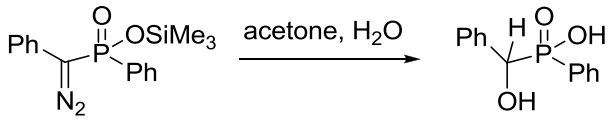
**Scheme 45. X-H Insertion Reaction of PCDCS**



### 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[98] reported that diazophosphinate **101** when reacted with aqueous acetone resulted in the hydrolysis of the silyl ester and the concurrent formation of the hydroxyl compound **102** by O-H insertion into the water (Scheme 46).

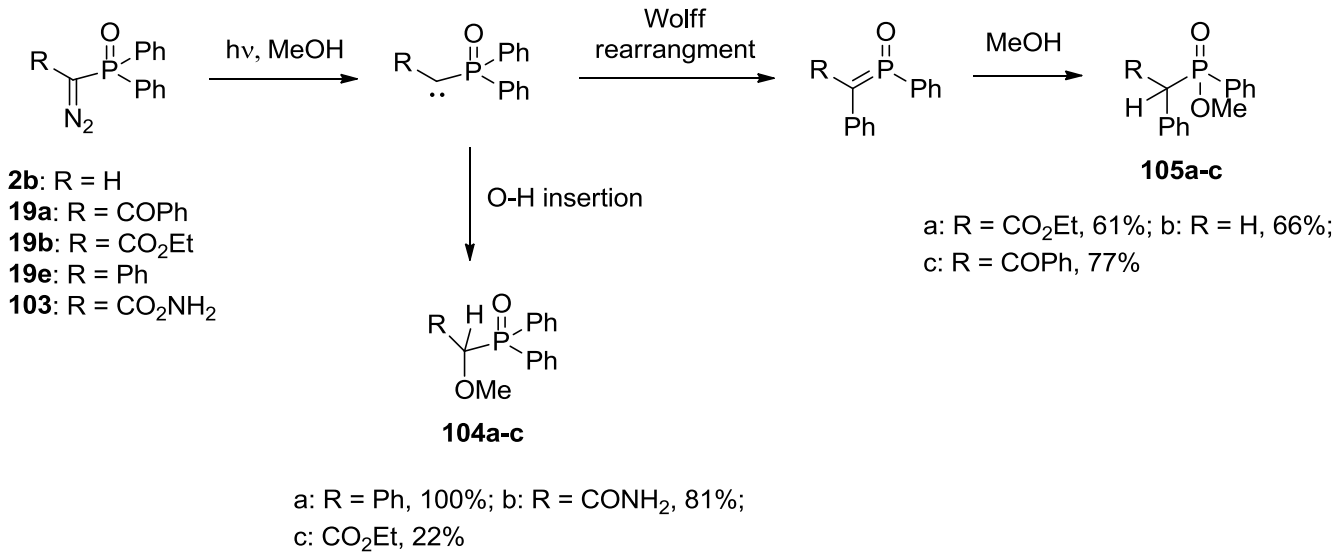
**Scheme 46. Thermal Decomposition of PCDC 101 in the Presence of Water**




**101** **102**, 40%

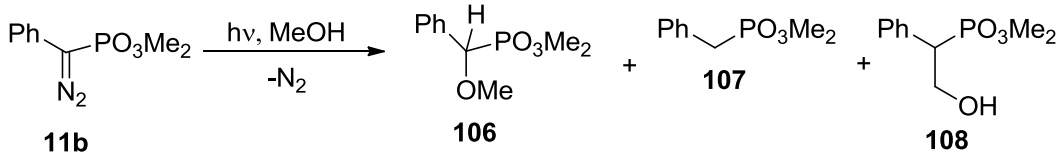
Regitz[44] was the first to study the photochemical decomposition of PCDCs in the presence of alcohols. He showed that competition between O-H and C-H insertion might occur in a series of diazophosphine oxides. When the photolysis of **5d, 19a,b,e** and **97** in methanol was studied, Regitz observed that the groups on the diazo portion exerted an effect on the product formed. In general, O-H insertion products **104a-c** were achieved in high yield when R was Ph, $CONH_2$, whereas in the case of R = H, COPh or $CO_2Et$, the products derived by 1,2-shift rearrangement **105a-c** proved to be those predominant. The structure-assignment of the products was carried out using IR and NMR analysis (**Error! Reference source not found.**).[99, 100]

**Scheme 47. Photochemical Decoposition of PCDCs: O-H Insertion *vs* Wolff Rearrangement**




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.[101] In particular, the photolysis of dimethyl α-diazobenzylphosphonate (**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.

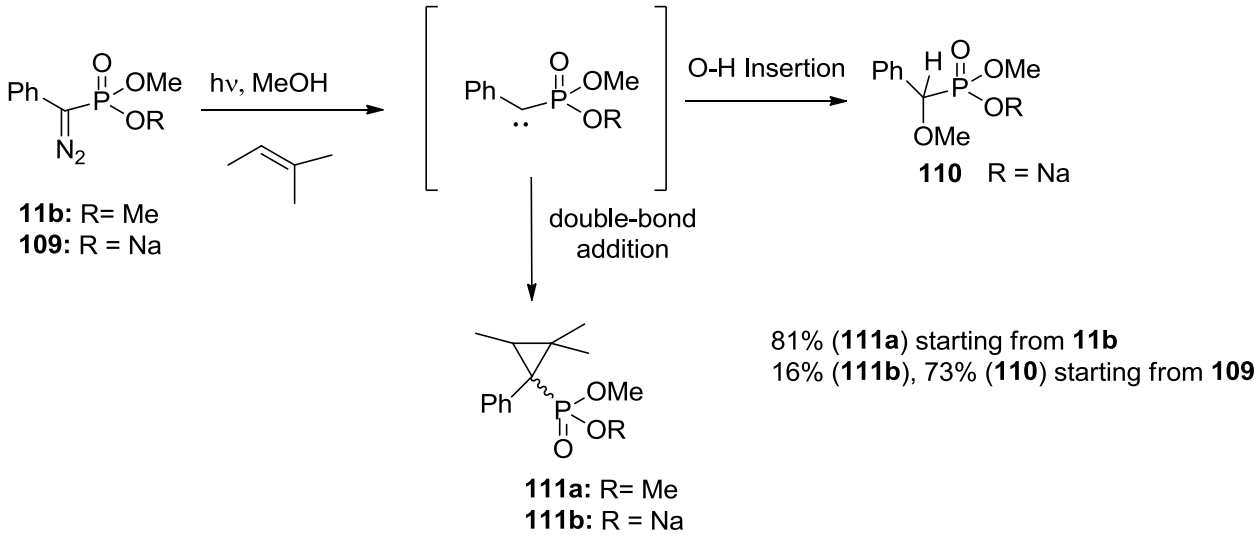
**Scheme 48. Photolysis of 11b in Methanol: O-H Insertion *vs* C-H Insertion Reaction *vs* Double Hydrogen Abstraction**



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.[101] 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*.[102] proved that the electrophilicity of phosphonylcarbenes 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).[102] 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.

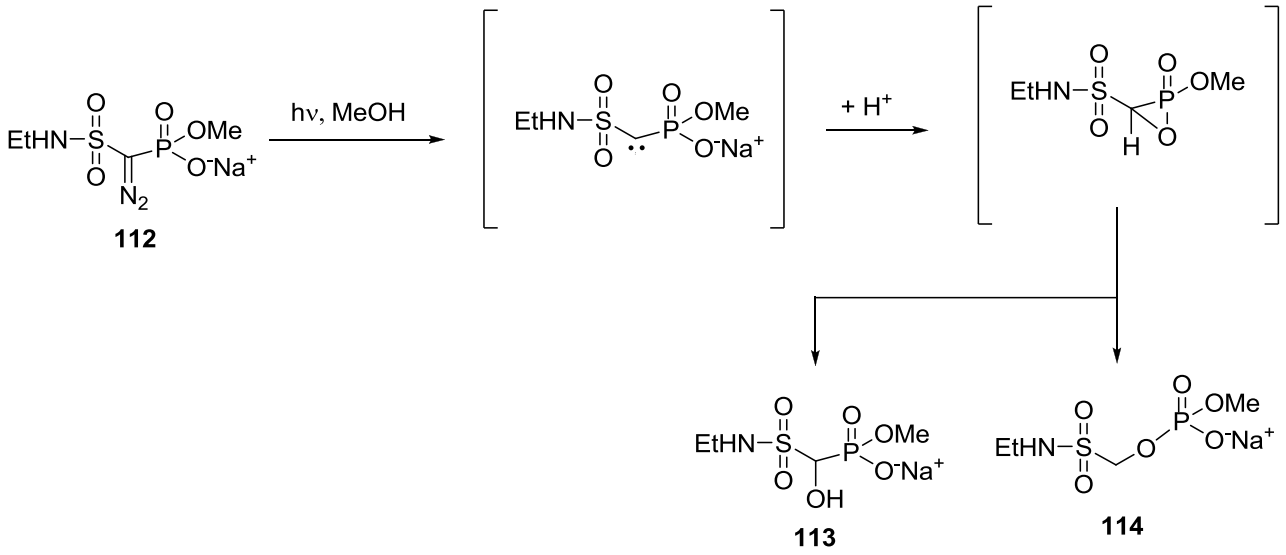
**Scheme 49. Photolysis of α-Diazobenzylphosponates: Effect of the Neighbouring Group on the**

**Carbene**




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 α-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.

**Scheme 50. Photolysis of PCDC 112 in Methanol**




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.

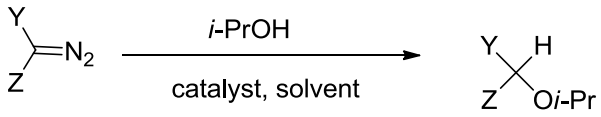
Julget and Drahn[105] reported kinetic investigations on the mechanism of hydrolysis of some PCDCs in dioxane–water with perchloric acid as a catalyst, showing that PCDCs were hydrolyzed in the same way as the cognate α-diazocarbonyl compounds with proton transfer as the rate-determining step, followed by rapid decomposition of the diazonium ion. However, no pratical 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,[106] Moody *et al.* investigated the rate at which different diazo compounds decomposed in the presence of 2-propanol and rhodium catalyst (**Error! Reference source not found.**).[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 *i*-PrOH**



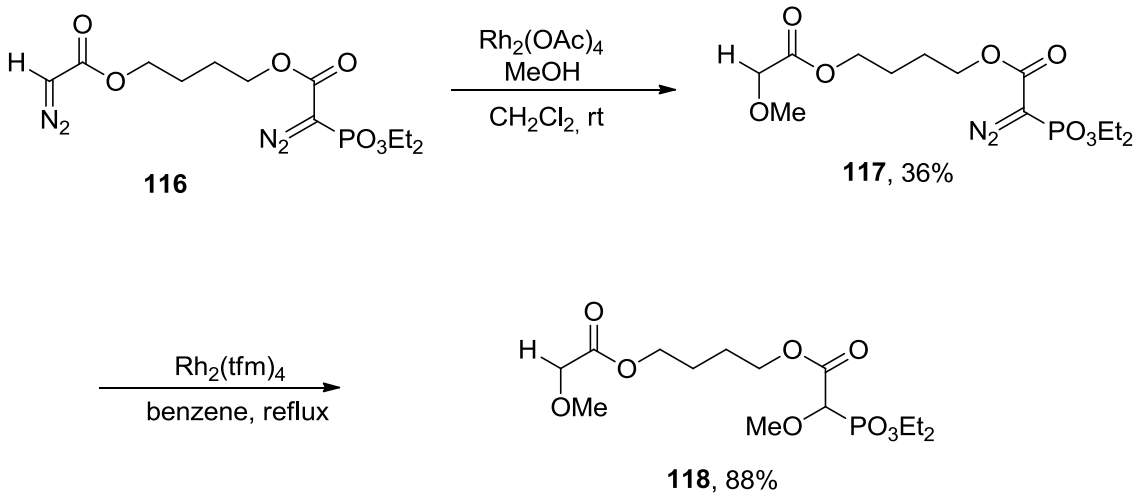

**115a-m**

| Entry | Y | Z | Product | Solvent | Temp. | Catalyst (1 mol%) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| **1** | H | $CO_2Et$ | **115a** | $CH_2Cl_2$ | rt | $Rh_2(OAc)_4$ | 0.5 | 64 |
| **2** | Ph | $CO_2Et$ | **115b** | $CH_2Cl_2$ | rt | $Rh_2(OAc)_4$ | 0.1 | 92 |
| **3** | $PhCH_2$ | $CO_2Et$ | **115c** | $CH_2Cl_2$ | rt | $Rh_2(OAc)_4$ | 2.0 | 32 |
| **4** | $Me_2NCO$ | $CO_2Et$ | **115d** | $CH_2Cl_2$ | rt | $Rh_2(OAc)_4$ | 32 | 66 |
| **5** | CN | $CO_2Et$ | **115e** | $CH_2Cl_2$ | rt | $Rh_2(OAc)_4$ | 3 | 86 |
| **6** | $CO_2Et$ | $CO_2Et$ | **115f** | $CH_2Cl_2$ | rt | $Rh_2(OAc)_4$ | 125 | 66 |
| **7** | $PhSO_2$ | $CO_2Et$ | **115g** | $CH_2Cl_2$ | rt | $Rh_2(OAc)_4$ | 18 | 64 |
| **8** | $Ph_2PO$ | $CO_2Et$ | **115h** | $CH_2Cl_2$ | reflux | $Rh_2(OAc)_4$ | 1.0 | 30 |
| **9** | $Ph_2PO$ | $CO_2Et$ | **115i** | $CH_2Cl_2$ | rt | $Rh_2(tfacm)_4$ | 22.5 | 45 |
| **10** | $PO_3Et_2$ | $CO_2Et$ | **115j** | $CH_2Cl_2$ | reflux | $Rh_2(OAc)_4$ | 10 | 83 |
| **11** | $PhSO_2$ | $PO_3Et_2$ | **115k** | $CH_3Ph$ | 110°C | $Rh_2(OAc)_4$ | 72 | 67 |
| **12** | $PhSO_2$ | $PO_3Et_2$ | **115l** | $CH_3Ph$ | 110°C | $Rh_2(tfacm)_4$ | 2 | 79 |
| **13** | $PO_3Et_2$ | $PO_3Et_2$ | **115m** | $CH_3Ph$ | 110°C | $Rh_2(tfacm)_4$ | 2 | 81 |

This marked difference in reactivity between α-diazocarbonyls and PCDCs was found to be extremely advantageous when a molecule contains two differently substituted diazo groups, such in

the case of **116**.[109] 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**



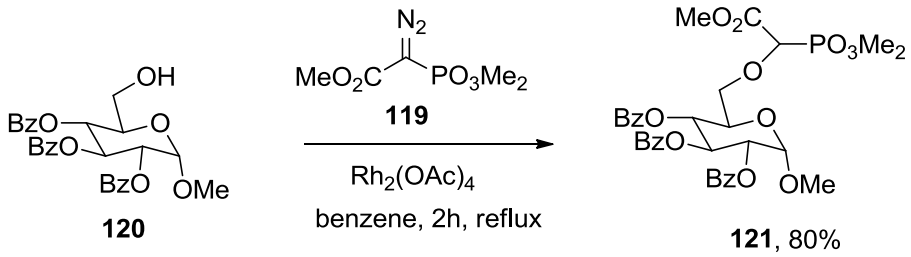

**116**

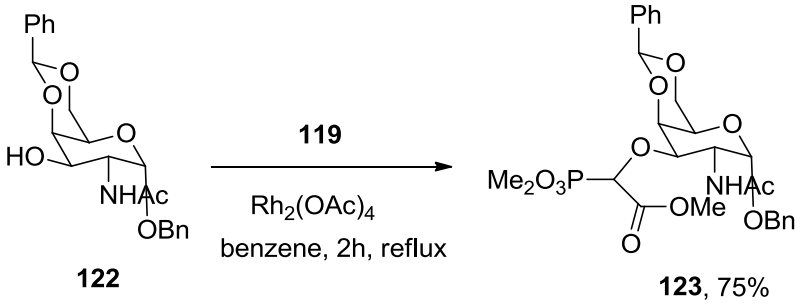
**117**, 36%

**118**, 88%

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**)[110] and into the secondary alcohol of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-*D*-galactopyranoside (**122**) (Scheme 52).[111]

**Scheme 52. O-H Insertion Reactions of 119 in 6'-O-H Functionality of Carbohydrate Scaffolds**

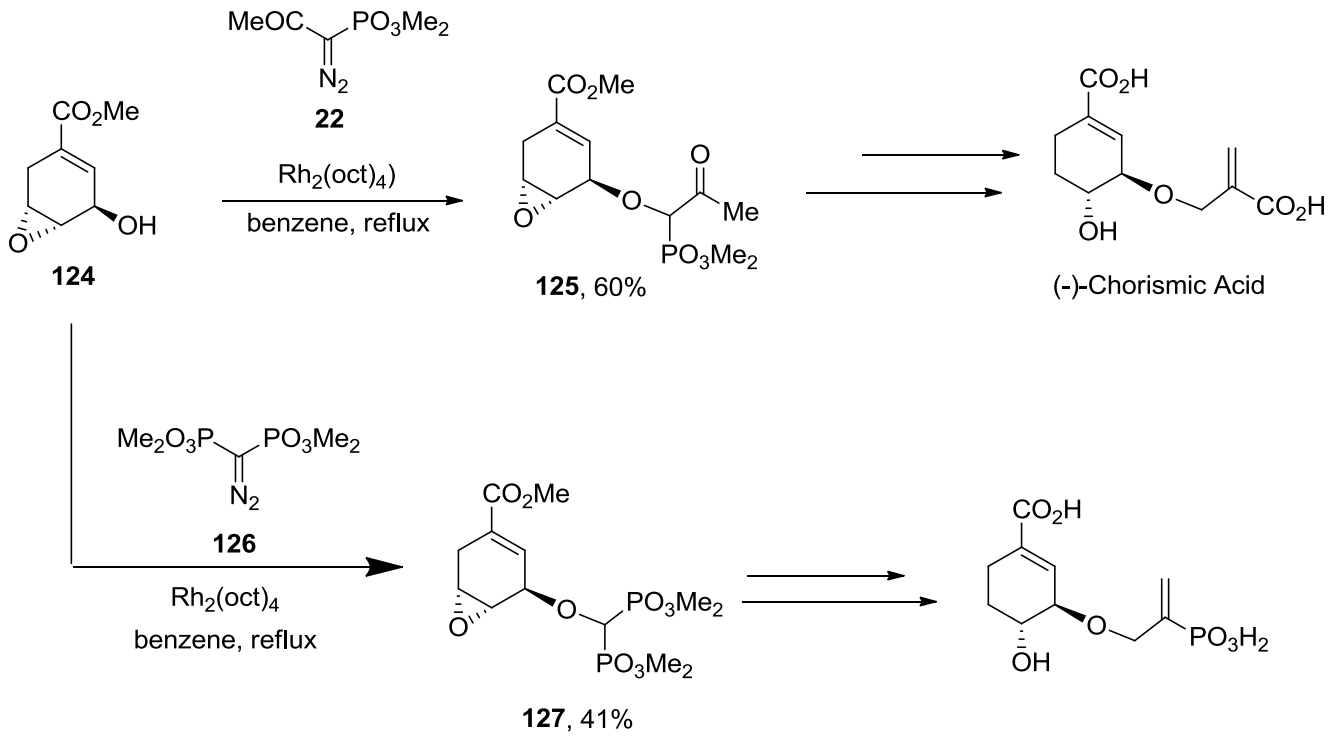



Subsequently, the rhodium-catalyzed insertion of PCDCs has been founding wide application in the synthesis of chorismic and shikimic acids derivatives. Pawlak *et al.* reported the reaction of alcohol **124** with PCDC **22**, in benzene at reflux in the presence of rhodium catalyst providing the corresponding 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**

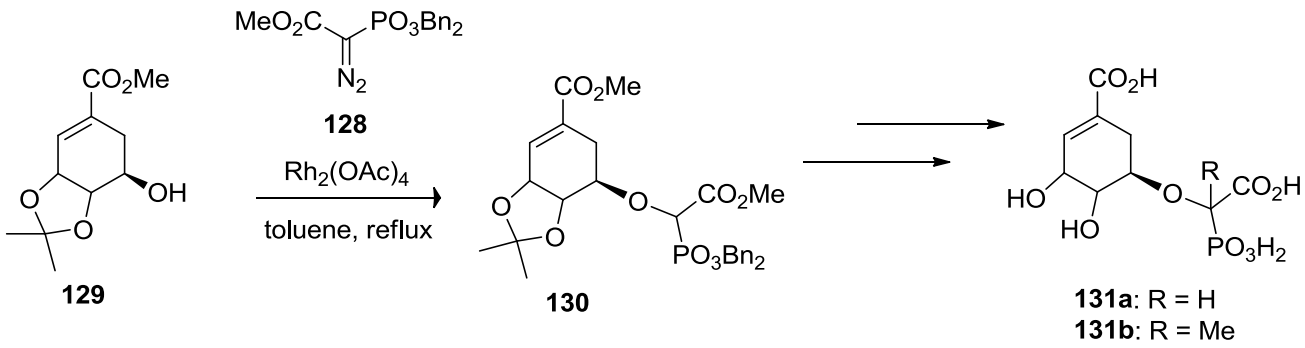
**Acid and its Phosphonate Analogue**




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(II) 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).[114]

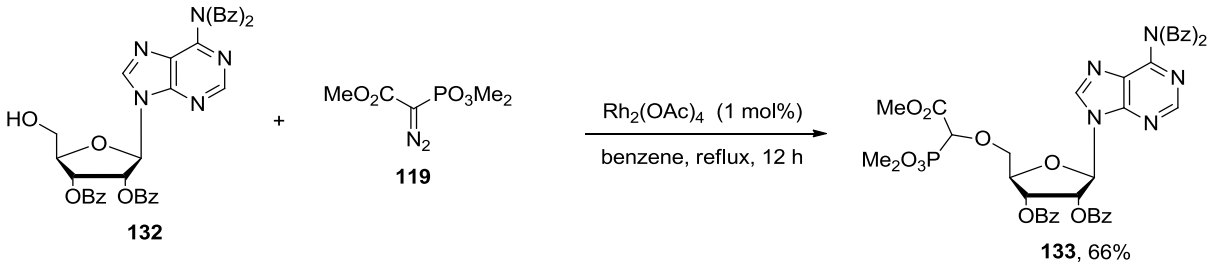
**Scheme 54. O-H Insertion Reaction of 128, as a Key Step in the Synthesis of (-)-Shikimic Acid**

**Analogues**



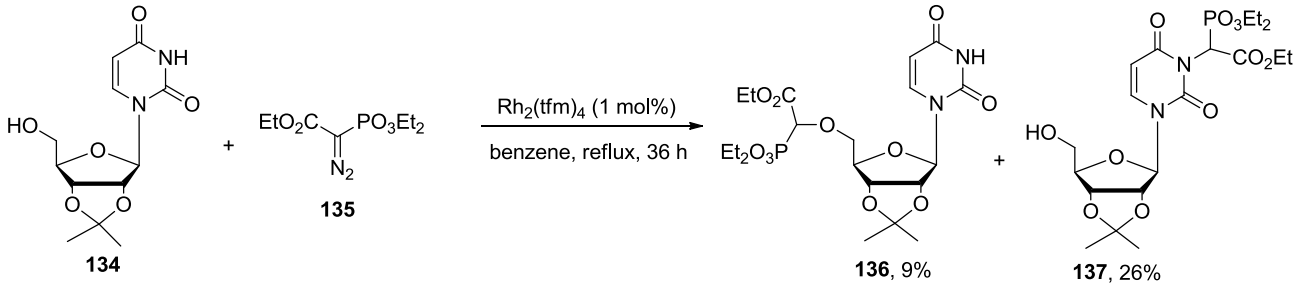

O-H insertion reactions with PCDCs were also exploited by the Maguire's group for the synthesis of α-carboxy-phosphononucleosides endowed with potential antiviral and anticancer activities.[115,116] Thus, rhodium-catalysed O-H insertion reactions of trialkyl diazophosphonoacetate **119** with a series 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 Nucleoside132**



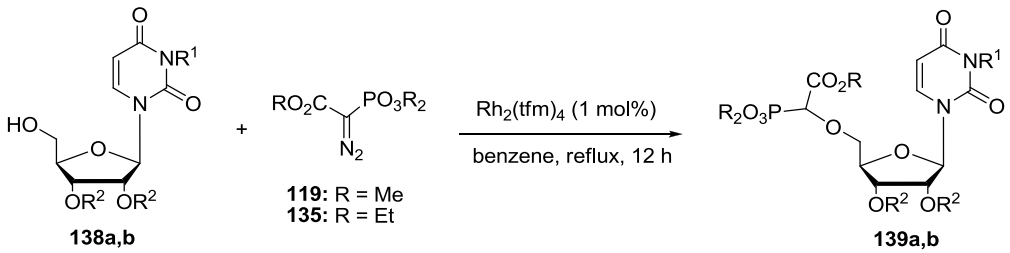
When the same reaction was assayed on pyrimidine nucleosides, no catalyst poison occured in the presence of unprotected pyrimidine bases. With NH unprotected uridine **134** as shown in Scheme 56 both compounds **136 and 137** were formed, with N-H insertion being favoured over O-H insertion.

**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).

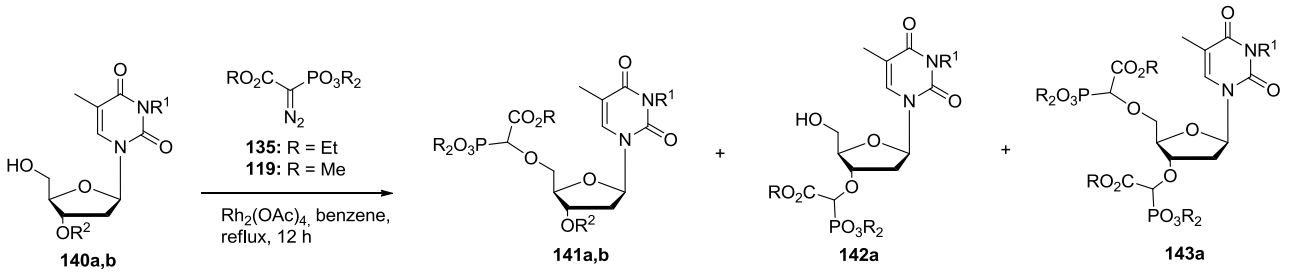
**Scheme 57. Rhodium- Catalysed O-H Insertion Reaction of PCDCs 119 and 135 with Pyrimidine Nucleosides 139a,b**




a: $R^1 = R^2$ = Bz, R = Me, 60%; b: $R^1$ = Bz, $R^2$ = *i*Pr, R = 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).

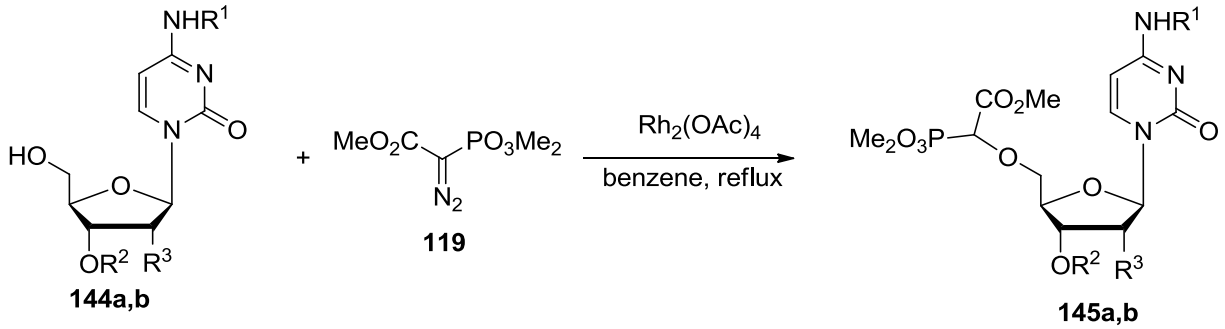
**Scheme 58. Rhodium-Catalysed O-H Insertions Reaction of PCDCs 119 and 135 with Pyrimidine Nucleosides 140a,b: 5'- *vs* 3'-OH Insertion**




a: R = Et; $R^1$ = Bz; $R^2$ = H, 34% (**141**), 7% (**142**), 21% (**143**); b: R = Me, $R^1 = R^2$ = Bz, 86% (**141**);

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**

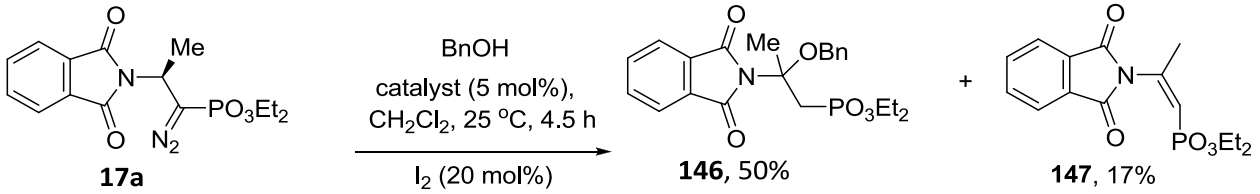



a: $R^1 = R^2$ = Bz, $R^3$ = OBz, 52%; b: $R^1 = R^2$ = Bz, $R^3$ = H, 52%;

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.[117, 118]

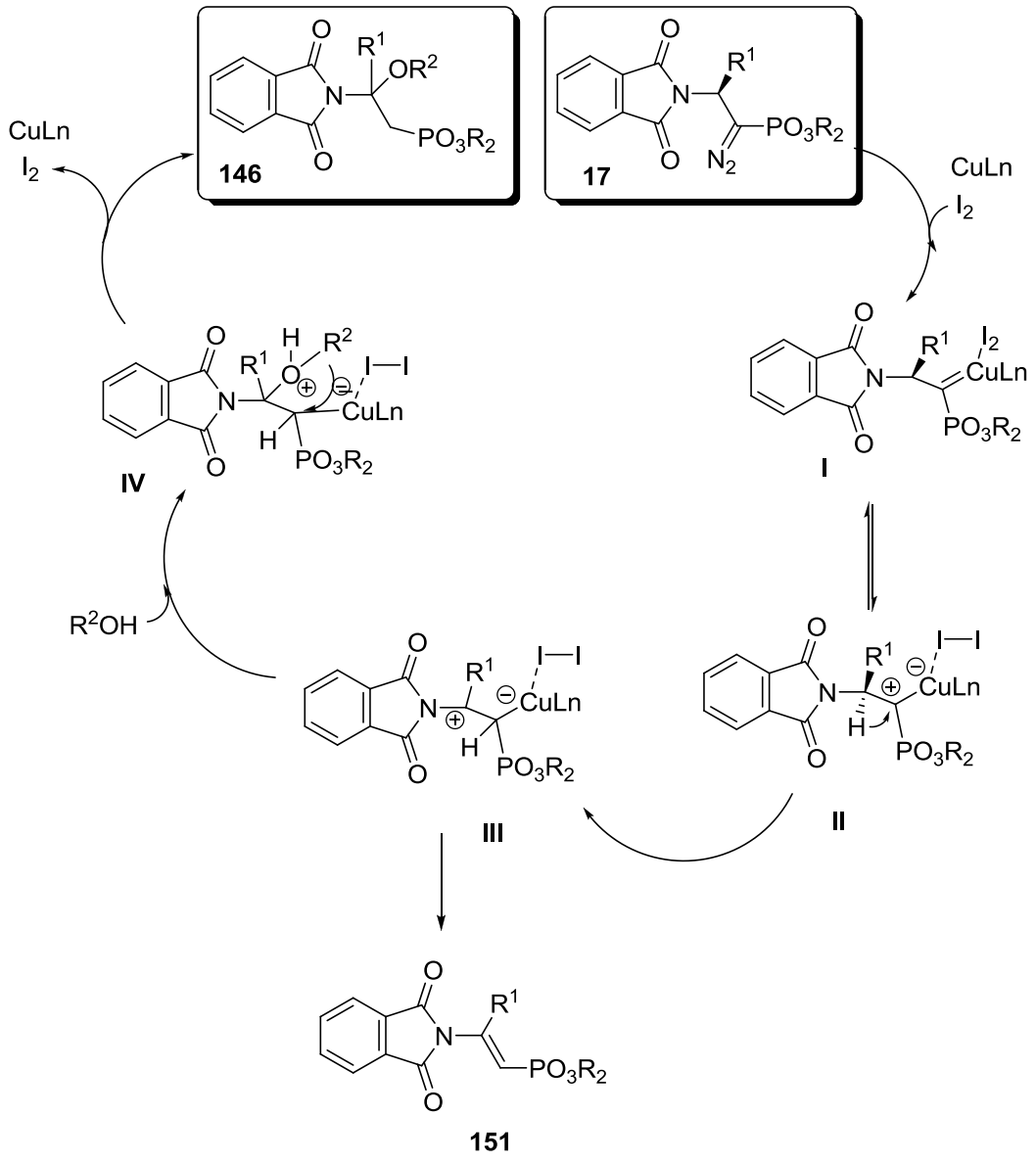
O-H insertion reaction with a series of natural amino acids-derived PCDCs **17a-e** was recently explored by Cai *et al*.[42] Surprisingly, reaction of **17a** with benzyl alcohol in the presence of 5 mol% $[Cu(MeCN)_4]PF_6$ as catalyst and 20 mol% $I_2$ as additive in dichloromethane at 25 °C did not afford the corresponding O-H insertion product but led to the formation of diethyl (2-(benzyloxy)-2(1,3-dioxoisoindolinyl)propyl phosphonate (**146**) in 50% yield along with (*Z*)-diethyl(2(1,3-dioxoisoindolin-2-yl)prop-1-en-yl)phosphonate (**147**), as by product, in 17% yield (Scheme 60).

**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 $[Cu(MeCN)_4]PF_6$ 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.**

**Scheme 61. Plausible Mechanism for the Combined C-H functionalization/O-H Insertion Reaction**

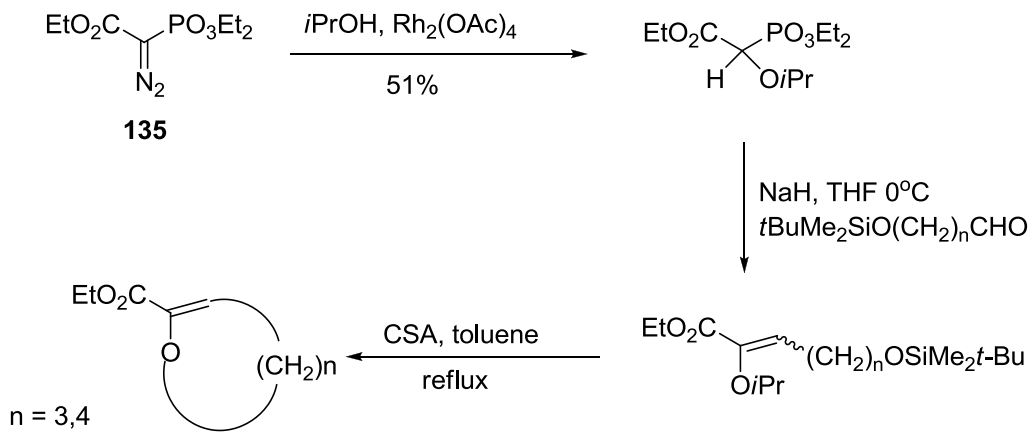



When different PCDCs were tested, the authors proved that the ester group at the phosphono moiety (R) had almost no influence, whereas the substituent group at the β-position ($R^1$) had an impact on the outcome of the reaction. It was indeed found, that bulky substituents impeded the reaction, most probably because they exerted steric hindrance on the carbocation **III** and that small groups,

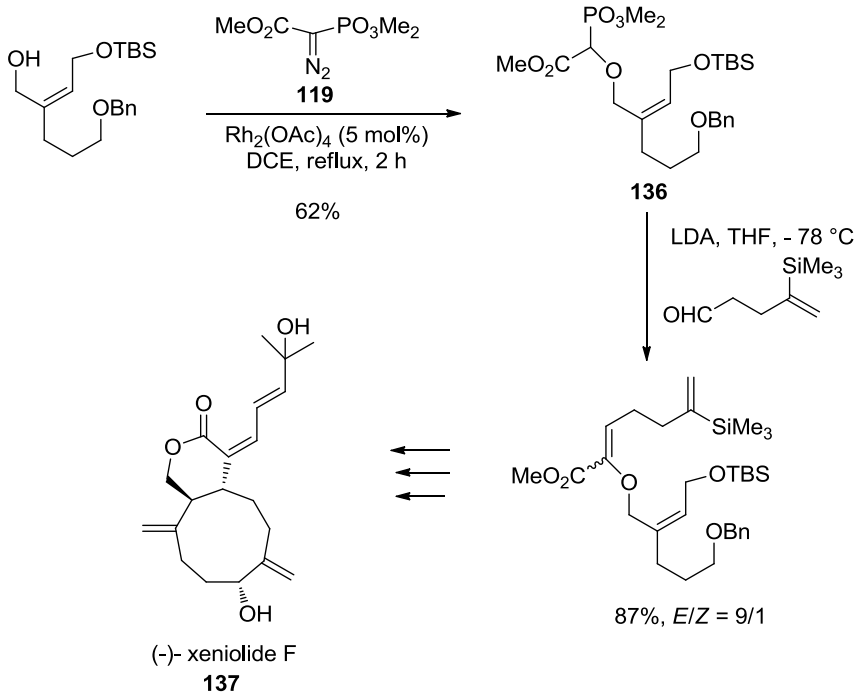
such as hydrogen, led only to trace of product due to the lack of stabilization of the carbocation **III**. As far as the scope of alcohol substrate is concerned, primary, secondary and electron-withdrawing group-substituted benzyl alcohols gave good yield and chemoselectivity, whereas electron-donating 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-aminophosphonates. $Rh_2(OAc)_4$-catalyzed O-H insertion reaction of α-diazo-β-ketophosphonates was also recently reported in aqueous medium.[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),[120,121] as well as in the functionalization of 2,5-disubstituted indoles, endowed with antiglycaemic properties,[122, 123] and acyl indoles derivatives for the treatment of dislipidemia and type 2 diabete.[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).[125,126]

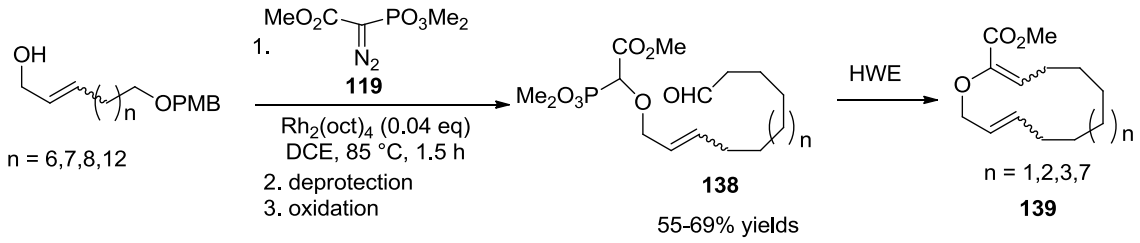
**Scheme 62. Example of Application of Alkoxyphosphonoacetates in the Preparation of Cyclic Enol Ethers**



**Scheme 63. Alkoxyphosphonacetate 136, as a Key Intermediate in the Synthesis of (-)-Xeniolide F (137)**



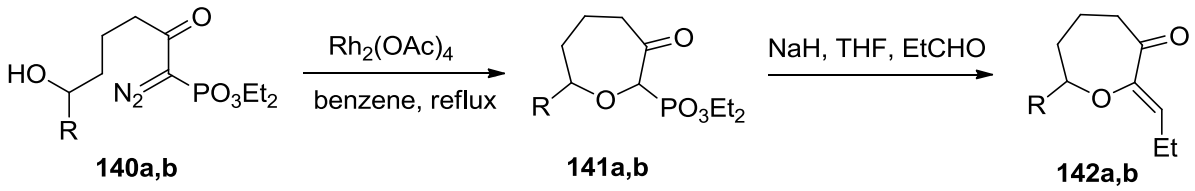

**Scheme 64. Alkoxyphosphonacetate 138, as a Key Intermediate in the Synthesis of Cyclic Allyl Vinyl Ethers 139**




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.[128] This synthetic procedure was expanded to the synthesis of other 2-substituted-3-oxepanones[129] and then specifically applied to the synthesis of *cis*-2,7-disubstitued-oxepane intermediates **142b** endowed with the skeleton of the marine natural product isolaurepinnacin (Scheme 65).[130]

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

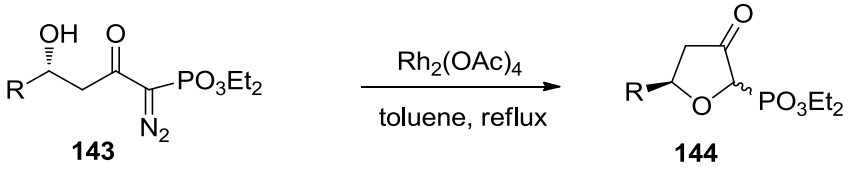



**140a,b** **141a,b** **142a,b**

a: R = H, 52% (**141**); b: R = $C_6H_{13}$, 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.[131] 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/aryltetrahydrofurans 144**

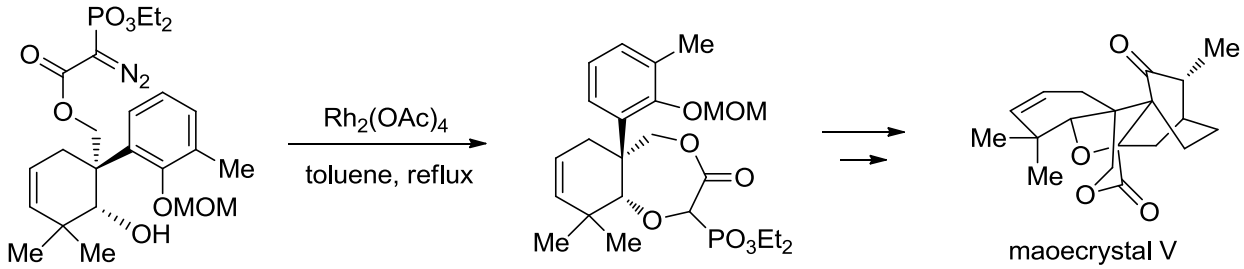



**143** **144**

R = Me, Et, vinyl, aryl 81-84 % yields

Another elegant example of intramolecular $Rh_2(OAc)_4$-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 α-diazophospono ester **145** allowed the formation of the seven-membered ether **146**, in quite good yield, as suitable intermediate toward the title compound (Scheme 67).

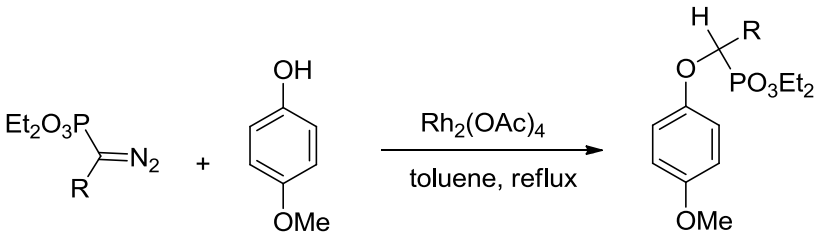
**Scheme 67. Intramolecular Rhodium-Catalyzed O-H Insertion Reaction of 145, as a Key Step in the Total Synthesis of Maoecrystal V (147)**




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-**

**Methoxyphenol**



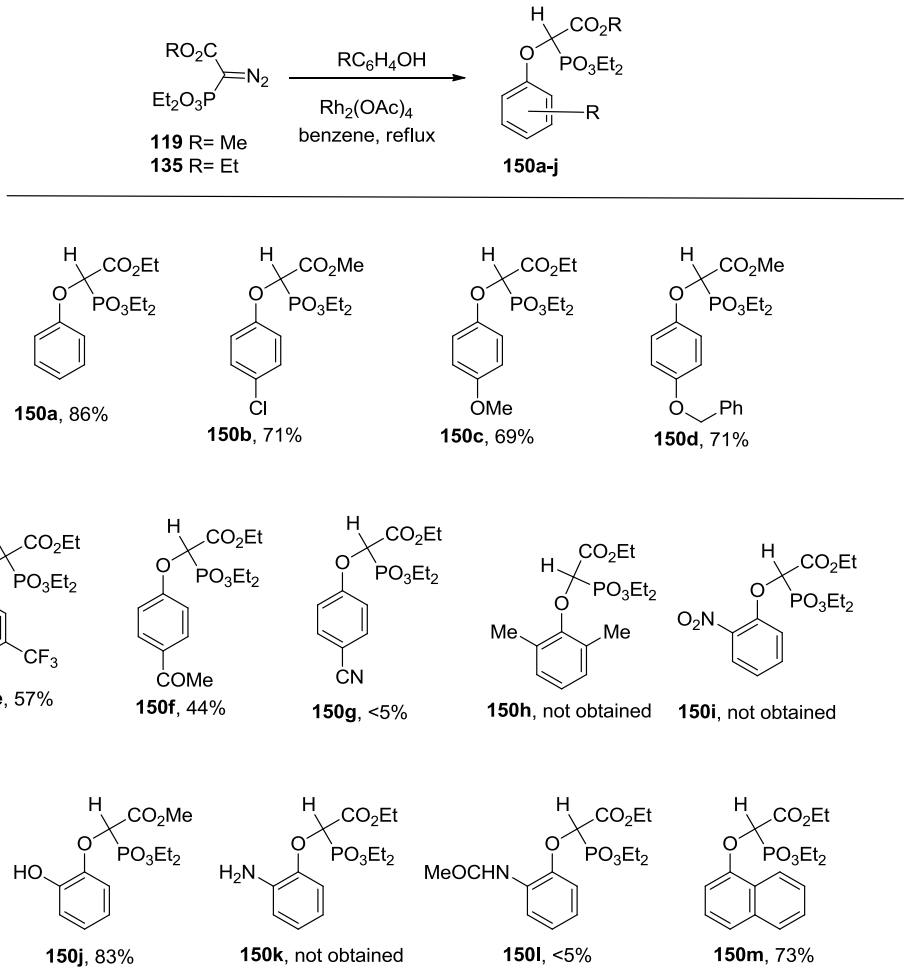

**135:** R = $CO_2Et$
**20f:** R = $PO_3Et_2$
**148:** R = $PhSO_2$

**149a-c**

a: R = $CO_2Et$, 78%; b: R = $SO_2Ph$, 81%; c: R = $PO_3Et_2$, no product

Independently, another group from SmithKline Beecham[134] reported on O-H insertion of trialkyl diazophosphonoacetes 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 bycycic phenols (Scheme 69).

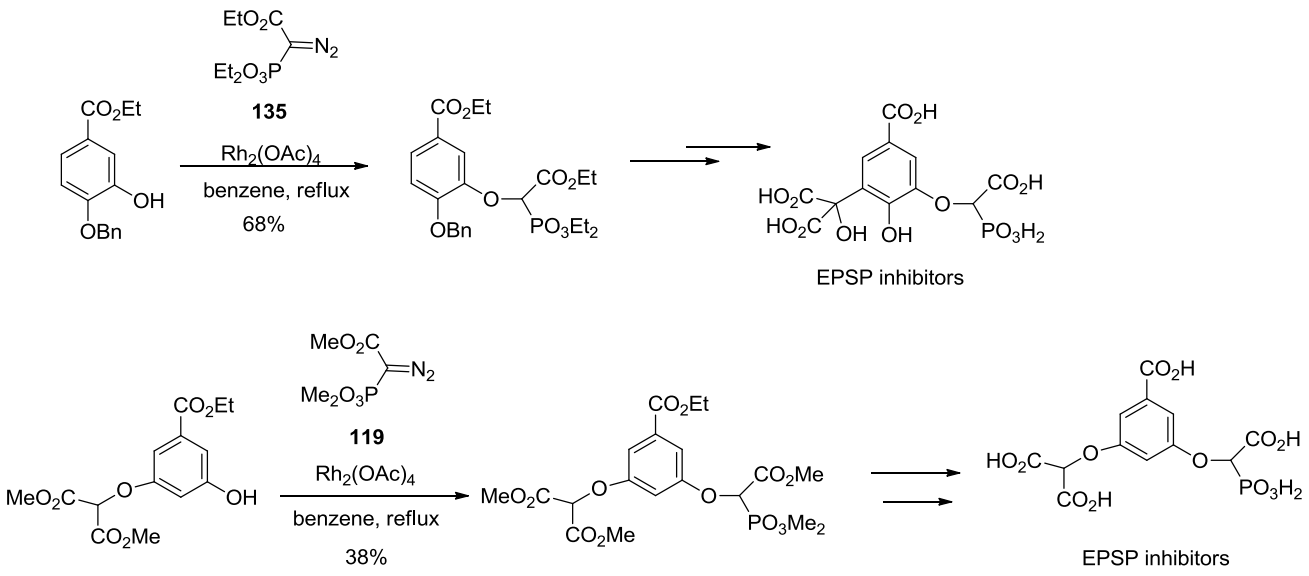
**Scheme 69. Rhodium-Mediated O-H Insertion Reaction of PCDCs 119 and 135 with Phenols**




Aller *et al.*[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 experiements 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

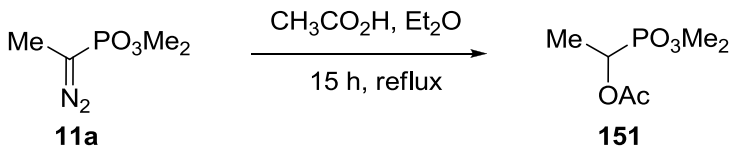
proved to be more efficient than to the phenol. Soon after these studies, applications in the synthesis of biologically active compounds appeared in the literature. In particular, the rhodium(II) acetate-catalyzed decompositions of PCDCs **135** and **119** with phenol derivatives have been reported to afford useful intermediates toward the synthesis of inhibitors of the 5-enolpyruvoylshikimate-3-phosphate synthase enzyme (EPSP) (Scheme 70).[136, 137]

**Scheme 70. Applications of PCDCs 135 and 119 in the Synthesis of EPSP Synthase Inhibitors**



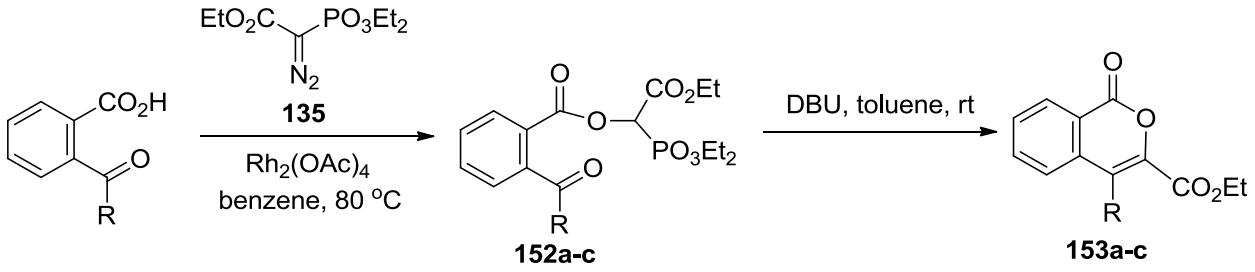

Investigations on the mechanism of decomposition of PCDCs in the presence of acids were described by Seyferth *et al*.[38] In particular, they reported on the decomposition of **11a** either in ethereal acetic acid or benzoic acid. The first acid proved to be very slow in catalyzing the decomposition of **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.**).

**Scheme 71. Metal-Free Decomposition of 11a in the Presence of Acetic Acid**



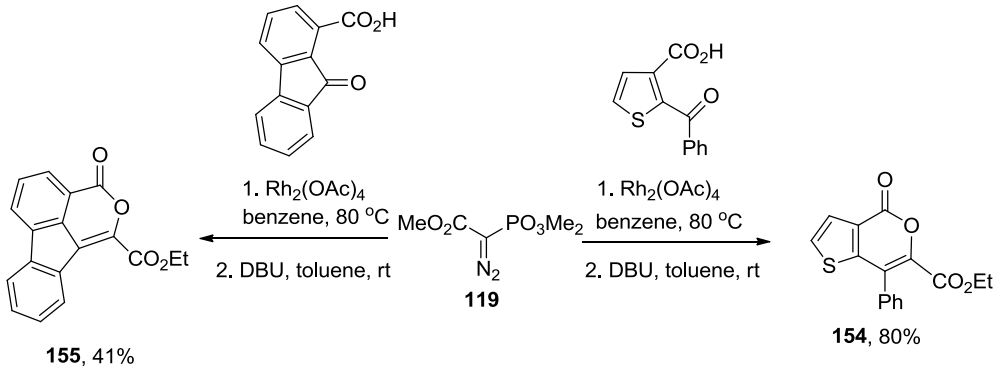
After this first attempt, Nakamura *et al*.[138] described the reaction of PCDC **135** with 2-benzoylbenzoic acid in the presence of rhodium(II) acetate in toluene at 80 °C, affording the insertion products **152a-c**. The subsequent base-catalyzed reaction gave access to 3,4-disubstituted isocoumarins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

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



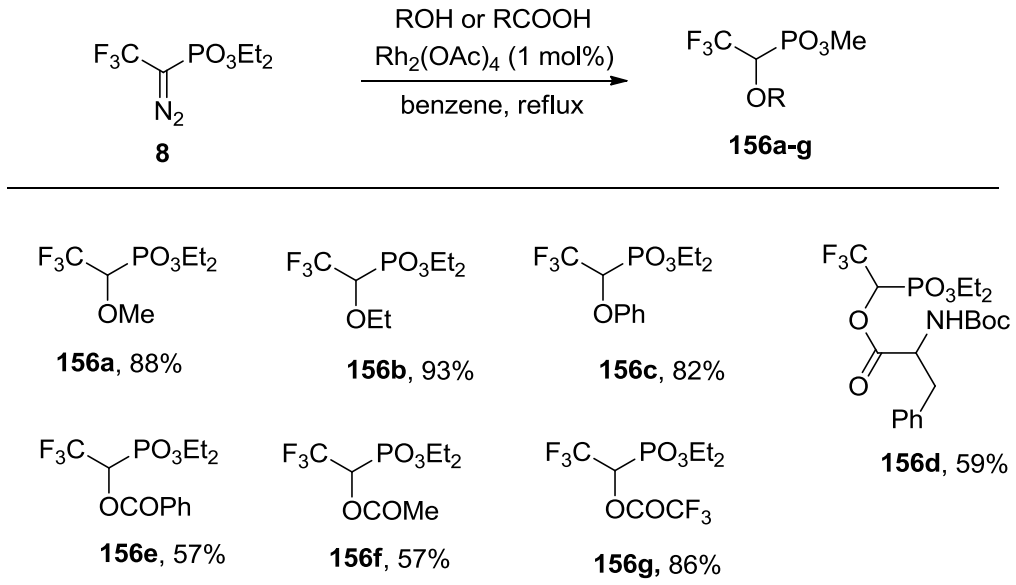

a: R = Ph, quantitative (**152**); b: R = H, quantitative (**152**); c: R = 3,4,5-$(MeO)_3C_6H_2$, quantitative (**152**)

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




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. ).[139]

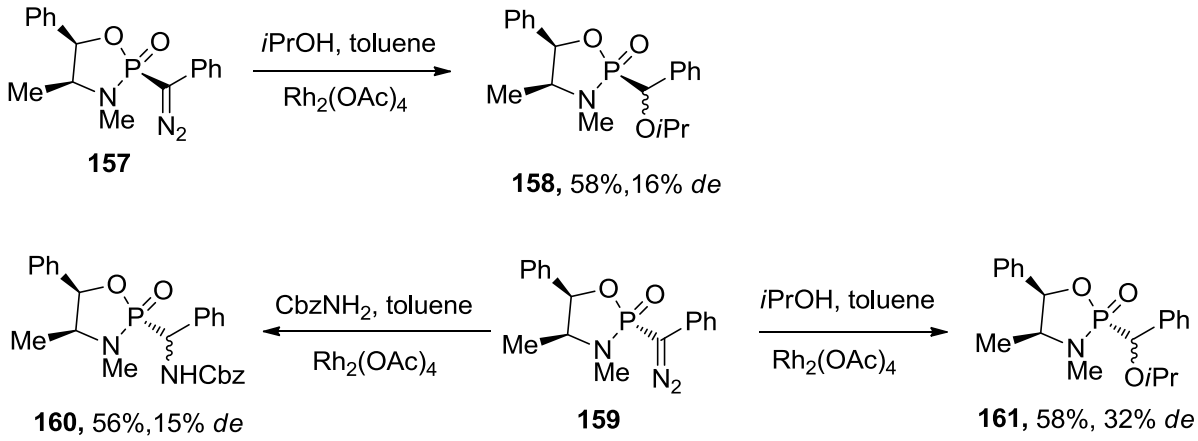
**Scheme 74. COO-H and O-H Insertion Reaction of PCDC 8**




### 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*.[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 *trans*-1,2-*bis*(*N*-methylamino)cyclohexane (Scheme 75). Although no products were observed with the diazocompounds bearing the latter auxiliary, the corresponding reaction of ephedrine derivatives **157** and **159** with 2-propanol and benzylcarbamate, in the presence of rhodium(II) acetate, led to the formation of the corresponding insertion products **158** and **161**, and **160**, respectively. However, this chiral group was shown to impart poor stereocontrol to the insertion reactions with *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.[135]

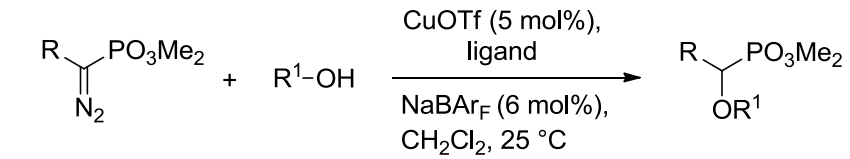
**Scheme 75. Rhodium-Catalyzed O-H and N-H Insertion Reactions of Chiral PCDCs 157 and 159**




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*,) 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%) α-Aryl-PCDCs gave better results than the α-alkyl ones. This methodology proved to be an efficient approach to access enantiomerically enriched α-alkoxyphosphonates starting from readily available materials.

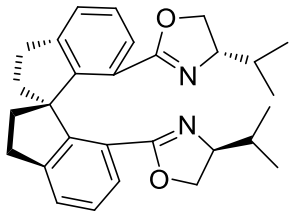
**Scheme 76. Enantioselective Copper-Catalyzed O-H Insertion Reaction**




R = Ph, aryl, Me
$R^1$ = alkyl, alkenyl, benzyl

19-98% yields
38-98% *ee*

ligand =

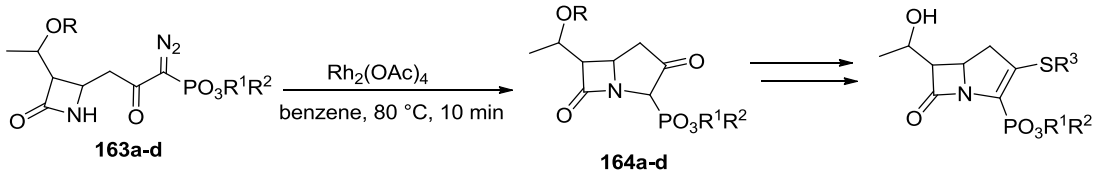



($S_\alpha$,*S*,*S*)-**162**

### 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).[141] The Merck group reported the same reaction leading to identical intermediates **164a,b** for the synthesis of different carbapenem analogues.[142]

**Scheme 77. Intramolecular N-H Insertion Reaction**




**163a-d**

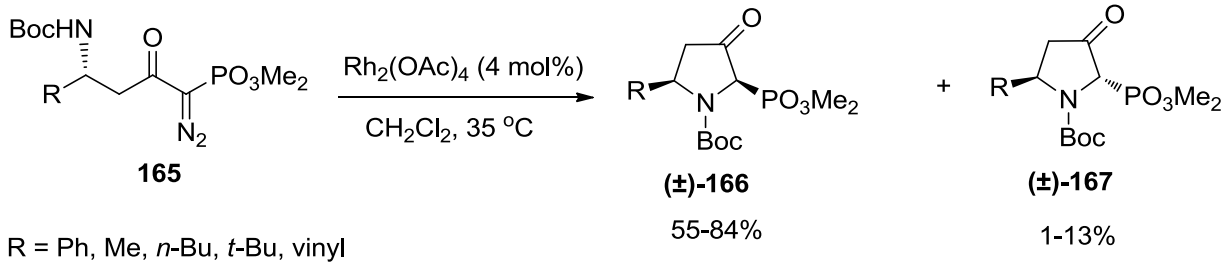
**164a-d**

60-90% yields

a: R = TBS, $R^1$ = $R^2$ = Me; b: R = TBS, $R^1$ = $R^2$ = Bn; c: R = H, $R^1$ = $R^2$ = Bn; d: R = H, $R^1$ = Me, $R^2$ = Bn

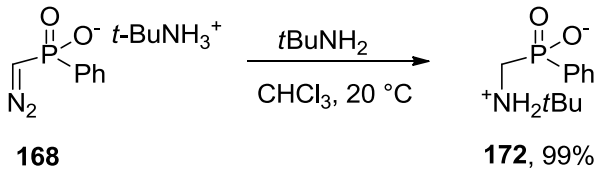
Intramolecular N-H insertion reaction was also exploited for the preparation of *cis*-5-substituted-pyrrolidine phosphonates **166** starting from the PCDCs **165**. The reaction proceeded with high stereoselectivity leading to no more than 13% of the corresponding *trans*-isomers **167** (Scheme 78).[143]

**Scheme 78. Asymmetric Synthesis of *cis*-Pyrrolidine-2-phosphonates 166**



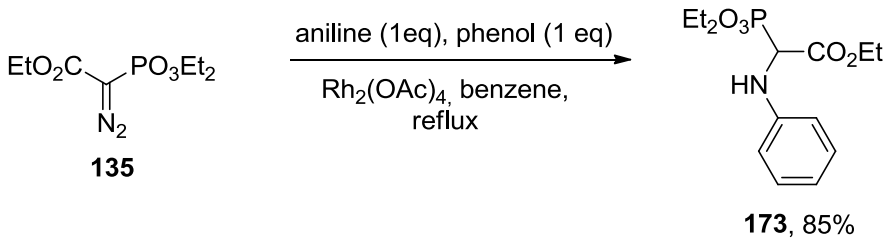

In 1985, Regitz and Martin reported the decomposition of the *t*-butylammonium salt of the α-diazo-phosphinate **168** in the presence of *t*-butyl amine affording the betain **172** in excellent yield (Scheme 79).[98]

**Scheme 79. Decomposition of PCDC 168 in the Presence of *tert*-Butylamine**




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).[134]

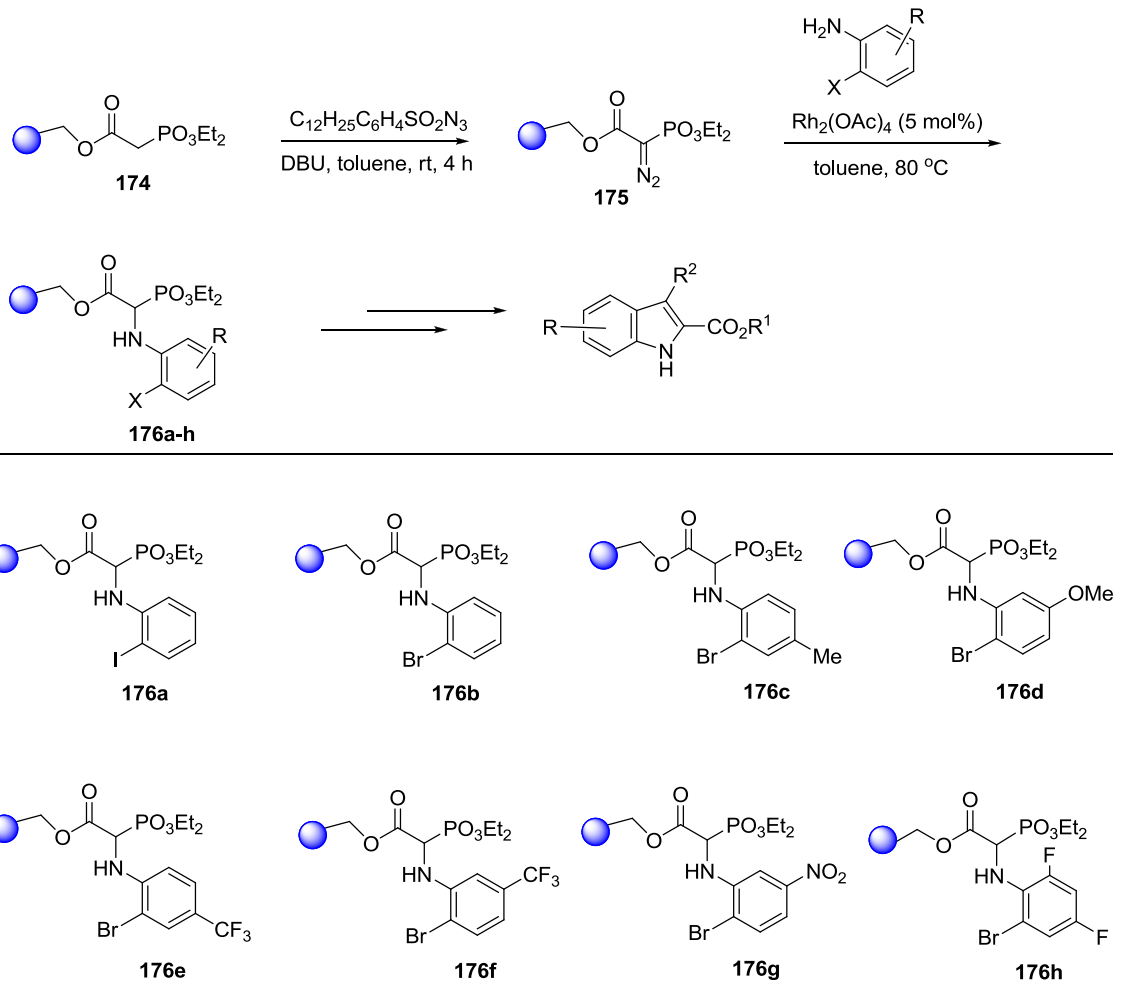
**Scheme 80. Metal-Catalyzed N-H *vs* O-H Insertion Reactions**




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.[144,145]

In 2003, the first report of N-H insertion reactions of rhodium carbenoids generated by a polymer-supported PCDC was published.[146] 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).

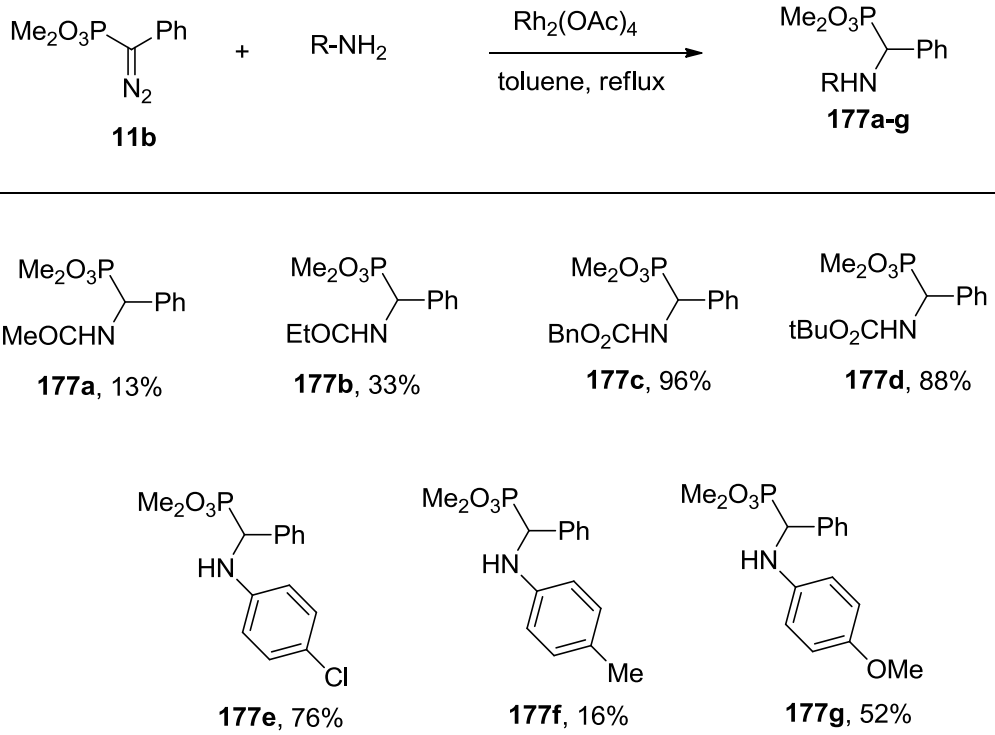
**Scheme 81. Solid-phase Synthesis of Indolecarboxylate Derivatives**




This synthetic procedure was subsequently applied to the synthesis of isocumarins *via* insertion of **175** into the COO-H bond of benzoic acid derivatives.

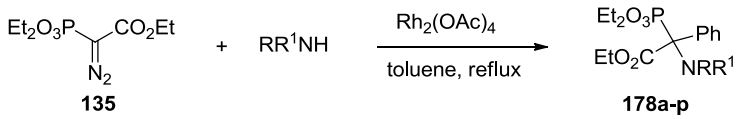
Aller *et al*.[147] assayed N-H insertion of PCDCs as a route to aminophosphonates by the investigation of the rhodium(II) acetate-catalysed decomposition of diazophosphonate **11b** with a limited series of primary amides, carbamates and anilines (Scheme 82). The reactions with benzyl and *t*-butyl carbamates gave the corresponding products **177c,d** in excellent yield, unlike the amides. The reaction with anilines was found to be strongly dependent on the aromatic ring substituent.

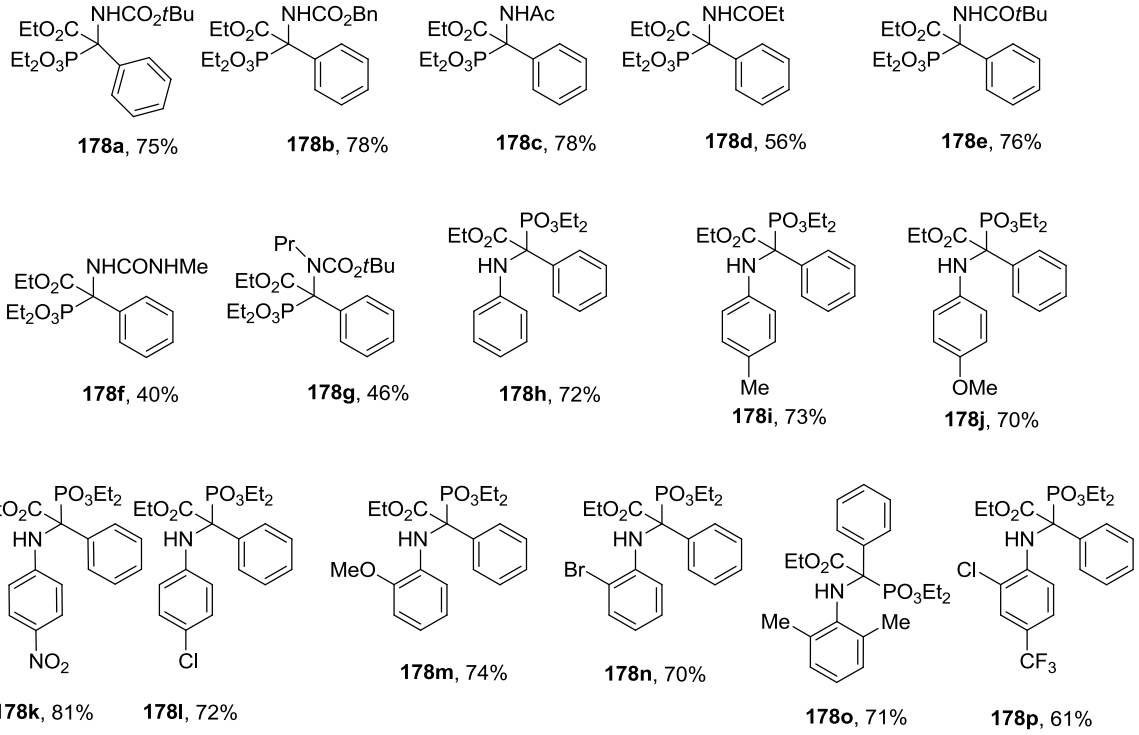
**Scheme 82. N-H Insertion Reaction of 11b as Route to α-Aminophosphonates 177a-g**




In a following report, Ferris *et al*.[148] investigated more deeply this synthetic strategy by starting from PCDC **135** (Scheme 83).

**Scheme 83. Preparation of *N*-Substituted Phosphorylglycine Esters 178a-p**

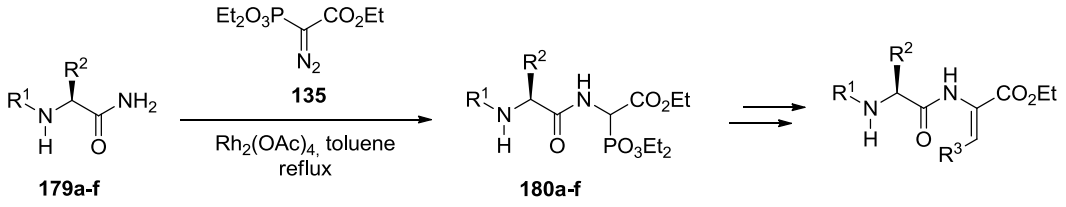


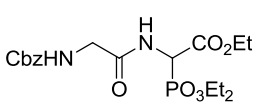




The N-H insertion reaction was also exploited for the synthesis of dipeptides of dehydroaminoacids.[149] Thus, by treatment of a series of protected amino acid amides **179a-f** with triethyl diazophosphonoacetate (**135**), under rhodium(II) acetate catalysis, the corresponding N-H insertion products **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.[150]

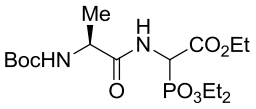
**Scheme 84. N-H Insertion Reaction as a Key Step toward the Synthesis of Dipeptides of**

**Dehydroaminoacids**

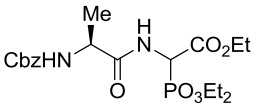


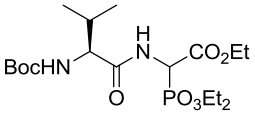

**180a**, 81%



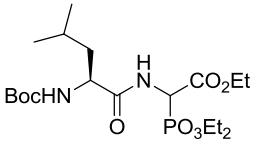

**180b**, 86%



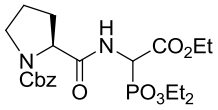

**180c**, 80%




**180d**, 80%



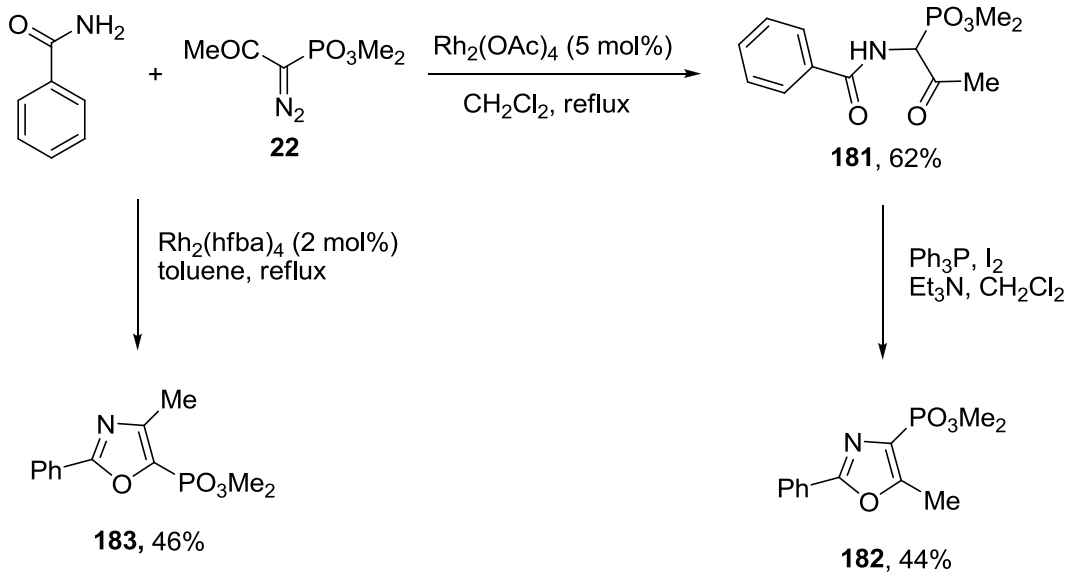

**180e**, 82%




**180f**, 80%

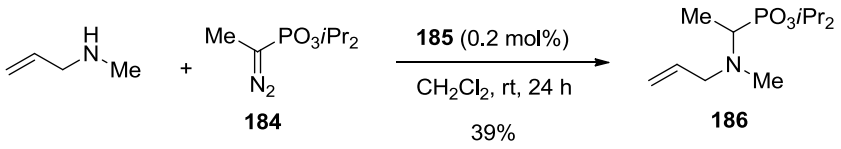
In an effort to elaborate new synthetic routes to anchoring the bisphosphonate moiety into alcohols, phenols, and amines, the metal-catalyzed insertion reaction of PCDC **20f** was also developed.[151,152] Rhodium(II)-catalyzed N-H insertion reaction of BOR (**22**) with arylcarboxamides was exploited for the synthesis of 2-aryloxazole-4-phosphonates (Scheme 85). In the presence of $Rh_2(OAc)_4$, 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-methyloxazole-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.[153,154]

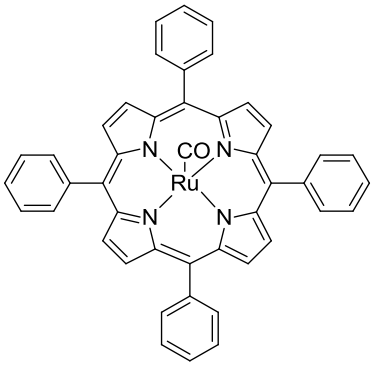
**Scheme 85. Synthesis of Oxazole-4-and 5-Phosphonates 182 and 183**




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.**).[155]

**Scheme 86. (TPP)Ru(CO)-Catalyzed N-H Insertion Reaction of Diisopropyl α-Diazoethylphosphonate (184) with *N*-Methyl Allyl Amine**



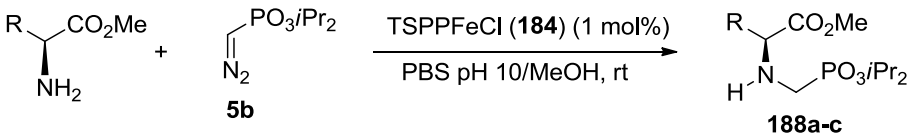




**(TPP)Ru(CO)**

**185**

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.[156]

**Scheme 87. TSPPFeCl-catalyzed N-H Insertion Reaction of 5b**

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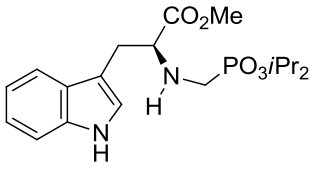
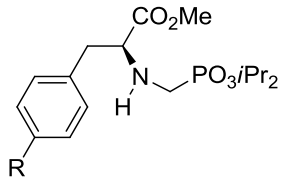
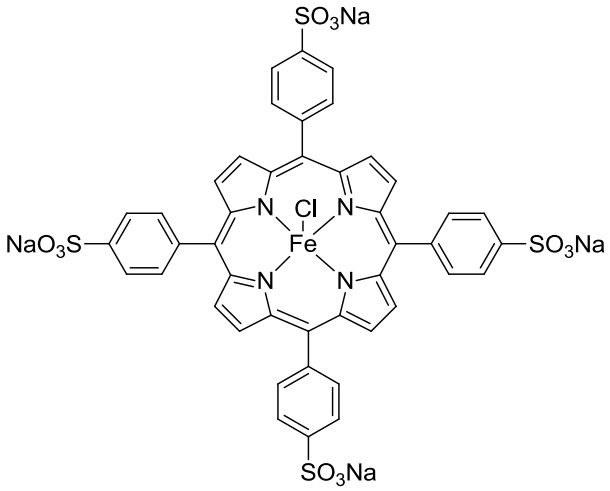



**188a**, 90%




R = OH, **188b**, 92%
R = H, **188c**, 81%

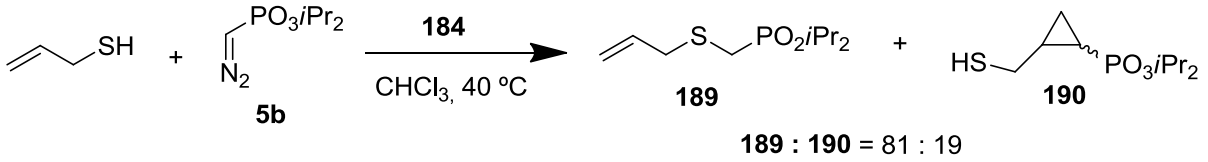



**TSPPFeCl**
**187**

### 3.2.4. Other X-H Insertion Reactions

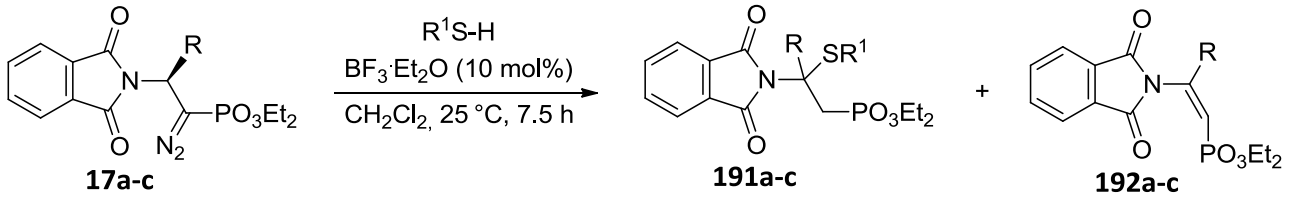
An example of insertion reaction of PCDCs into S-H bond was reported by Paul-Roth *et al.*,[157] who obtained the methylthio-substituted derivative **189** by the (TPP)Ru(CO)-catalyzed reaction of **5b** with 2-propene-1-thiol. The competitive cyclopropanation reaction led to the concomitant formation of the cyclopropyl derivative **190** althought as minor component (Scheme 88).

**Scheme 88. (TPP)Ru(CO)-Catalyzed Intermolecular S-H Insertion Reaction**




In the wake of their previous works on the catalyzed decomposition of amino acid- derived PCDCs, Cai *et al*.[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,[42] a combined C-H functionalization/S-H insertion reaction occured affording the corresponding products **191a-c** along with variable amounts of the β-hydride elimination-derived side-products **192a-c** (Scheme 89).

**Scheme 89. $BF_3{\cdot}Et_2O$-Catalyzed Combined C-H Functionalization/S-H Insertion Reaction**

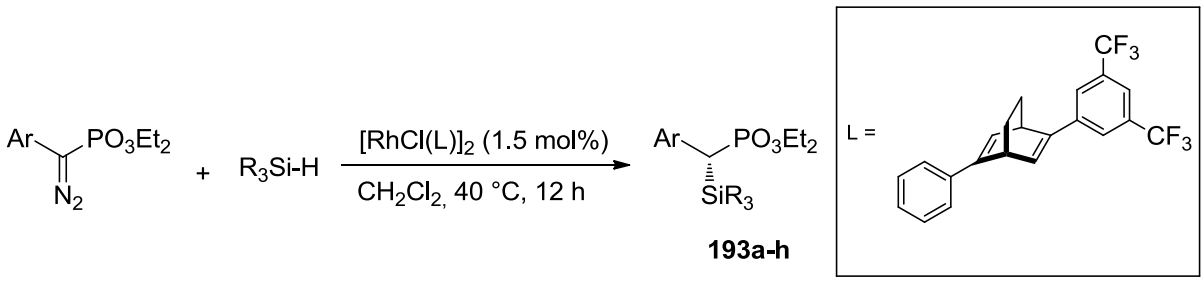


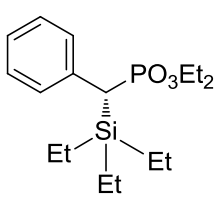

a: R = Me, $R^1$ = Et, 55% (**191**), 84:16 ratio (**191**/**192**); b: R = *i*Pr, $R^1$ = Et, 51% (**191**), 77:23 ratio (**191**/**192**);
c: R = *i*Bu, $R^1$ = Et, 52% (**191**), 75:25 ratio (**191**/**192**); d: R = Me, $R^1$ = *i*Pr, 52% (**191**), 84:16 ratio (**191**/**192**);
e: R = Me, $R^1$ = *t*Bu, 29% (**191**), 68:32 ratio (**191**/**192**); f: R = Me, $R^1$ = 4-$MeC_6H_4$, 60% (**191**), 90:10 ratio (**191**/**192**)

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.

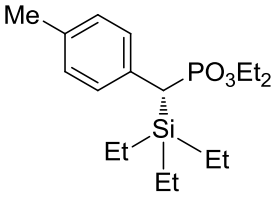
Highly innovative characteristics are present in the paper recently published by Chen *et al*.,[159] who reported the first enantioselective rhodium(I)-catalyzed Si-H insertion of α-diazoesters and PCDCs. The Rh(I)-carbene chemistry has been so far little explored and only recently has demonstrated to exhibit ability in the catalytic asymmetric formation of C-C bonds.[160–163] 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**

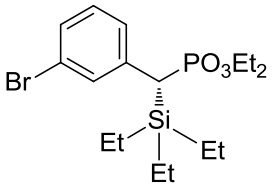


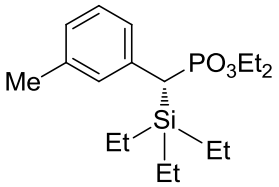

**193a**
59%, 93% *ee*



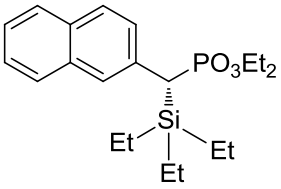

**193b**
53%, 93% *ee*



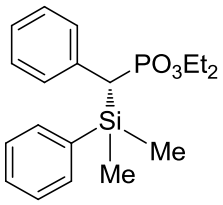

**193c**
63%, 92% *ee*



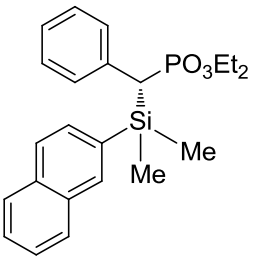

**193d**
57%, 97% *ee*



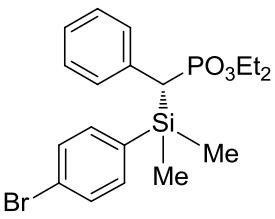

**193e**
46%, 97% *ee*




**193f**
48%, 95% *ee*




**193g**
55%, 97% *ee*




**193h**
52%, 92% *ee*

## 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,[164,165] as well as a versatile building block being able to be converted into a range of other functionalities.[166,167,168] 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.[27,169–171,172] High diastereo-and enantio-control have been demonstrated by the use of a number of chiral transition metal complexes, rhodium- and

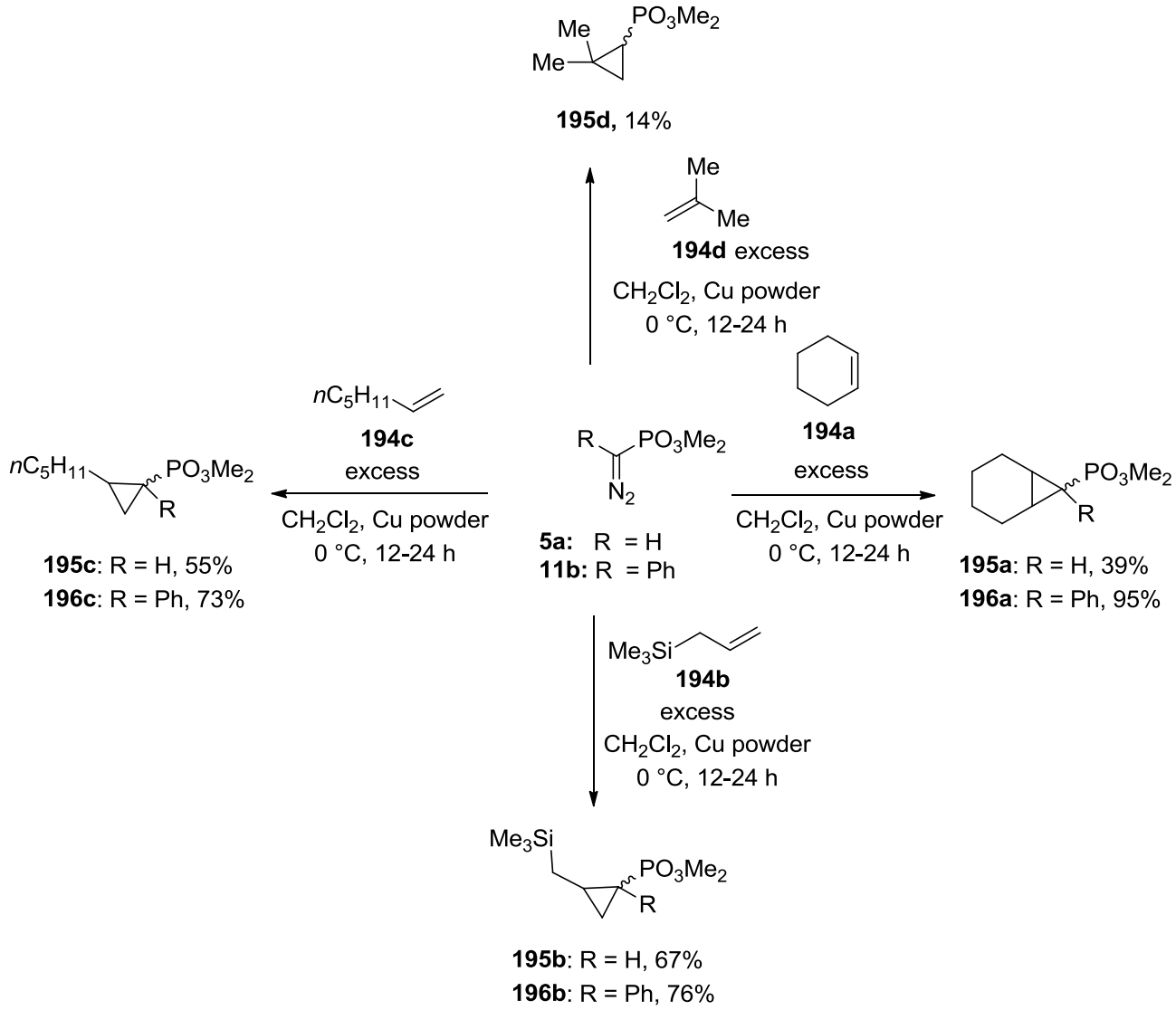
ruthenium-based catalysts, in particular. However, the possibility to direct the reaction toward the preferential formation of the *cis* isomer still remains unsuccessful. Moreover there are only few applications of alkene cyclopropanation of substrates other than styrene derivatives.

### 3.3.1. Intermolecular Alkene Cyclopropanation

Seyferth *et al.*[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).[6,30] Similarly, α-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.[30] The author did not mention any informations about the diastereoselectivity achieved.

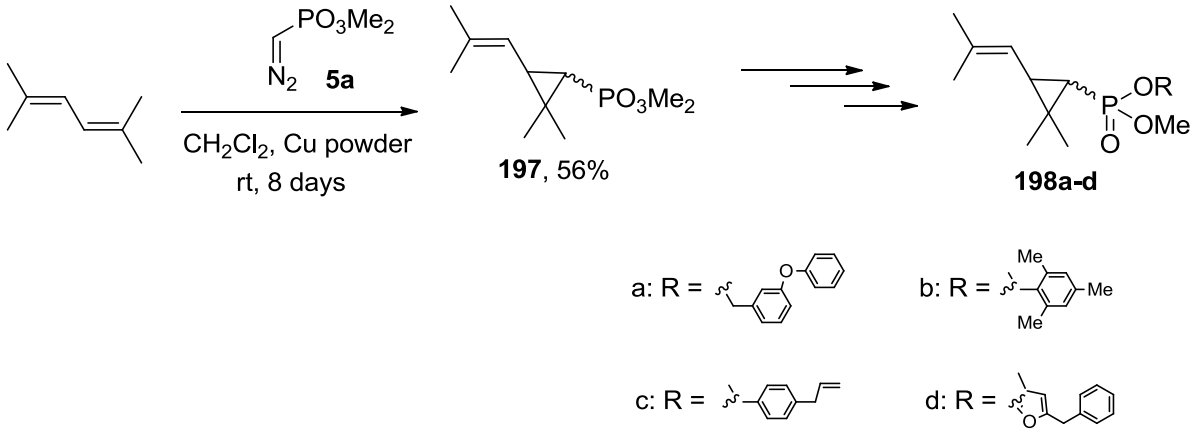
**Scheme 91. Cyclopropanation Reaction of 5a and 11b with Olefins 194a-c under Copper Powder**

**Catalysis**



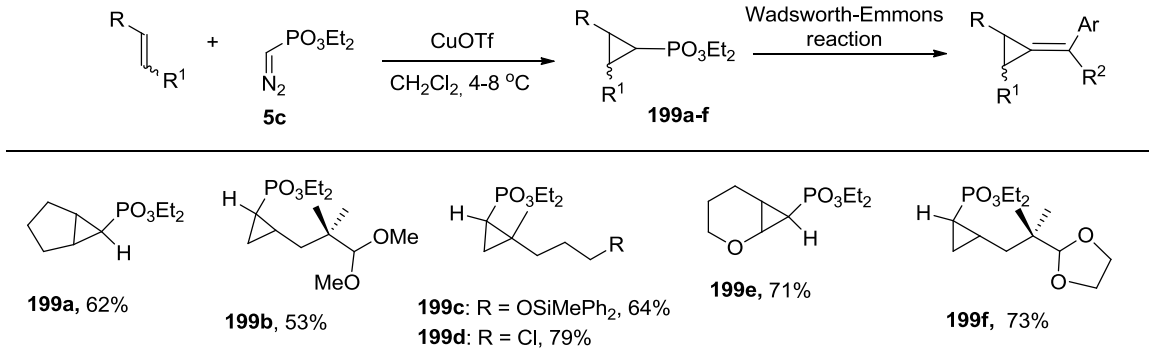

The copper-catalysed cyclopropanation methodology reported by Seyferth,[6,30] was successively applied by Reid *et al*.[173] to the synthesis of phosphonate-analogs of the natural insecticidal pyrethrins (Scheme 92). Cyclopropylphosphonate **197** was obtained in 56% yield as a mixture of *cis*- and *trans*-isomers, which, without separation of the structural or optical isomers, were than further modified to obtain the desired cyclopropyl phosphonate derivatives **198a-d**.

**Scheme 92. Synthesis of Phosphonochrysanthemates 198**




In order to study the chemical reactivity of alkylidene cyclopropane units, Lewis *et al*.[174] re-investigated Seyferth procedure[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 **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,[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 **199a-f**, used then as the starting materials for the susequent HWE reaction (Scheme 93).

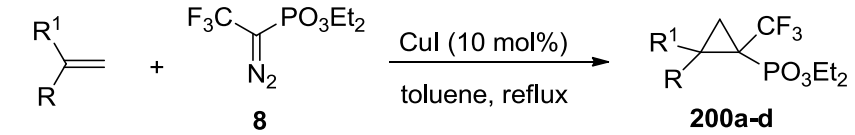
**Scheme 93. Copper(I) Triflate-Catalyzed Cyclopropanation of Olefins with 5c.**

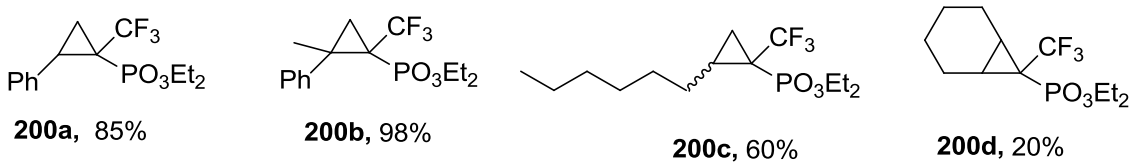



Copper iodide was found to be the best catalyst for the decomposition of diethyl 1-diazo-2,2,2-trifluoroethylphosphonate (**8**) in the presence of alkenes to give the corresponding trifluoromethyl-substituted cyclopropyl phosphonates **200a-d** (Scheme 94).[175] The screening of a small series of different 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 94. Synthesis of Trifluoromethyl Cyclopropyl Phosphonates via CuI-Catalyzed**

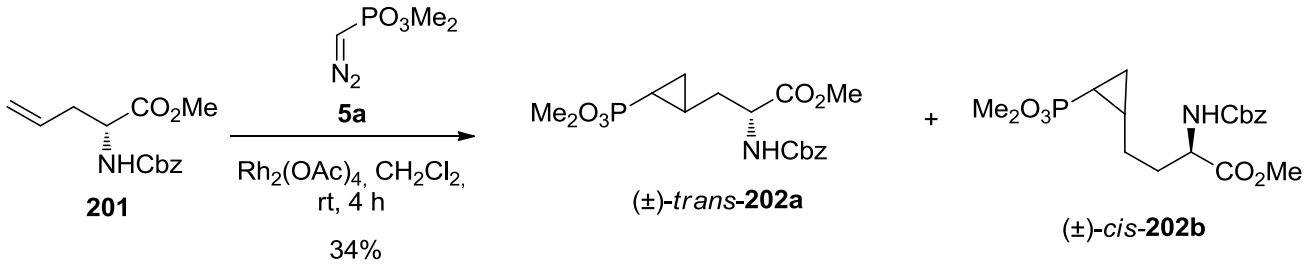
**Decomposition of Diethyl 1-Diazo-2,2,2-trifluoroethylphosphonate (8)**




$Rh_2(OAc)_4$ was instead the catalyst used by Dappen *et al*.[176] for the synthesis of phosphono cyclopropyl derivatives **202a,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 **202a,b** by cyclopropanation with **5a**. The desired acid derivatives were then obtained after hydrolysis with 6N HCl (Scheme 95).

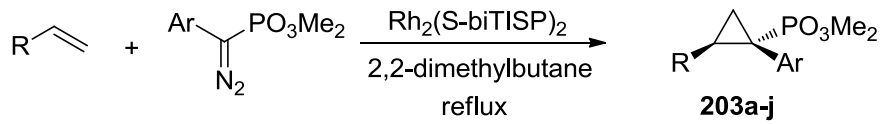
**Scheme 95. Synthesis of Cyclopropyl Analogues of 2-Amino-5-phosphonopentanoic Acid**




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**

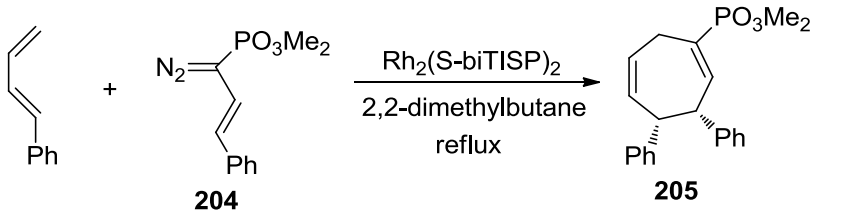



**203a-j**

a: R = Ar = Ph, 89%, 98% *de*, 88% *ee*; b: R = 4-MeO-$C_6H_4$, Ar = Ph, 93%, 98% *de*, 89% *ee*; c: R = 4-Cl-$C_6H_4$, Ar = Ph, 95%, 98% *de*, 85% *ee*; d: R = 2-naphthyl, Ar = Ph, 93%, 98% *de*, 87% *ee*; e: R = styryl, Ar = Ph, 96%, > 98% *de*, 83% *ee*; f: R = *n*BuO, Ar = Ph, 91%, 44% *de*, 86% *ee*; g: R = *n*Bu, Ar = Ph, 6%, 98% *de*, 98% *ee*; h: R = Ph, Ar = 4-MeO-$C_6H_4$, 84%, >98% *de*, 82% *ee*; h: R = Ph, Ar = 4-Cl-$C_6H_4$, 80%, 98% *de*, 88% *ee*; i: R = Ph, Ar = 2-naphthyl, 85%, >98% *de*, 76% *ee*; j: R = Ph, Ar = styryl, 76%, >98% *de*, 68% *ee*

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,[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.[179] In the same paper, the $Rh_2$(*S*-biTISP)$_4$-catalyzed reaction between α-styryl-PCDC **204** and (1*E*)-buta-1,3-dien-1-ylbenzene was exploited for the construction of the seven-membered carbocyle **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*.

**Scheme 97.Tandem Cyclopropanation/Cope Rearrangement**

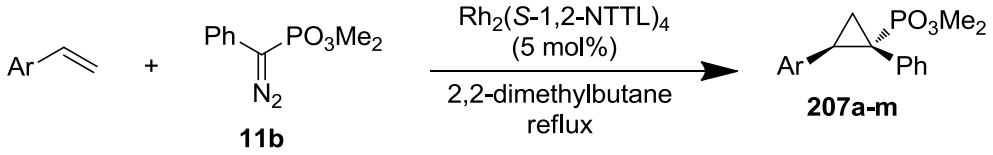



75% yield, >98% *de*, 65% *ee*

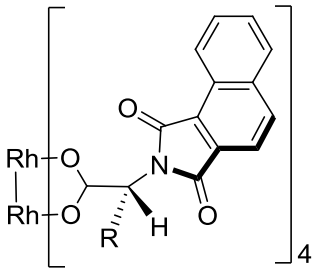
Later on Davies *et al*. reported $Rh_2$(*S*-PTTL)$_4$ (**99**) and $Rh_2$(S-PTAD)$_4$ (**100**) as far superior catalysts than $Rh_2$(*S*-biTISP)$_4$ (**98**), in the cyclopropanation of styrene with dimethyl α-diazobenzylphosphonate (**11b**), achieving levels of enantioselectivity of 97% and 99%, respectively.[96]

In 2014, Adly *et al*.[180] studied the effects of lowering the ligand's symmetry around the rhodium center on the cyclopropanation of styrene. Along with two commercial catalyst $Rh_2$(S-PTTL)$_4$ (**99**) and $Rh_2$(S-NTTL)$_4$, (**206a**) four new catalysts (**206b-e**), were evaluated in standard donor-acceptor cyclopropanation reactions using dimethyl α-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 $Rh_2$(*S*-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**




a: Ar = Ph, 93%, >20:1 *dr*, 92% *ee;* b: Ar = 4-Cl-$C_6H_4$, 92%, >20:1 *dr*, 94% *ee;* c: Ar = 4-MeO-$C_6H_4$, 93%, >20:1 *dr*, >99% *ee;* d: Ar = 4-Me-$C_6H_4$, 90%, >20:1 *dr*, 95% *ee;* e: Ar = 1-naphthyl, 86%, >20:1 *dr*, >98% *ee*



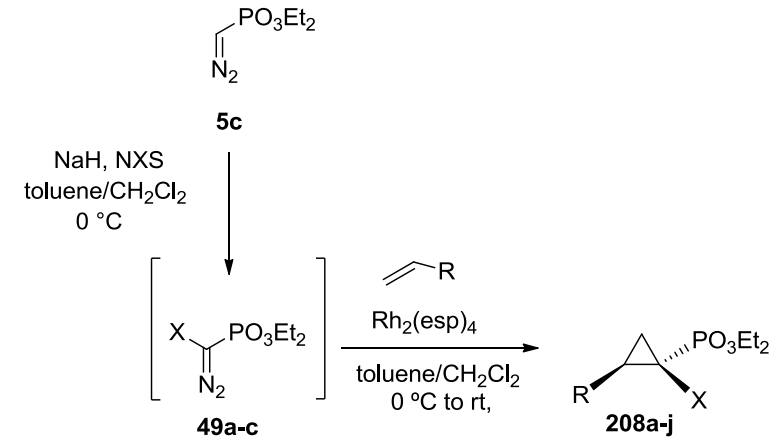

206a-e

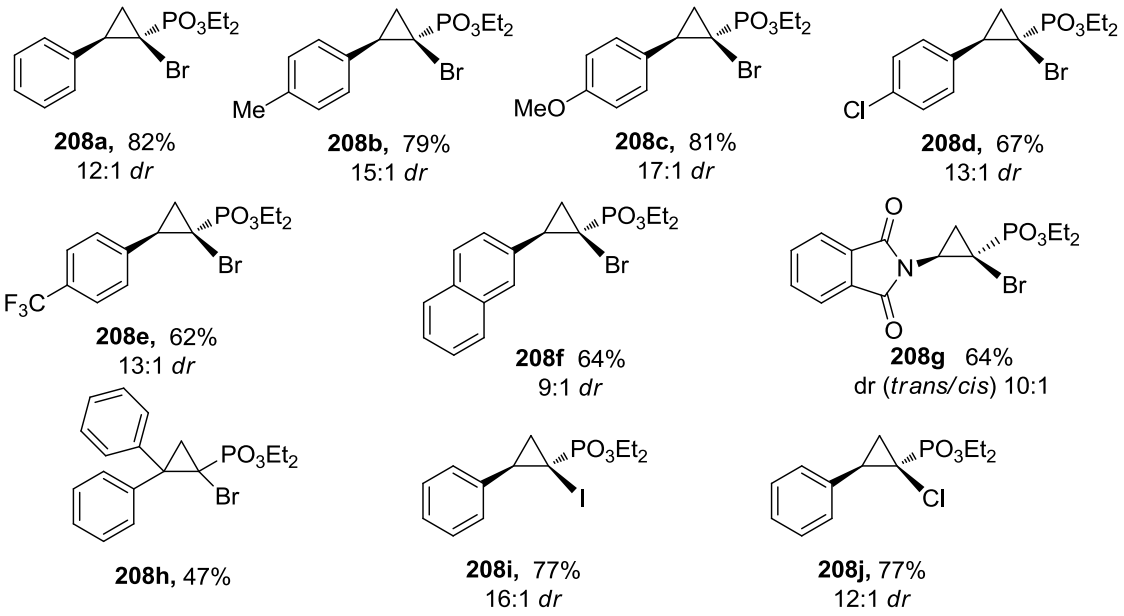
**a** R = *t*-Bu; $Rh_2$(*S*-1,2-NTTL)$_4$
**b** R = Bn; $Rh_2$(*S*-1,2-NTPA)$_4$
**c** R = *i*-Bu; $Rh_2$(*S*-1,2-NTLU)$_4$
**d** R = (1*H*-indol-3-yl)methyl; $Rh_2$(*S*-1,2-NTTR)$_4$
**e** R = *4*-OH-$C_6H_4$; $Rh_2$(*S*-1,2-NTTY)$_4$

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 diastereisomeric ratios in favour of the *trans* isomer.

**Scheme 99. Diastereoselective Rh(II)-Catalyzed Cyclopropanation of Styrene Derivatives with α-**

**Halo-α-diazomethylphosphonates 49a-c**



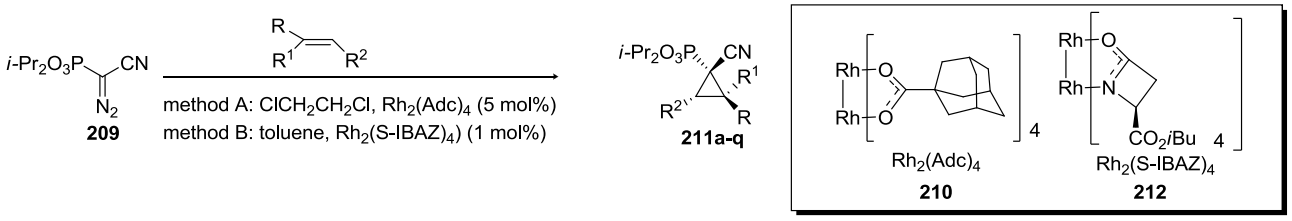

Later on, the same research group investigated other methodologies for the preparation of PCDCs **49a-c** to submit to *in-situ* cyclopropanation reaction. However, the obtained results were not better than the precedent ones. [70]

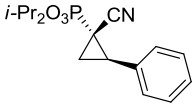
Considering the high potential of acceptor-acceptor cyclopropanes in asymmetric synthesis, Lindsay *et al*.[181] described in 2013, the first catalytic asymmetric synthesis of cycloprop(en)ylphosphonate derivatives, using α-cyano-α-diazomethylphosphonate (**209**), as the starting material. The choice 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 Asymetric Synthesis of Cyclopropylphosphonate Derivatives using α-Cyano-**

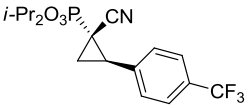
**α- Diazomethylphosphonate 209**



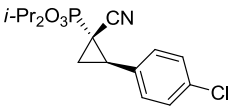

**211a**

method A: 99%, 89:11 *dr*
method B: 96%, 93:7 *dr*, 99% *ee*



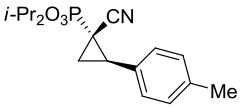

**211b**

method A: 97%, 95:5 *dr*
method B: 96%, 93:7 *dr*, 99% *ee*



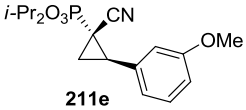

**211c**

method A: 99%, 90:10 *dr*
method B: 96%, 93:7 *dr*, 99% *ee*



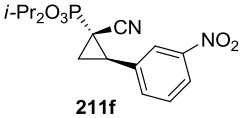

**211d**

method A: 98%, 83:17 dr
method B: 97%, 93:7 dr, 98% ee



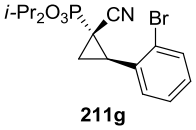

**211e**

method A: 98%, 87:13 *dr*
method B: 94%, 93:7 *dr*, 99% *ee*



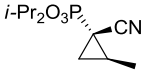

**211f**

method A: 99%, 94:6 *dr*
method B: 96%, 93:7 *dr*, 99% *ee*



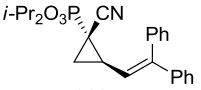

**211g**

method A: 98%, 97:3 *dr*
method B: 98%, 93:7 *dr*, 99% *ee*



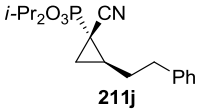

**211h**

method A: 96%, 65:35 *dr*
method B: 93%, 93:7 *dr*, 92% *ee*



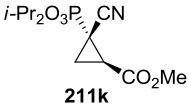

**211i**

method A: 96%, 69:31 *dr*
method B: 87%, 93:7 *dr*, 96% *ee*



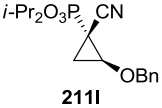

**211j**

method A: 97%, 95:5 *dr*
method B: 79%, 93:7 *dr*, 99% *ee*



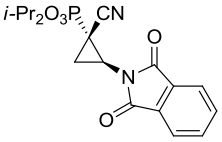

**211k**

method A: 81%, 82:181 *dr*
method B: 17%, 93:7 *dr*, nd *ee*



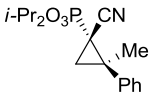

**211l**

method A: 99%, 95:51 *dr*
method B: 97%, 93:7 *dr*, 99% *ee*



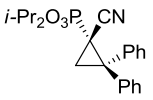

**211m**

method A: 97%, 78:22 *dr*
method B: 89%, 83:17 *dr*, 93% *ee*



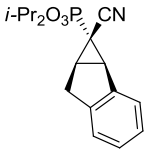

**211n**

method A: 98%, 62:38 *dr*
method B: 96%, 40:60 *dr*, 95% *ee*



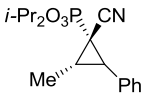

**211o**

method A: 99%,
method B: 25%




**211p**

method A: 93%, 97:3 *dr*
method B: 65%, 57:43 *dr*, 91% *ee*



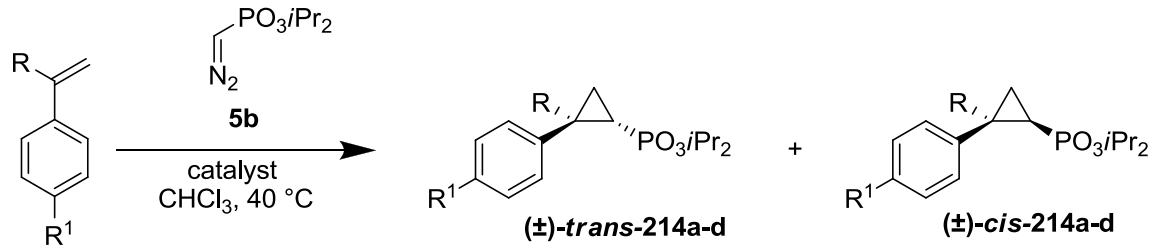

**211q**

method A: 82%, > 95:5 *dr*
method B: 4%, > 90:10 *dr*

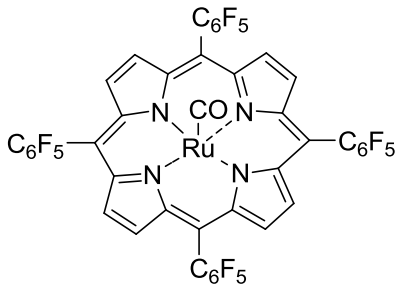
As far as concern ruthenium catalysts, in 2002 Simonneaux *et al*. described the use of homochiral porphyrins-ruthenium complexes (**184** and **213**), generally employed for the asymmetric epoxidation of olefins, in the cyclopropanation of styrene derivatives with diisopropyl α-diazomethylphosphonate (**5b**).[182] Under the experimental conditions already tested in analogous

reactions with ethyl diazoaceatate (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**




a: R = $R^1$ = H, 90% (TPP), 12 *trans*/*cis* ratio (TPP), 95% (TPP), 104 *trans*/*cis* ratio (TPFPP);
b: R = $R^1$ = OMe, 95% (TPP), 47 *trans*/*cis* ratio (TPP), 95% (TPP), 316 *trans*/*cis* ratio (TPFPP);
c: R = $R^1$ = $CF_3$, 93% (TPP), 4 *trans*/*cis* ratio (TPP), 94% (TPP), 10 *trans*/*cis* ratio (TPFPP);
d: R = $R^1$ = H, 80% (TPP), 17 *trans*/*cis* ratio (TPP), 90% (TPP), 1 *trans*/*cis* ratio (TPFPP)

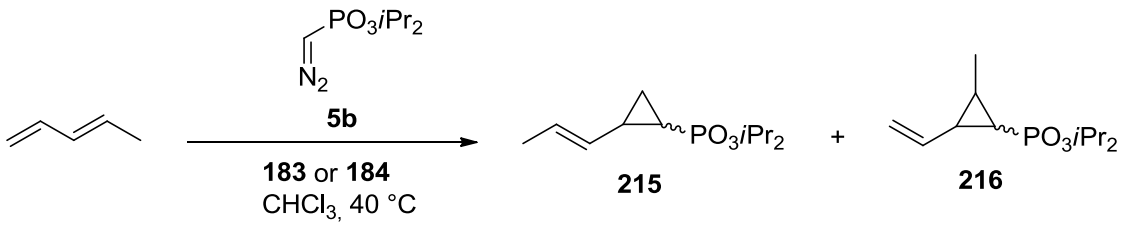



(TPFPP)Ru(CO)
**213**

With the aim of extending the synthetic application of these catalytic systems, Paul-Roth *et al*. also investigated the reaction between **5b** and dienes.[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

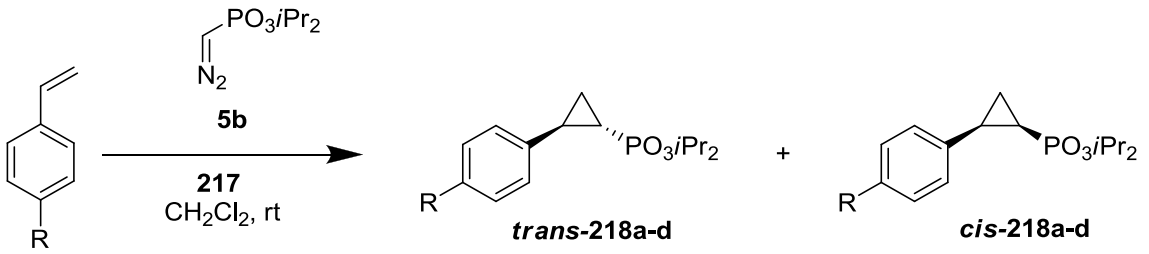
corresponding cyclopropyl derivatives **215** and **216** in very good yields. The reaction was not regioselective by using **184**, whereas the electron-deficient complex **213**, was able to preferentially drive the reaction toward the terminal double bond (Scheme 102).

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

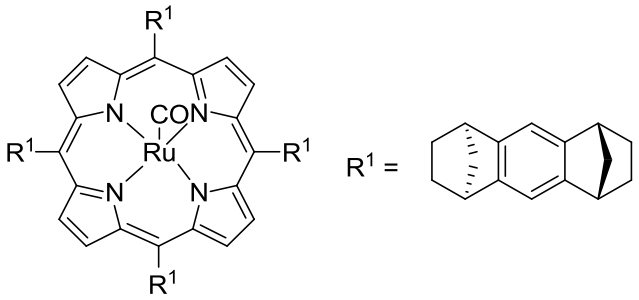



In 2004, Simonneaux *et al*.,[183] reported the enantioselective synthesis of cyclopropylphosphonates using, as catalyst, the chiral ruthenium-porphyrin complex (**217**) ( ). The reactivity of **5b** was assessed against a series of styrene derivatives. In all cases the reaction showed to be very efficient 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**

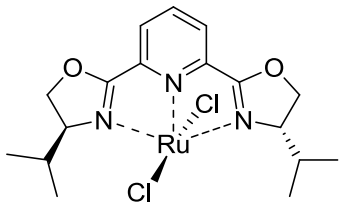



a: R = H, 90%, 96/4 *trans*/*cis,* 90% $ee_{trans}$, 34% $ee_{cis}$; b: R = OMe, 90%, 97/3 *trans*/*cis,* 90% $ee_{trans}$, 23% $ee_{cis}$; c: R = $CF_3$, 92%, 95/5 *trans*/*cis,* 92% $ee_{trans}$, 5% $ee_{cis}$; d: R = Me, 87%, 99/1 *trans*/*cis,* 87% $ee_{trans}$, 23% $ee_{cis}$; e: R = Cl, 88%, 97/3 *trans*/*cis,* 88% $ee_{trans}$, 27% $ee_{cis}$




**217**

In 2005, also Charette group investigated the transition metal-catalysed enantioselective synthesis of cyclopropyl phosphonates.[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 diastereocontrol (91:19 *dr*). In the presence of the chiral Nishiyama catalyst (**219**), cyclopropanation of diverse olefins was realized with high diastereoselectivitiy as well as excellent *ee* (up to 97 % for *trans* isomer) (Figure 5).

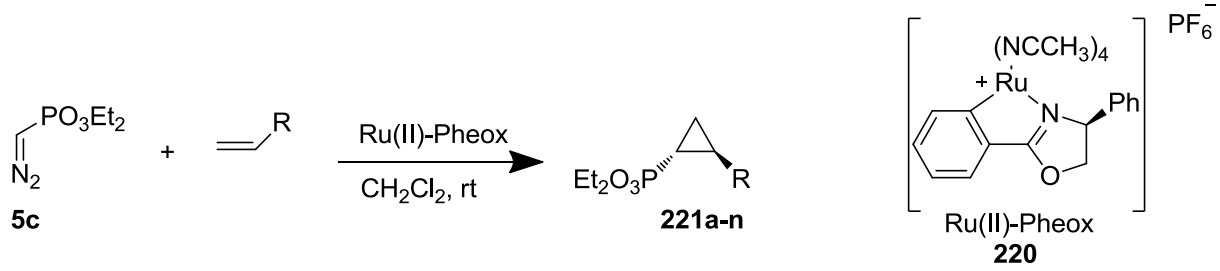


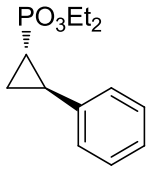

**219**

**Figure 5. Structure of Chiral Nishiyama catalyst (219)**

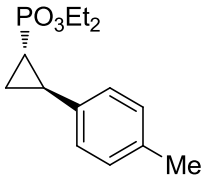
Despite the existence of several methodologies for the cyclopropanation of olefins, styrene derivatives in particular, the applications to electro-deficient alkenes, such as α,β-unsaturated carbonyl compounds, still remains rare. Only recently, Chanthamath *et al*.[185] reported the stereoselective cyclopropanation of alkenes, including α,β unsaturated carbonyl compounds catalyzed by a Ru(II)-Pheox complex (**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%), *trans/cis* ratio (62:38 to 99:1) and *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 *cis*- and *trans*-2-hexene. Vinylamine derivatives could also be cyclopropanated under the same reaction conditions to afford the corresponding cyclopropanes **221h-i** in excellent yield and with high distereo- and enantioselectivity. When phenyl acrylate was cyclopropanated under the optimized conditions, the corresponding cyclopropane **221j** was obtained in 65% yield with excellent *trans/cis* ratio (99:1) and *ee* (98%). Similar results gave α-vinylbenzophenone, whereas, among acrylamides, only cyclopropane **221l** was obtained in good yield and *ee*.

**Scheme 104. Ru(II)-Pheox-Catalyzed Enantioselective Cyclopropanation Reaction**

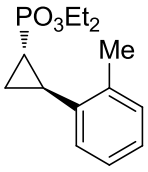


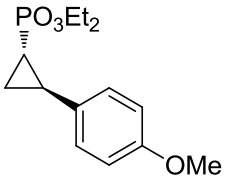

**221a**, 93%
99:1 *dr*, 97% *ee*



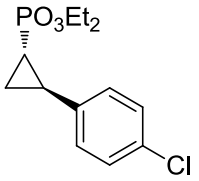

**221b,** 87%
99:1 *dr*, 98% *ee*



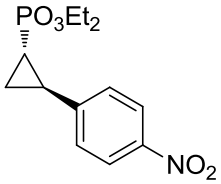

**221c,** 92%
98:2 *dr*, 97% *ee*



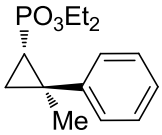

**221d,** 87%
99:1 *dr*, 96% *ee*



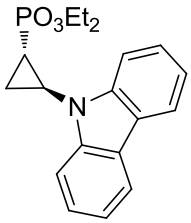

**221e,** 84%
98:2 *dr*, 98% *ee*



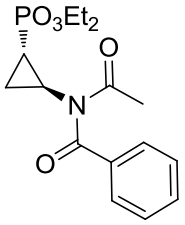

**221f,** 92%
98:2 *dr*, 99% *ee*



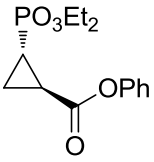

**221g,** 72%
62:38 *dr*, 99% *ee*



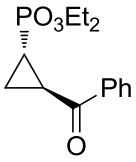

**221h,** 84%
93:7 *dr*, 98% *ee*



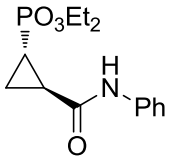

**221i**, 79%
99:1 dr, 94% *ee*



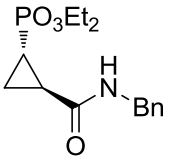

**221j,** 65%
99:1 *dr*, 98% *ee*



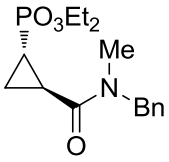

**221k**, 87%
98:2 *dr*, 98% *ee*




**221l,** 71%
99:1 *dr*, 98% *ee*




**221m**, 33%
98:2 *dr*, 78% *ee*

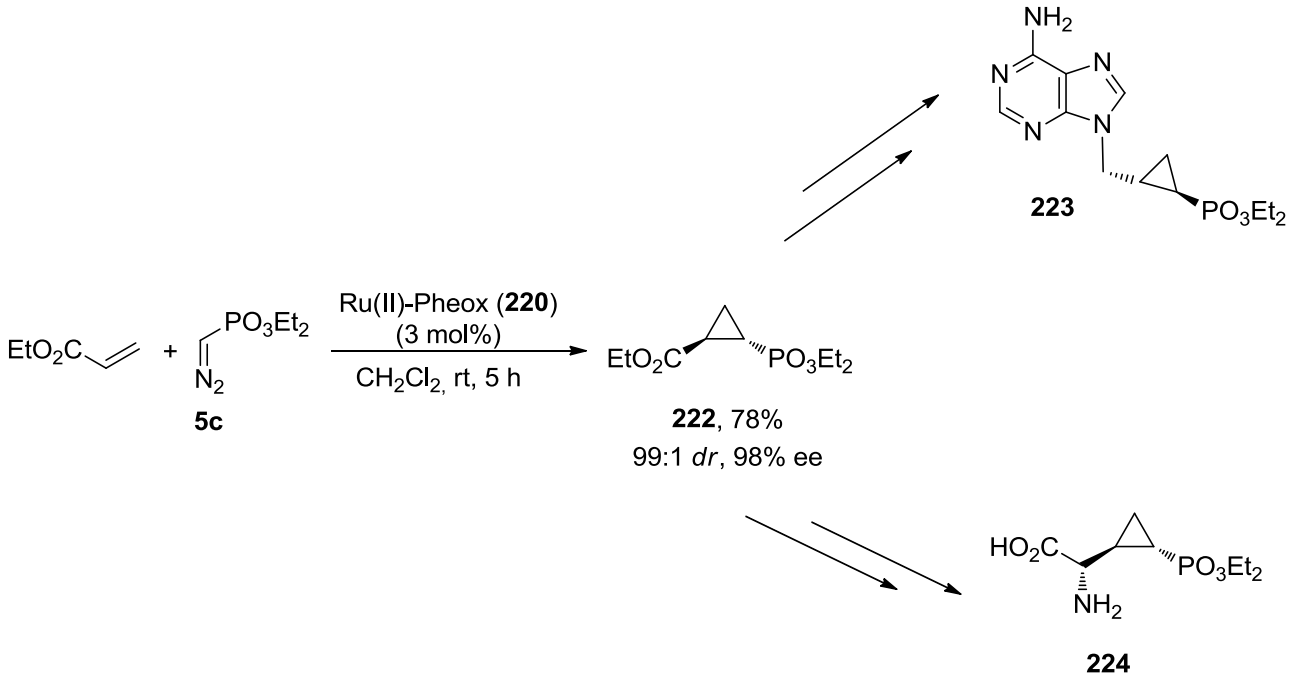



**221n**, 40%
98:2 *dr*, 87% *ee*

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.**.

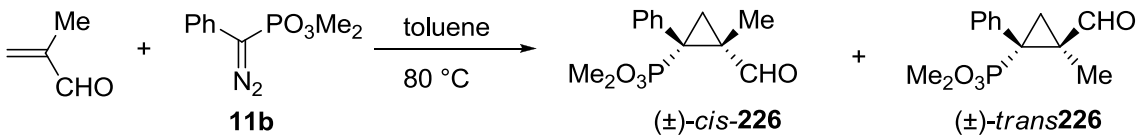
**Scheme 105. Ru(II)-Pheox-Catalyzed Enantioselective Cyclopropanation Reaction, as a Key Step in**

**the Synthesis of the Acyclic Nucleoside Analogue (223) and the Glutamic Acid Analogue (224)**

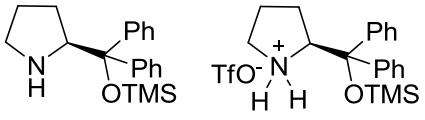



Only one example describes the use of organocatalysis in cyclopropanation reaction with PCDCs. Since the thermally-induced cyclopropanation of α-methylacrolein by α-diazobenzylphosphonate (**11b**) proceeded slowly and with low diastereoselectivity, the use of the two proline-derived catalysts, **225a** and **225b**, was investigated. Although the reaction time was greatly reduced, the effect on the diastereocontrol was scarce (Scheme 106).[186]

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



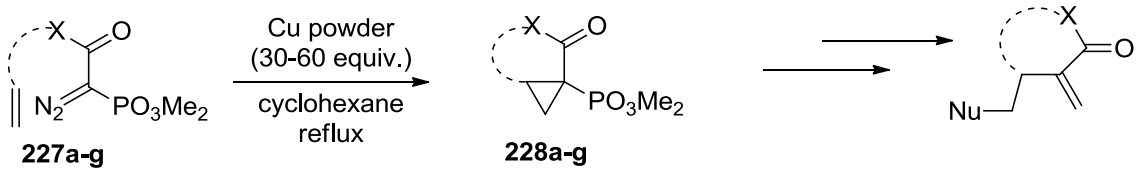

without catalyst: 36h, 72%, 56/44 (*trans*/*cis*);
with **225a** catalyst: 12h, 54%, 61/39 (*trans*/*cis*);
with **225b** catalyst: 12h, 74%, 62/38 (*trans*/*cis*)

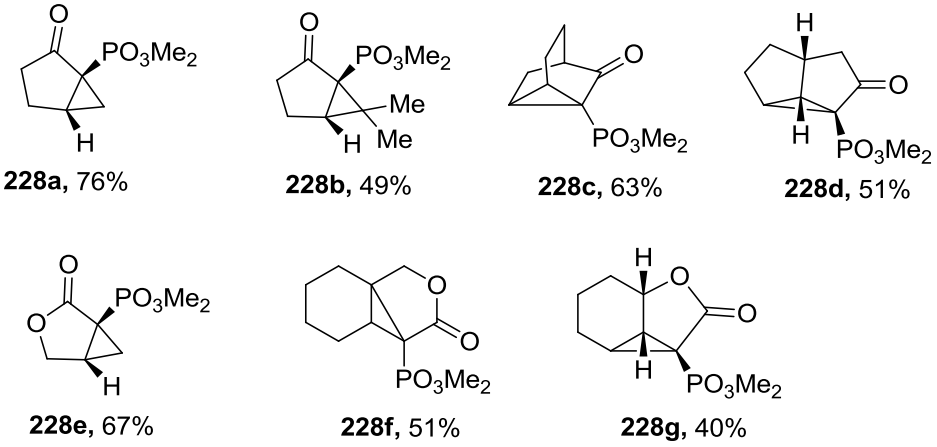


### 3.3.2. Intramolecular Cyclopropanation

Olefinic 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).[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 $Rh_2(OAc)_4$, or $Cu(acac)_2$ were ineffective in this transformation.

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

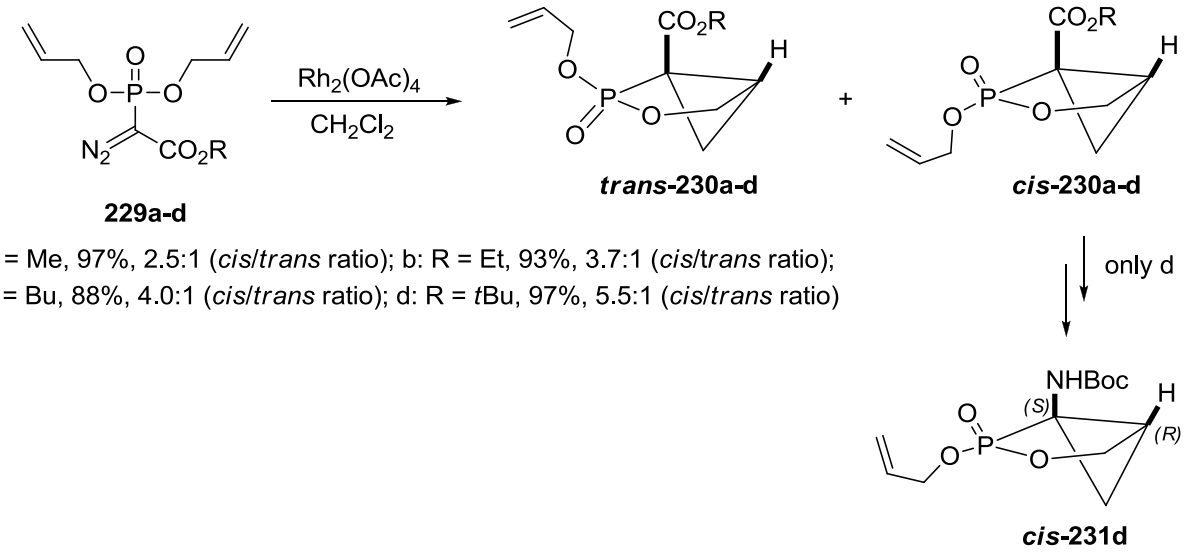



Hanson's group reported the synthesis of P-heterocyclic compounds *via* intramolecular cyclopropanation of suitable phosphonate templates. In the first example of this reaction, published

in 1999, PCDCs **229a-d** were converted into the corresponding P-heterocycles **230a-d** in good yield (88-97%), but moderate diastereoselectivity (Scheme 108).[188] 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. [189]

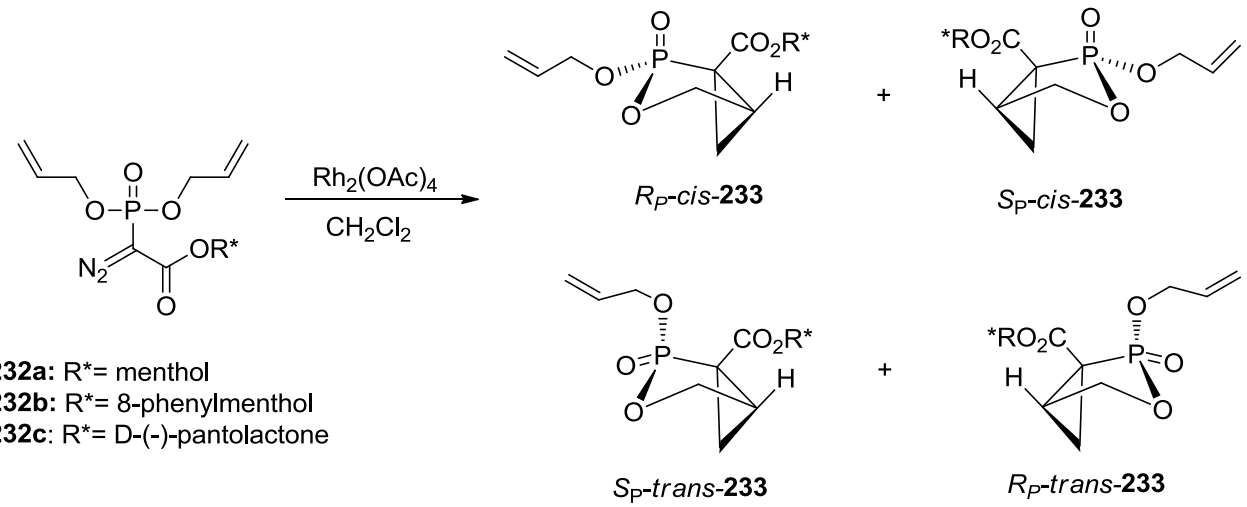
**Scheme 108. $Rh_2(OAc)_4$-Catalyzed Intramolecular Cyclopropanation of PCDCs 229a-d**




Before obtaining the crystal structure of *cis*-**231,** attempts to assign its stereochemistry were made on the basis of $^1$H-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".[190,191] The diastereoselectivity observed in this transformation was rationalized on the basis of the widely accepted Doyle/Davies model.[192] 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 anomeric 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)*.[192] 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*-$R_p$-**233** diastereoisomer was evidenced (Scheme 109).**Error! Reference source not found.**

**Scheme 109. $Rh_2(OAc)_4$-Catalyzed Intramolecular Cyclopropanation of PCDCs 232a-d**




**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 acces to the *re*-face of the olefin. The unfavourable interactions occuring 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 rodhium carbenoid, dictaded by electronic stabilization.

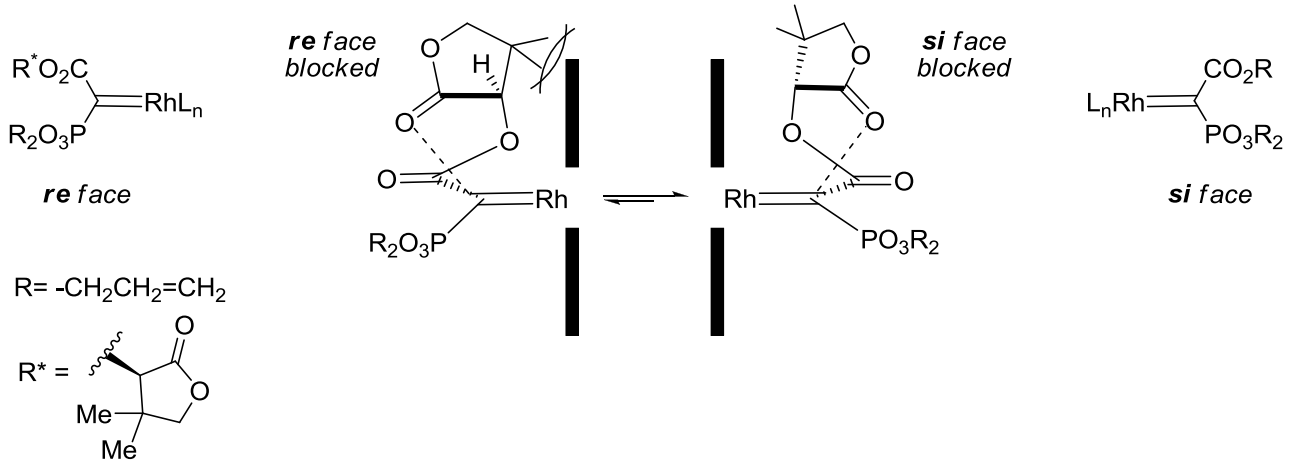
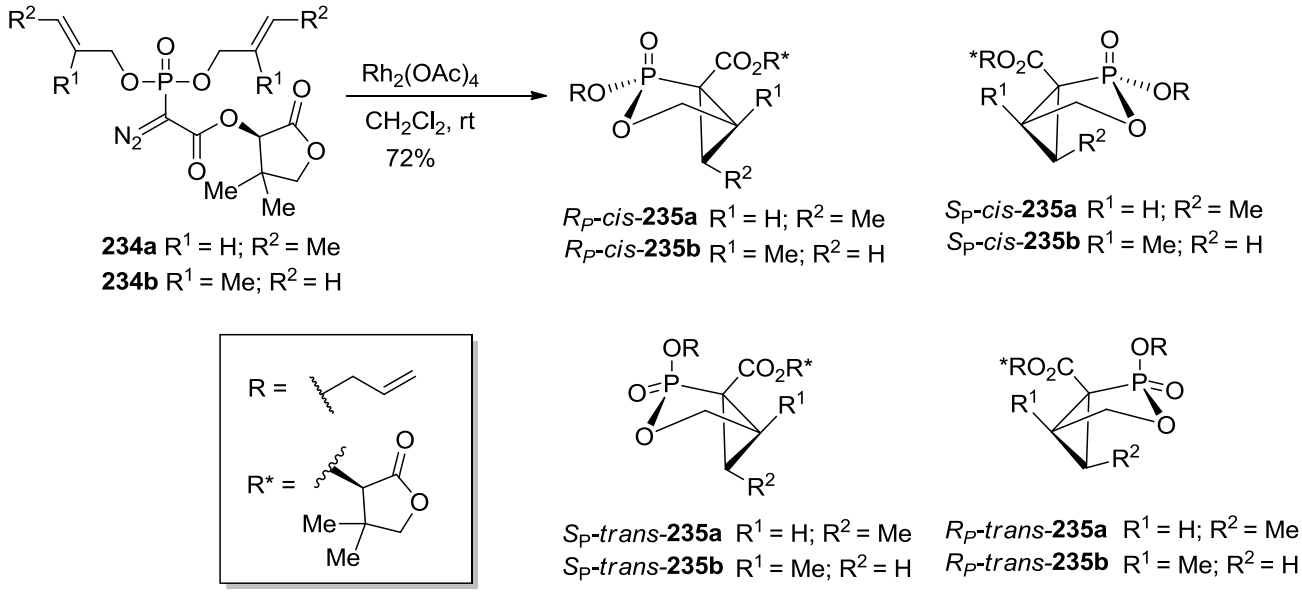



**Figure 6. Steric Clash between *gem*-Dimethyl Group of the Chiral Auxiliary and the Rhodium Carbenoid**

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.[193] In the case of **234a**, the result obtained was in contrast with the previus 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 exent when compared to those of the original allyl series.

**Scheme 110. $Rh_2(OAc)_4$-Catalyzed Intramolecular Cyclopropanation of PCDCs 234a,b**

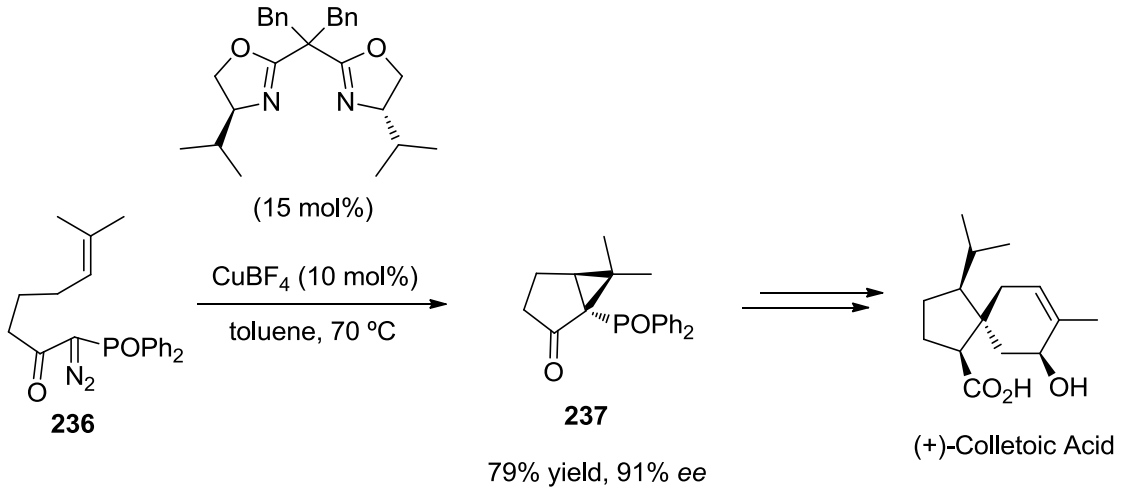



| *RP*-*cis*-**235a** | *SP*-*cis*-**235a** | *SP*-*trans*-**235a** | *RP*-*trans*-**235a** |
|---|---|---|---|
| 1.2 | 1.5 | 1.0 | **4.6** |
| *RP*-*cis*-**235b** | *SP*-*cis*-**235b** | *SP*-*trans*-**235b** | *RP*-*trans*-**235b** |
| **20.1** | 2.3 | 6.1 | 1.0 |

Diphenyl β-keto-α-diazophosphinoxide **236** turned out to be a key intemediate toward the synthesis of (+)-colletoic acid (Scheme 111).[194] Thanks to the bulky phospinoxide 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.[195]

**Scheme 111. Enantioselective Intramolecular Cyclopropanation of 236, as the key Step in the**

**Synthesis of (+)-Colletoic Acid**

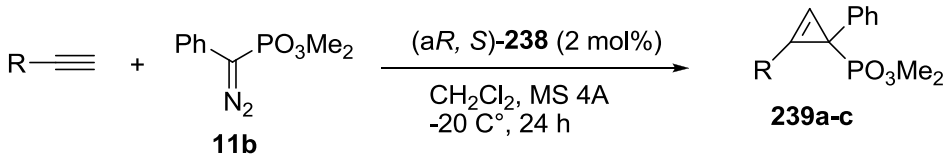



### 3.3.3. Cyclopropenation of Alkynes

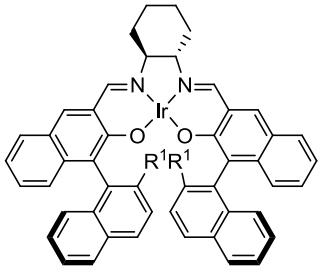
Donor-acceptor substituted diazo compounds have also been used as carbenoid precursors in the enantioselective synthesis of chiral cyclopropenes using iridium-Salen chiral catalysts.[196] Although the authors reported the reaction mainly with diazocarbonyl-derived carbenoids, they also screened dimethyl 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 **239a-c** were obtained in good to excellent yield (

Scheme 112).

**Scheme 112. Cyclopropenation of Alkynes with 11b**




a: R = 4-$MeOC_6H_4$, 96%, 86% *ee*; b: R = *n*-$C_8H_{14}$, 65%, 85% *ee*; c: 4-$BrCH_6H_4$, 72%, 89% *ee*



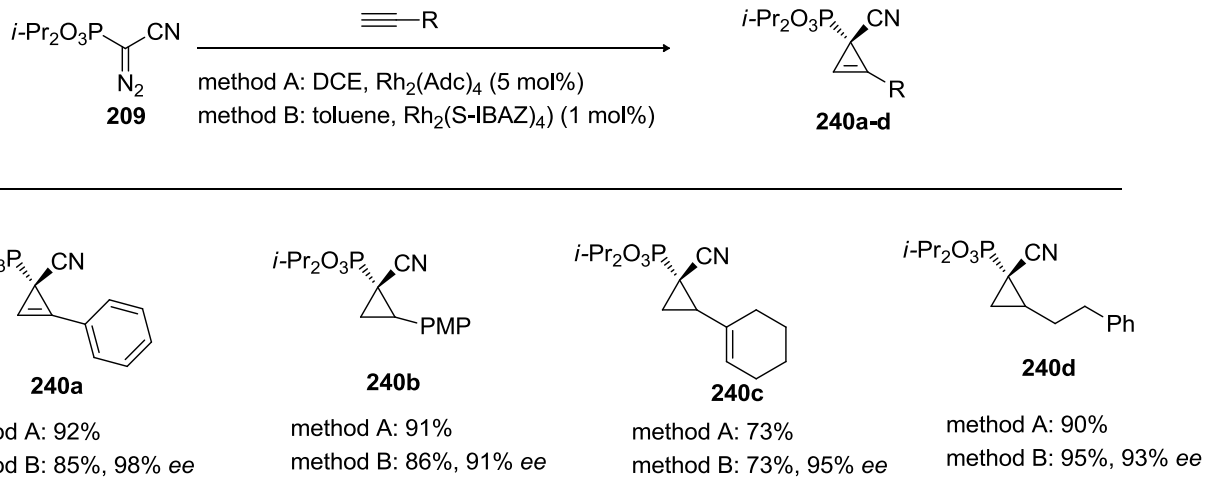

$R^1$ = 4-$TBDPSC_6H_4$
(a*R, S*)-**238**

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.[181]

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




### 3.4. Reactions with Aromatic Compounds

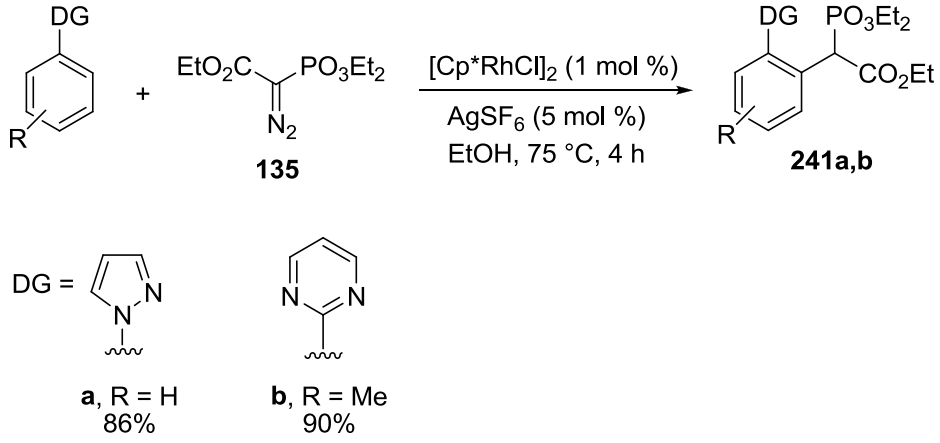
The reaction of arenes with photochemically generated phosphorylcarbenes (the Buchner reaction), leading to an equilibrating mixture of the corresponding norcaradiene and cycloheptatriene derivatives was reviewed by Regitz.[27] Later on Maas *et al*. reported about the substituent dependence of this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

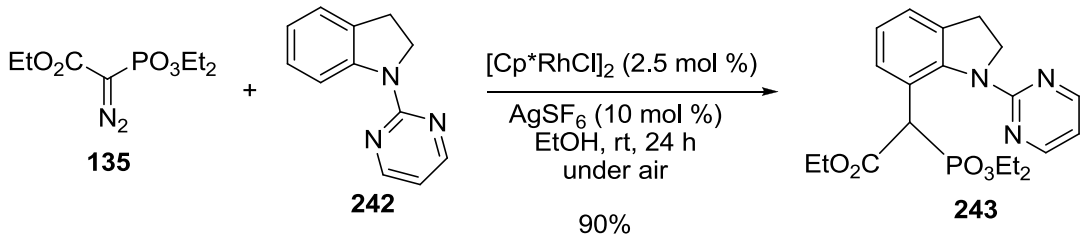
In the frame of a study predominantly directected to the rhodium(III)-catalyzed reaction of diazocarbonyl compounds with aromatics bearing azacyclic directing groups, the reactivity of **135** was also explored (Scheme 114).[198] The reaction, performed in the presence of $[Cp^*RhCl]_2$ ($Cp^*$ = pentamethylcyclopentadiene) and $AgSbF_6$, allowed the obtainment of the *ortho*-alkylated derivatives **92a,b** in excellent yield.

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



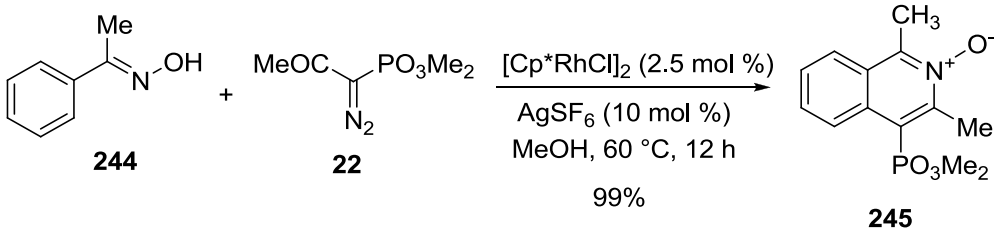

The same catalytic system was shown to be able to promote the regioselective alkylation of *N*(2-pyrimidyl)indoline (**242**) by PCDC **135** (Scheme 115).[199]

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



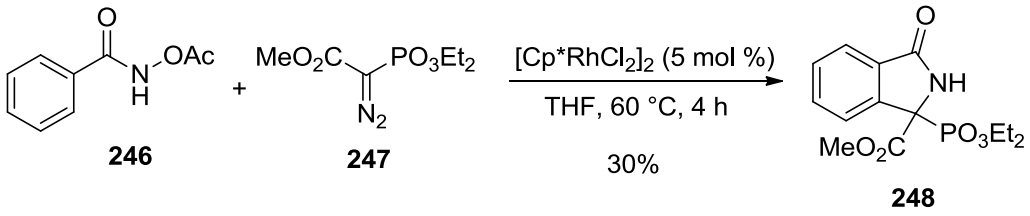
C-H activation mediated by Rh(III) resulted to be the cyclization-initiating event in the annulation reaction of oximes and diazo compounds. In particular BOR (**22**) was reported to react with the oxime **244** to give the isoquinoline *N*-oxide **245** in almost quantitative yield (Scheme 116).[200]

**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 $Rh_2(OAc)_4$ 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, tha 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 thuis stydy 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 avariety of biological interesting products.

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

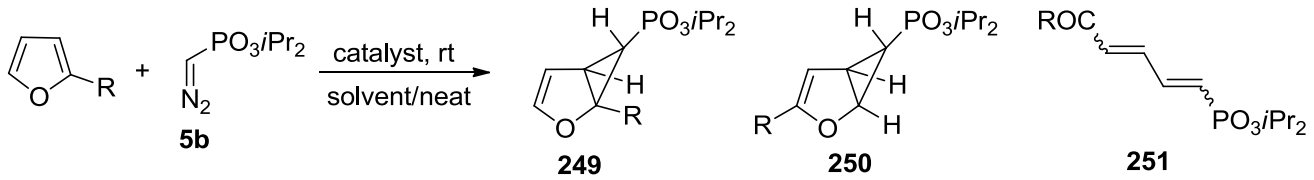



**Table 3. Metal-Catalyzed Decomposition of 5b in the Presence of Furans**

| Entry | Catalyst (%) | Solvent | R | Yield (%) | Product | Product ratio |
|---|---|---|---|---|---|---|
| **a** | $Rh_2(OAc)_4$ (5) | neat | H | 81 | **249**/(1*Z*,3*E*)-**251**/(1*E*,3*E*)-**251** | 1:1.2:3.8 |
| **b** | $Rh_2(OAc)_4$ (5) | $CH_2Cl_2$ | H | 80 | **249**/(1*Z*,3*E*)-**251**/(1*E*,3*E*)-**251** | 1:5.5:17.5 |
| **c** | CuOTf (0.05) | neat | H | 85 | **249**/(1*Z*,3*Z*)-**251**/(1*E*,3*Z*)-**251** | 1:0.2:1.2 |
| **d** | CuOTf (1) | $CH_2Cl_2$ | H | 80 | **249**/(1*Z*,3*Z*)-**251**/(1*E*,3*Z*)-**251** | 1:0.4:1.6 |
| **e** | CuOTf (0.05) | neat | Me | 68 | **249**/**250**/(1*Z*,3*Z*)-**251**/(1E,3*Z*)-**251** | 1.1:1:2.0:5.8 |
| **f** | $Rh_2(OAc)_4$ (5) | neat | Me | 89 | **249**/(1*Z*,3*E*)-**251**/(1*E*,3*E*)-**251** | 1:3.9:11 |
| **g** | CuOTf (1) | $CH_2Cl_2$ | OMe | 61 | (1*Z*,3*Z*)-**251**/(1*E*,3*Z*)-**251** | 1:2 |

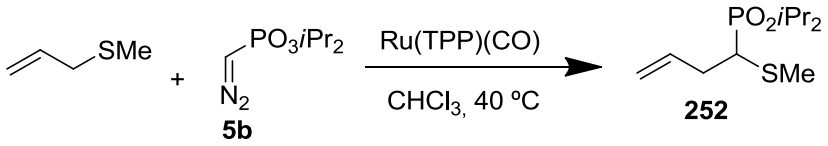
### 3.5. Ylide Formation and Subsequent Reactions

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

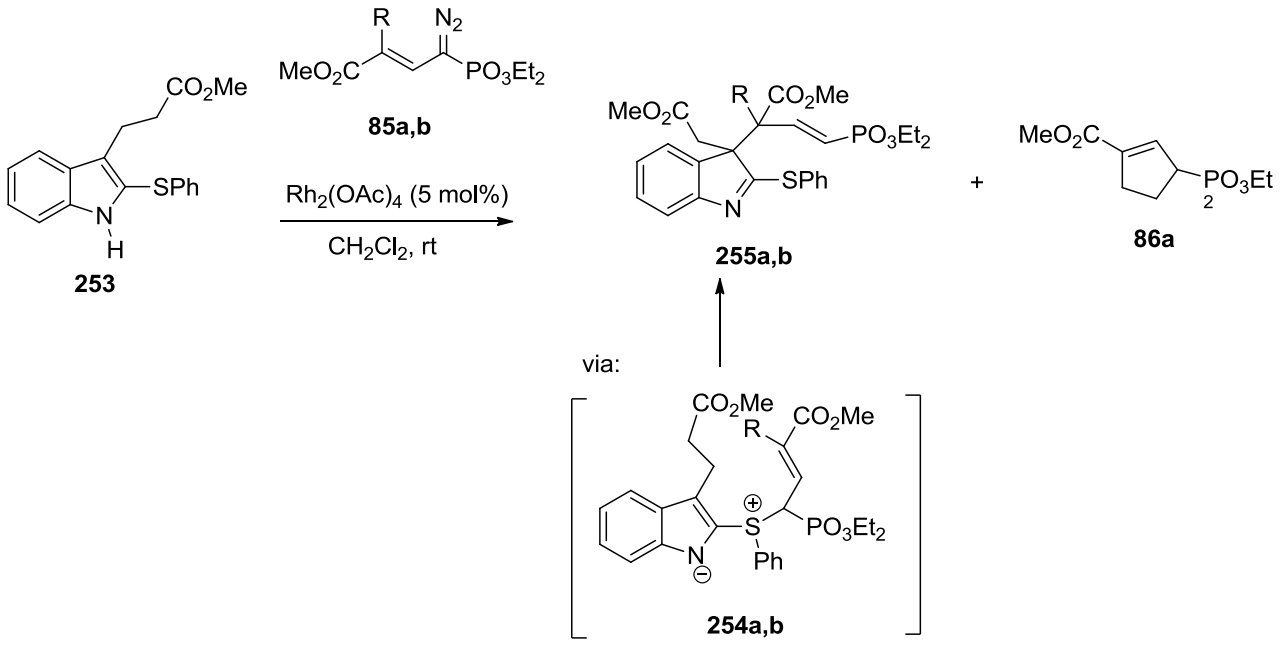
The (TPP)Ru(CO)-catalyzed reaction of diisopropyl α-diazomethyphosphonate (**5b**) with 2-propene-1-thiol afforded, as the major product the α-methylthio-substituted derivative **252**, as consequence of the [2,3]-sigmatropic rearrangement of the intermediate sulphonium ylide (Scheme 119). [157]

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




Wang *et al*.[86] prepared quaternary substituted indolines, such as **255a,b**, by coupling of α-vinyl-α-diazophosponate **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 hyphotized 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 competive intramolecular C-H insertion reaction of the starting PCDC.

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

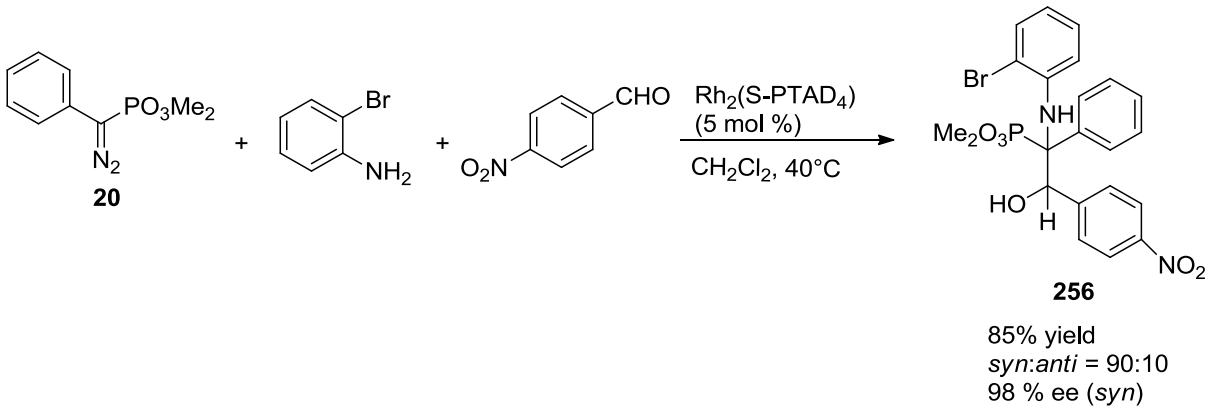



a: R = Me, 87%, > 20:1 d.r. (**255a**); b: R = Et, 27%, > 20:1 d.r (**255b**), 55% (**86a**)

### 3.5.2. Ammonium Ylide

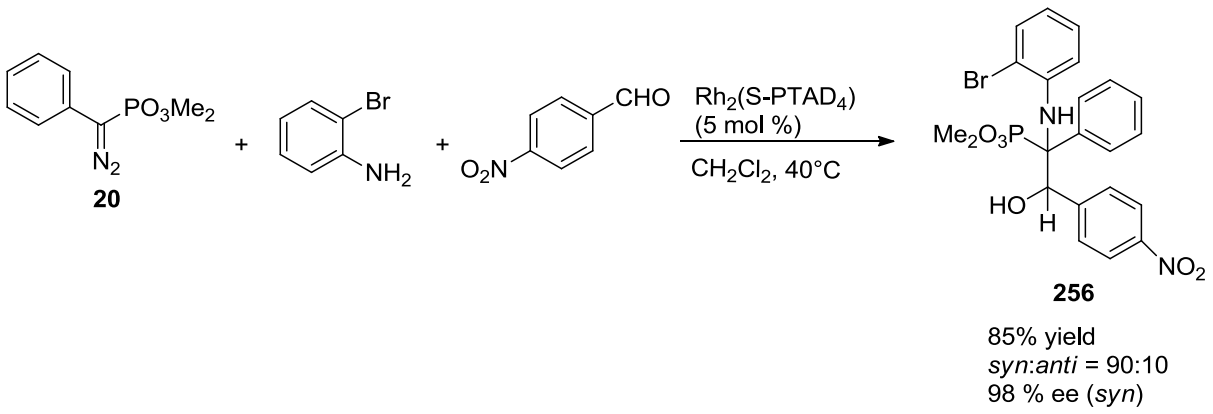
In the chemistry of diazocarbonyl compounds numerous are the examples of polyfunctional molecules prepared by the reaction of different electrophiles with an ammonium ylide, which was in turn generated from diazo reagents and amines. Having to be the trapping of the ammonium ylide by the external electrophile 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.[1] On the contrary, only one example of reaction of PCDCs involving ammonium ylide can be found in the literature.

In 2012, Zhou *et al*.[203] 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

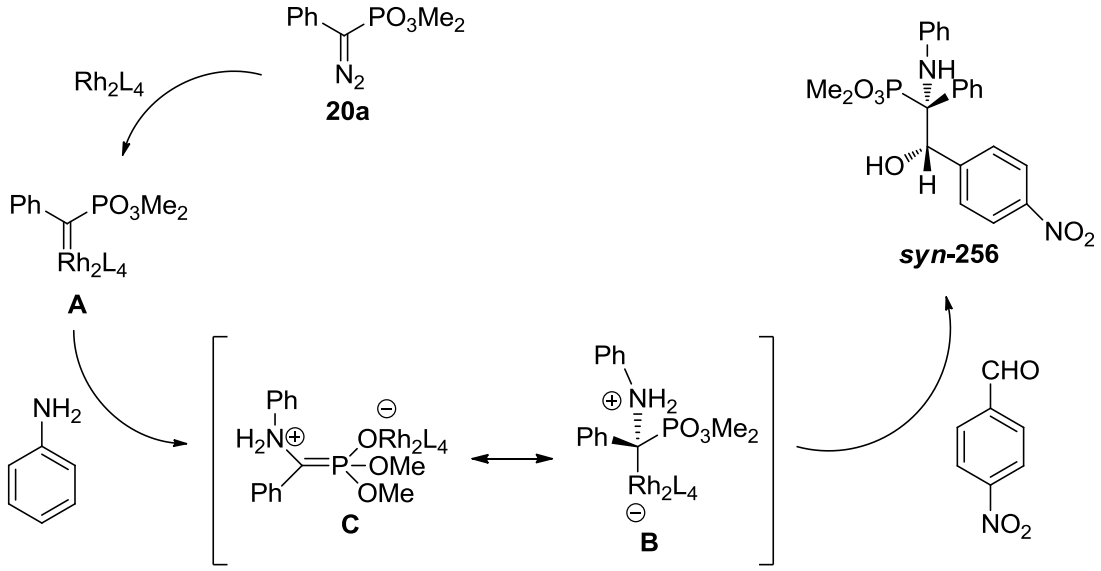



. The *syn*-diastereoisomer was the major component in each case. The screening of a series of rhodium- and copper chiral catalysts were also examined, establishing the optimal conditions as 2 mol% [$Rh_2$(*S*-PTAD)$_4$] in dichloromethane at 40 °C. The scope of the enantioselective reaction was examined 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**



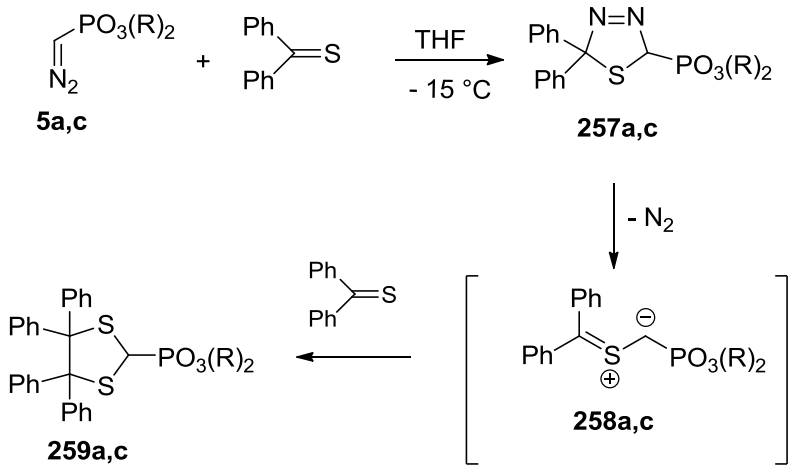
**Scheme 122. Proposed Mechanism for the Three-Component Coupling Reaction**




### 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.

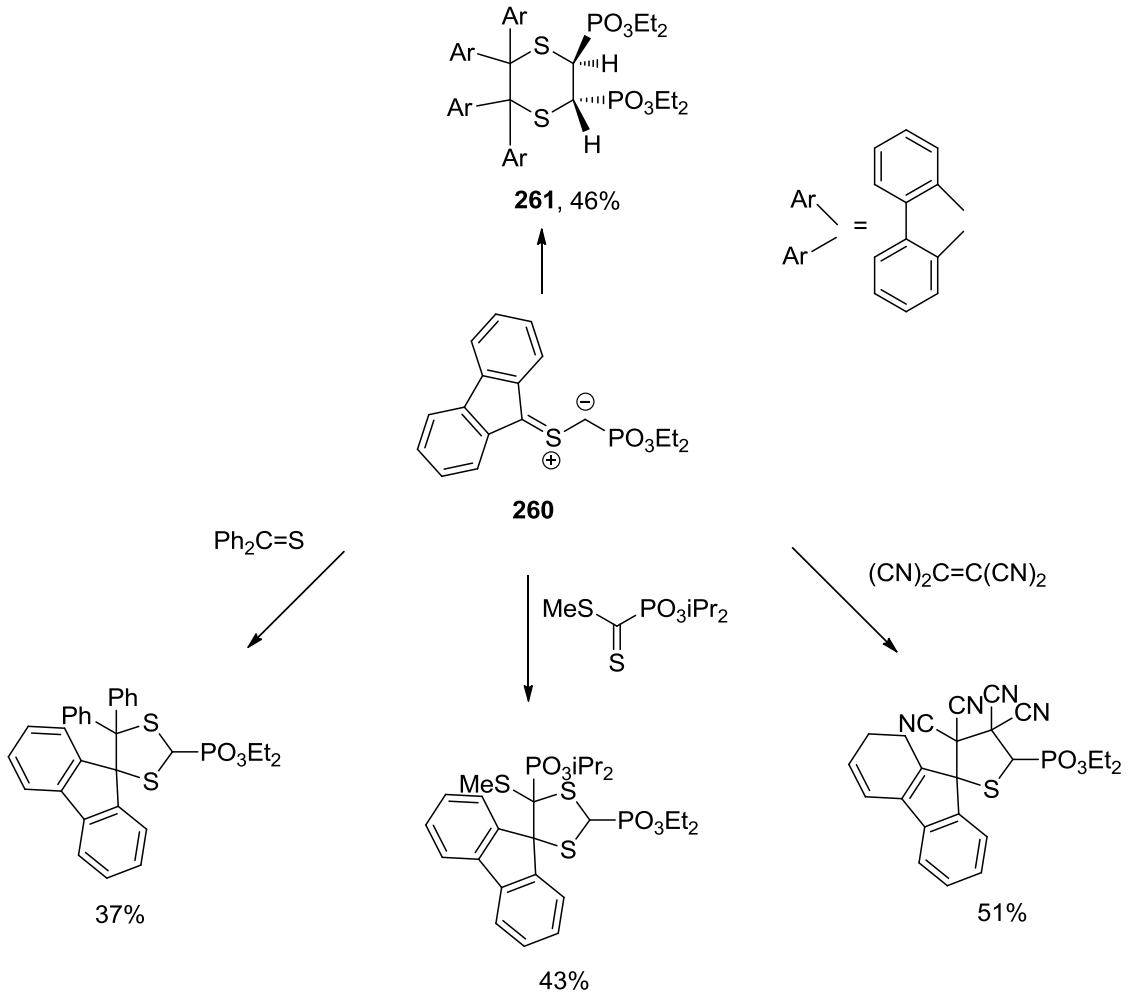
**Scheme 123. Reaction of Dialkyl α-Diazomethylphosphonates 5a,c with Diphenylmethanethione**




a: R = Me, 74%; c: R = Et, 96%

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 tetracyano-ethane(Scheme 124).[204]

**Scheme 124**. **Reaction of the Thiocarbonyl Ylide 260**

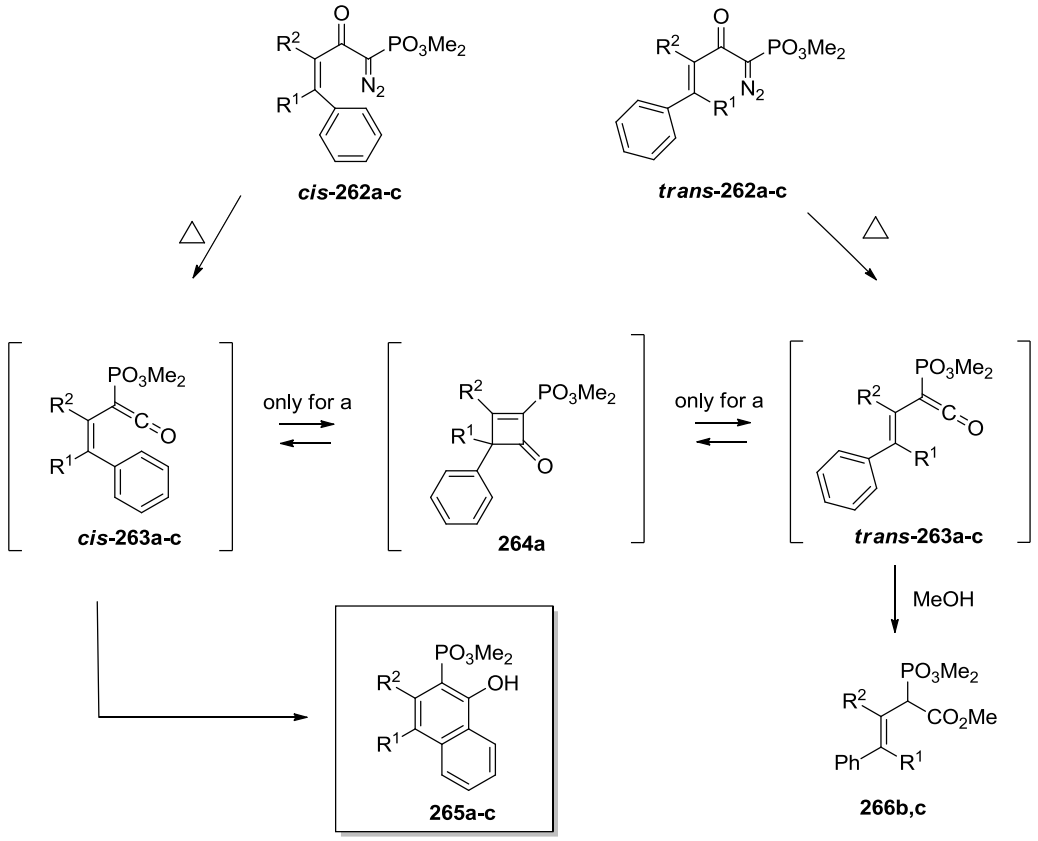



### 3.6. Wolff Rearrangement

Since Wolff rearrangement is a specific 1,2-rearrangement of a diazo ketone,[205] a PCDC to be able to undergo this transformation has to be characterized by the presence of a β-keto-α-diazophosphonate 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 6π-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**.

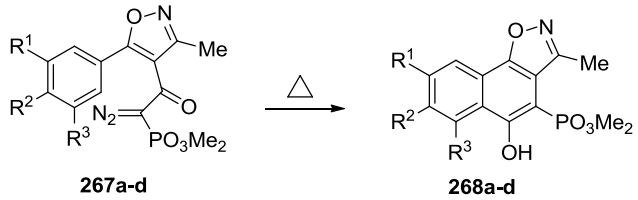
**Scheme 125**. **Benzannulation of PCDCs *cis*-and *trans*-262a-c *via* Vinyl Ketenes




a: $R_1$ = H, $R_2$ = OMe; b: $R_1$ = $R_2$ = H; c: $R_1$ = H, $R_2$ = Me

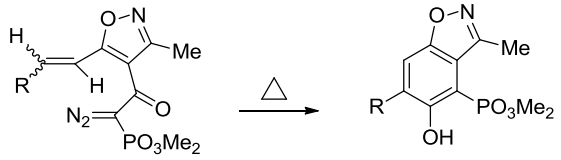
Thermolyis of PCDCs **267a-h,** bearing a γ,δ-double bond as a part of an isoxazole ring afforded a series of 4-phosphono-5-hydroxy-fused isoxazoles **268a-h** (Scheme 126). Since experimental evidences showed that the electrocyclization step was slower than the formation of the ketenes, the reaction was performed by heating a benzene solution of the substrate in a sealed vessel to accelerate the ring closure step.[208]

**Scheme 126. Benzannulation of PCDC 120a-h *via* Vinyl Ketenes**




**267a-d** **268a-d**

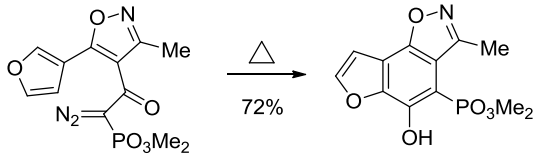
a: $R^1 = R^2 = R^3 = H$, 67%; b: $R^1 = R^3 = H$, $R^2 = OMe$, 60%; c, $R^1 = R^3 = H$, $R^2 = Cl$, 73%; d, $R^1 = R^3 = Cl$, $R^2 = H$, 80%




**267e,f** **268e,f**

e: R = Ph, 65%; f: R = *n*Pr, 73%


**267g** **268g**

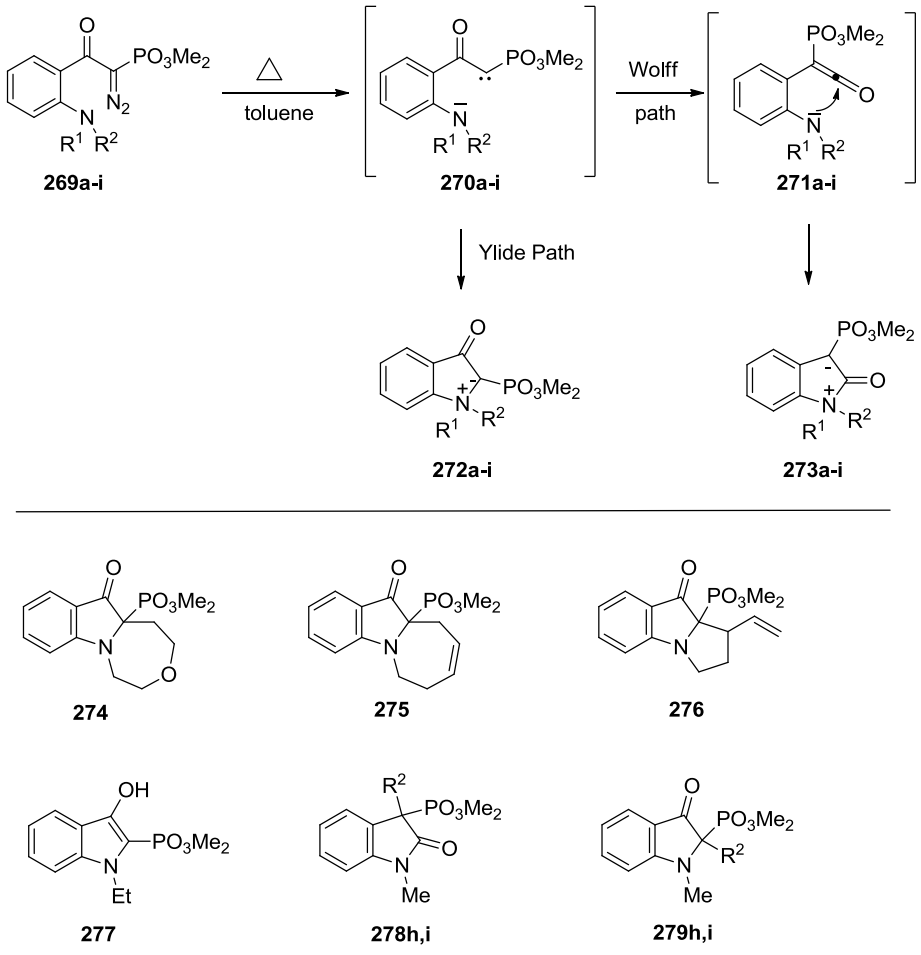



**120h** **121h**

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 unsatured 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 mesoionic 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).[209,210]

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

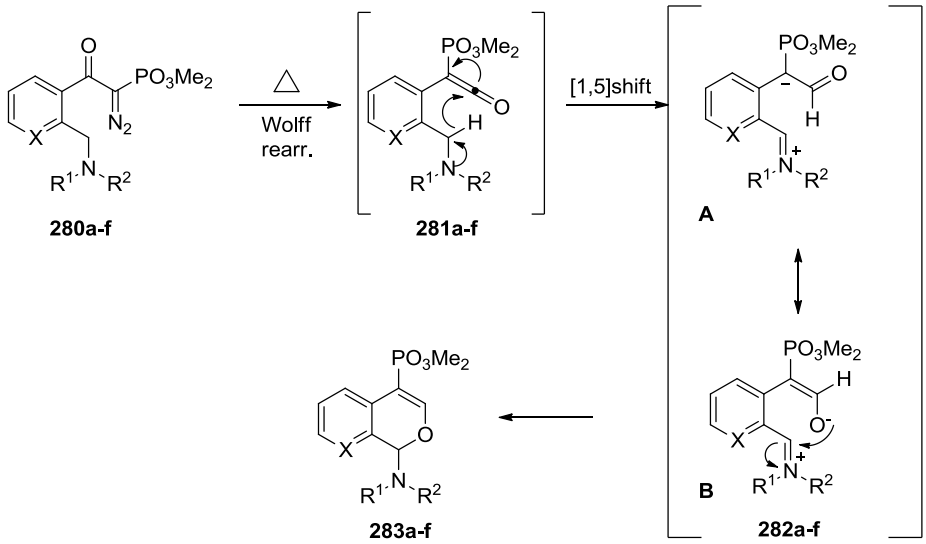



a: $R^{1,}$ $R^2$ = -$(CH_2)_5$-; b: $R^{1,}R^2$ = -$(CH_2)_4$-; c: $R^{1,}$,$R^2$ = -$CH_2$-CH=CH-$CH_2$-; d: $R^{1,}$,$R^2$ = -$(CH_2)_6$-; e: $R^{1,}$,$R^2$ = -$(CH_2)_2$-O$(CH_2)_2$-; f: $R^{1,}$,$R^2$ = -$CH_2$-CH=CH-$(CH_2)_2$-; g: $R^{1,}$ = $R^2$ = Et; h: $R^1$, = Me; $R^2$ = allyl; i: $R^1$, = Me; $R^2$ = 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.

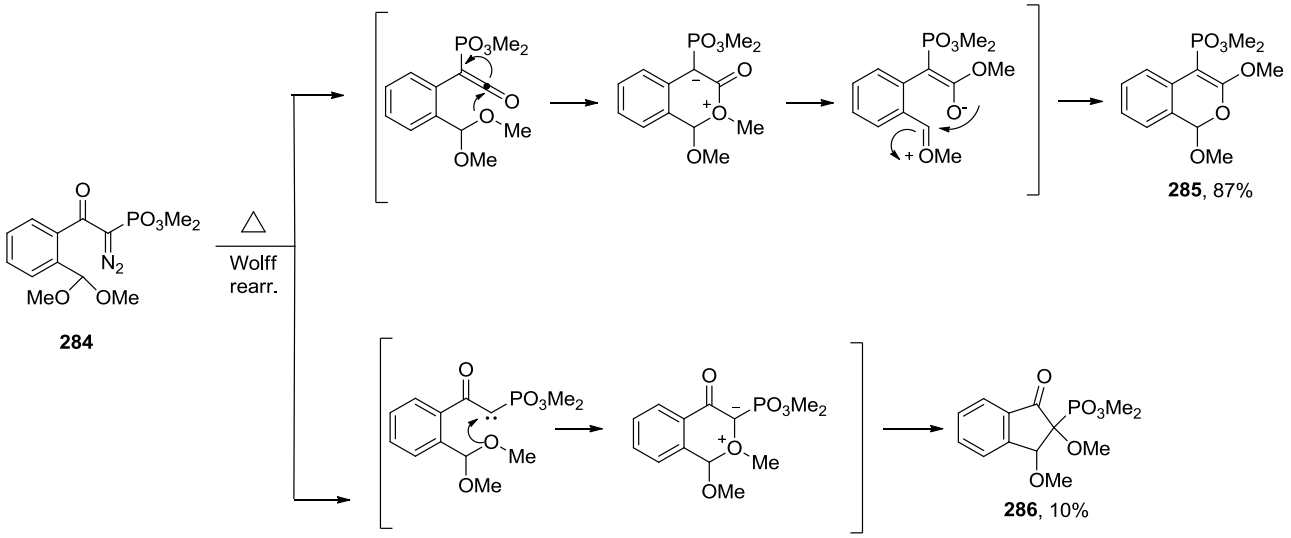
A completely different reactivity was evidenced in the thermolysis of substrates **280a-f** characterized by the presence a methylene linker between the nitrogen atom and the aromatic ring: the exclusive formation of 1*H*-2-benzopyran derivatives **283a-f** was, indeed, obtained. The result could be 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).[211] The thermolysis of dimethoxymethine-substituted PCDC **284** was also investigated. A different reactivity was in this case observed with 1,3-dimethoxy-4-dimethylphosphono-1*H*-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**



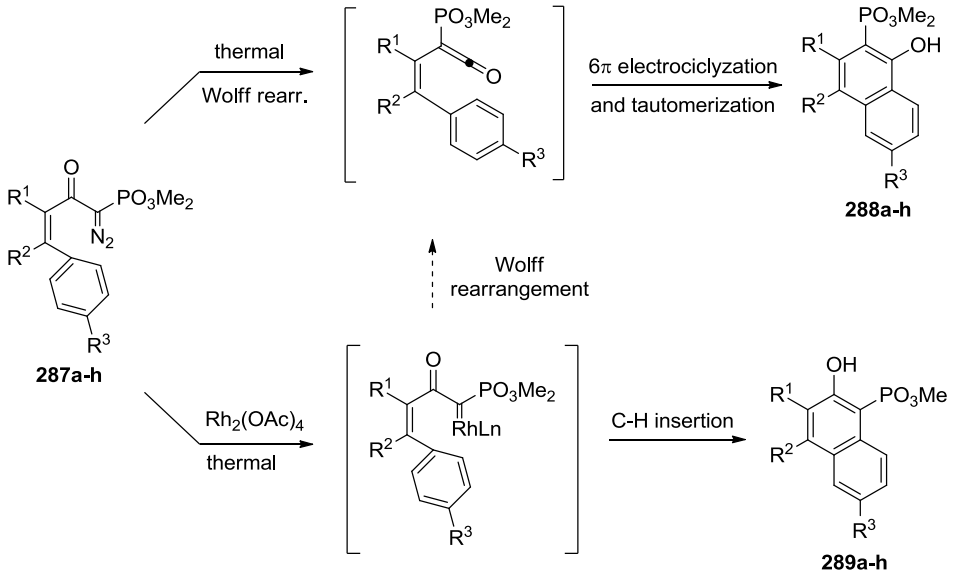

a: $R^1$, $R^2$ = -$(CH_2)_5$-, X = CH, 42%; b: $R^1$, = Me, $R^2$ = Ph, X = CH, 78%; c: $R^1$, = $CH_2Ph$, $R^2$ = Ph, X = CH, 88%; d: $R^1$, = $CH_2Ph$, $R^2$ = Me, X = CH, 48%; e: $R^1$, = $R^2$ = Et, X = CH, 30%; f: d $R^1$, = $CH_2Ph$, $R^2$ = Ph, X = N, 75%

**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 $Rh_2(OAc)_4$ to afford **288a-h** and **289a-h** in variable ratios depending on the substitution pattern at the γ,δ-double bond (Scheme 130).[52]

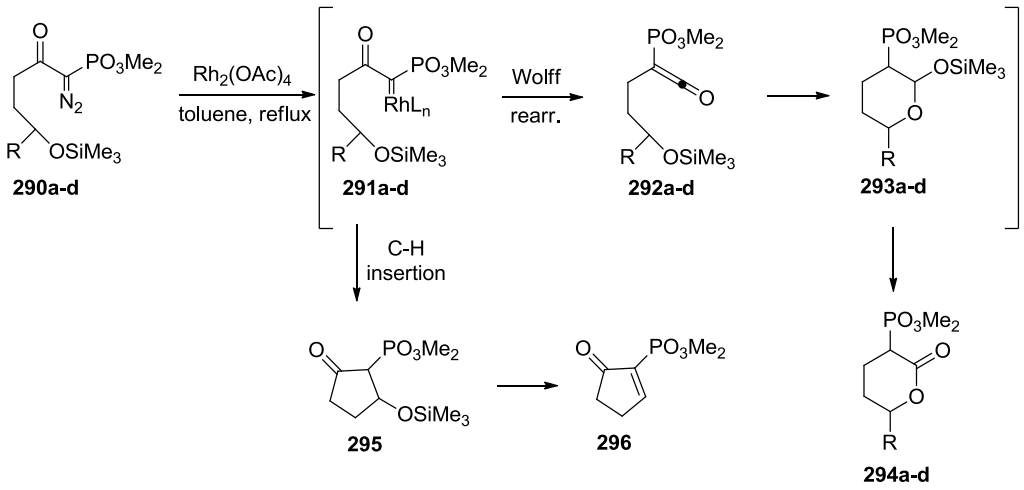
**Scheme 130. Wolff Rearrangement *vs* C-H Insertion Reaction**




a: $R^1$ = OMe, $R^2$ = H, $R^3$ = H, 42%, 37/63 = **288**/**289**; b: $R^1$ = $R^2$ = $R^3$ = H, 86%, 12/88 = **288**/**289**; c: $R^1$ = $R^3$ = H, $R^2$ = Ph, 78%, 85/15 = **288**/**289**; d: $R^1$ = H, $R^2$ = 4-MeO$C_6H_4$ , $R^3$ = OMe, 90%, **288** only; e: $R^1$ = H, $R^2$ = 4Cl-$C_6H_4$, $R^3$ = Cl, 77%, 92/8 = **288**/**289**; f: $R^1$ = $R^3$ = H, $R^2$ = Me, 90%, 47/53 = **288**/**289**; g: $R^1$ = $R^3$ = H, $R^2$ = $CF_3$, 75%, **289** only; h: $R^1$ = F, $R^2$ = $R^3$ = H, 81%, 5/95 = **288**/**289**

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).[53] 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 the can be further hydrolysed during aqueous work-up. On the contrary **296** would be the result of an intramolecular $C_5$-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 $C_5$-H bond is less accessible.

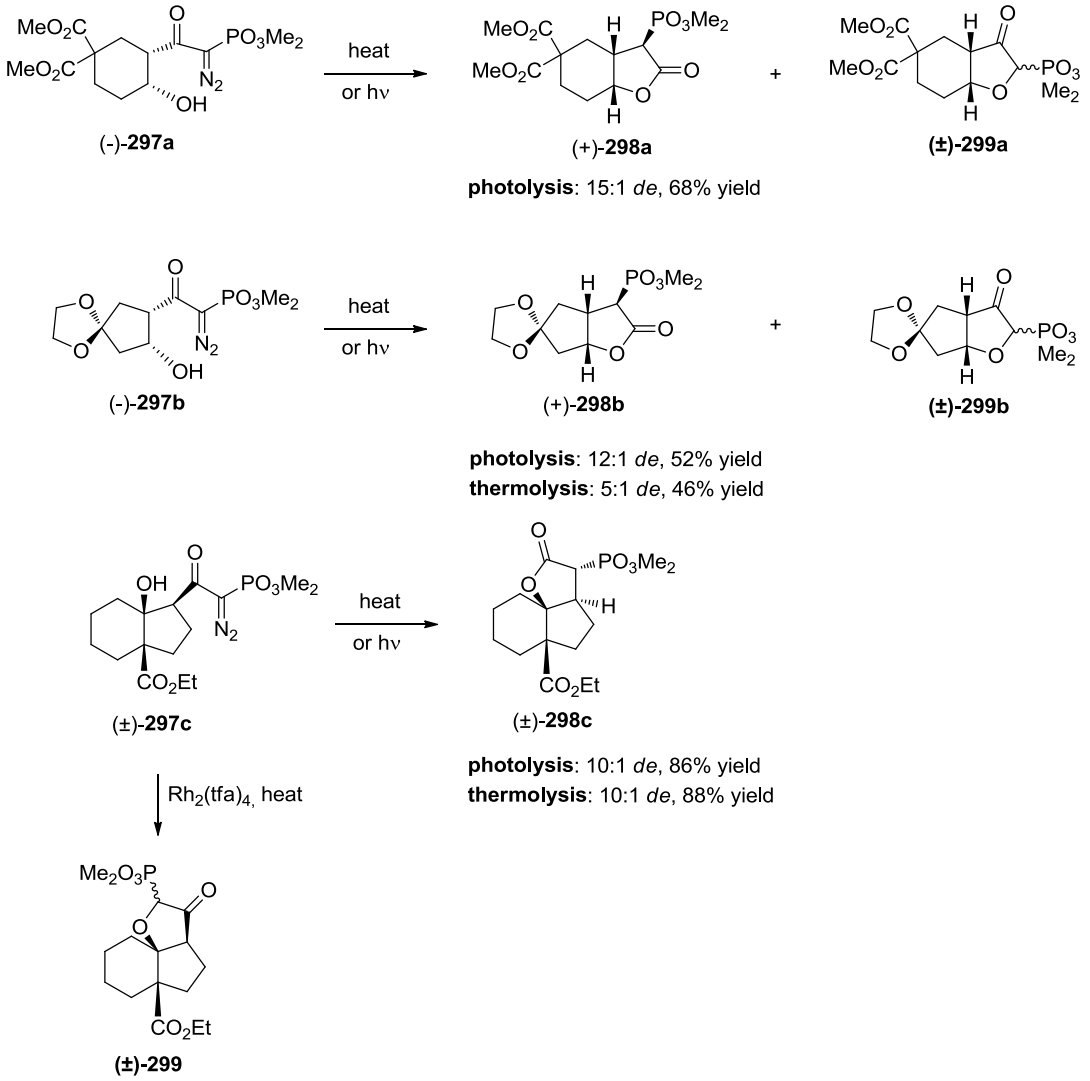
**Scheme 131**. **Combined Wolff Rearrangement and O-Si Trapping *vs* C-H Insertion Reaction**




a: R = H, 17% (**294**), 37% (**296**); b: R = Me, 73% (**294**) c: R = Et, 78% (**294**); d, R = *n*-Hex, 80% (**294**)

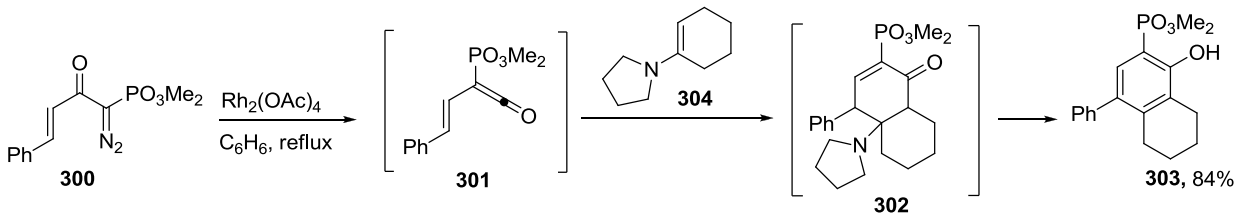
A tandem Wolff rearrangement/lactonization process was also exploited for the preparation of α-phosphono-γ-lactones **298a-c,** starting from the corresponding δ-hydroxy-α-diazo-β-ketophosphonates **297a-c** (Scheme 132). The ketenes, generated under either thermolytic or photolytic conditions, were 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 competive O-H intramolecular insertion reactions, which lead to the concomitant formation of the corresponding 3(2*H*)-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 $Rh_2(tfa)_4$, a more reactive, electrophilic rhodium catalyst, was used O-H insertion reaction was favoured affording the expected 3(2*H*)-furanone **299c** in excellent yield. [212]

**Scheme 132**. **Combined Wolff Rearrangement and O-H Trapping *vs* O-H Insertion Reaction**




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]

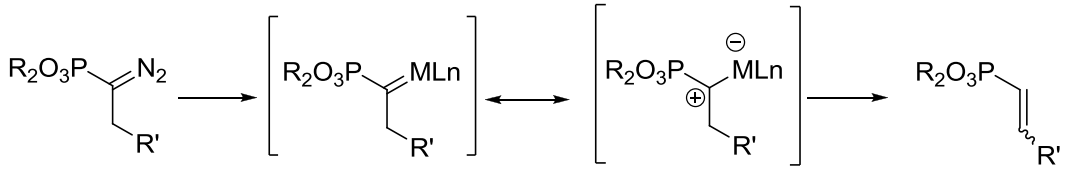
**Scheme 133. Combined Wolff Rearrangement and [4+2]-Cycloaddition Involving Enamine**




### 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 alkenylphosponates derives from the putative metal-bound carbene intermediate within which the 1,2-hydride shift occurs (Scheme 134).

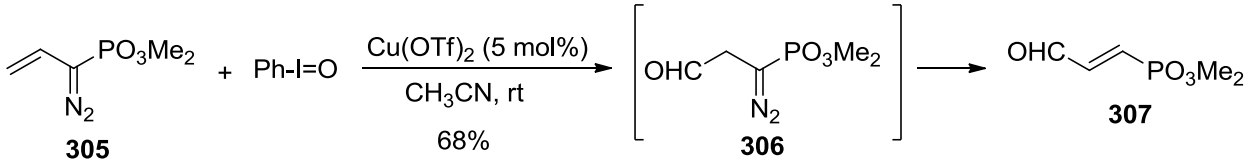
**Scheme 134. Formation of Alkenylphosphonates from PCDCs *via* 1,2-Hydride Shift Rearrangement**




Barluenga *et al*. observed an unexpected β-hydride elimination during the copper(II)-catalyzed reaction of the vinyl diazophosponate **305** with iodosylbenzene. Indeed, in contrast with the behaviour of vinyldiazocarbonyl compounds, instead of the expected oxodiazo derivative **306**, dimethyl

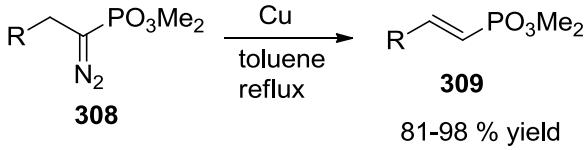
(1*E*)-3-oxoprop-1-enyl phosphonate (**307**) was obtained, due to an instantaneous β-H elimination within **306** itself (Scheme 135).[214]

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




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**

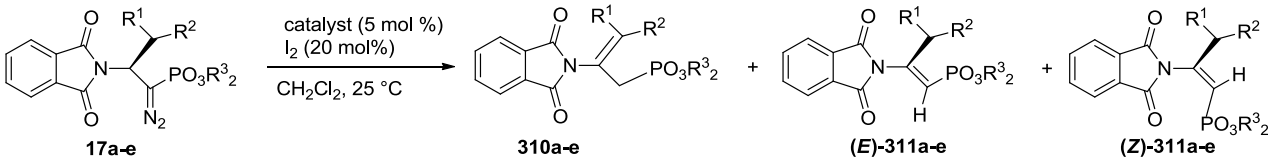



R = aryl, heteroaryl, benzyl, vinyl

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.

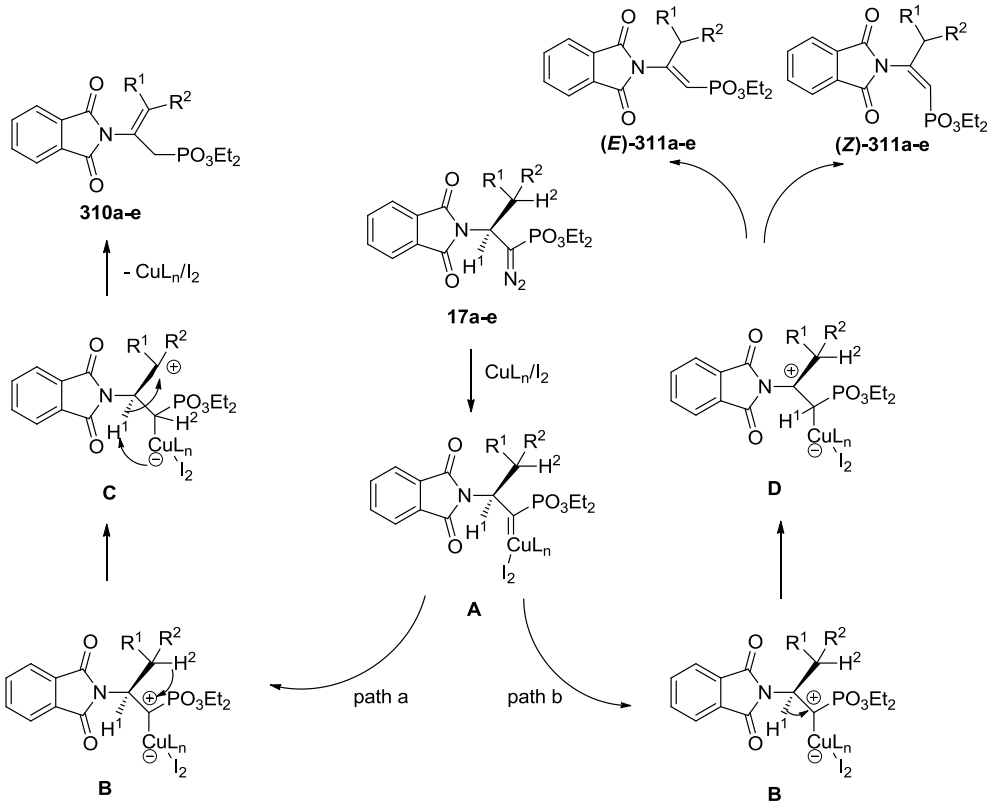
**Scheme 137. 1,2-Hydride Migration *vs* β,γ-Dihydrogen Shift in the Metal-Catalyzed Decomposition**

**of PCDCs 17a-e**




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 give 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 esclusively obtained,[216] the same research group focalized the attention on the optimization of the stereoselectivity between (*Z*) and (*E*) isomers.[217] 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 $R^1$ 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 17**

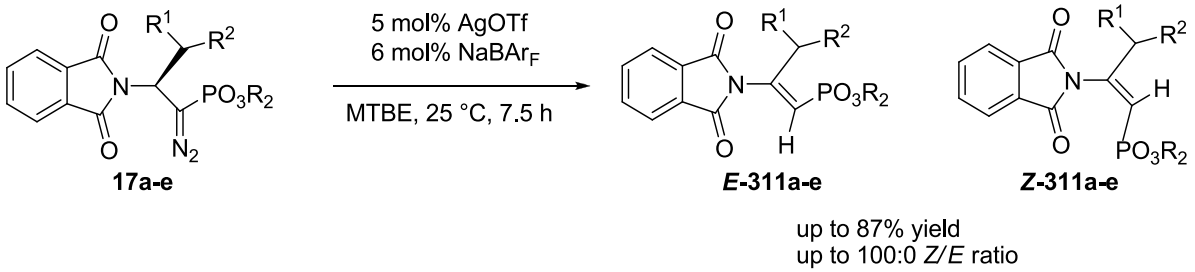
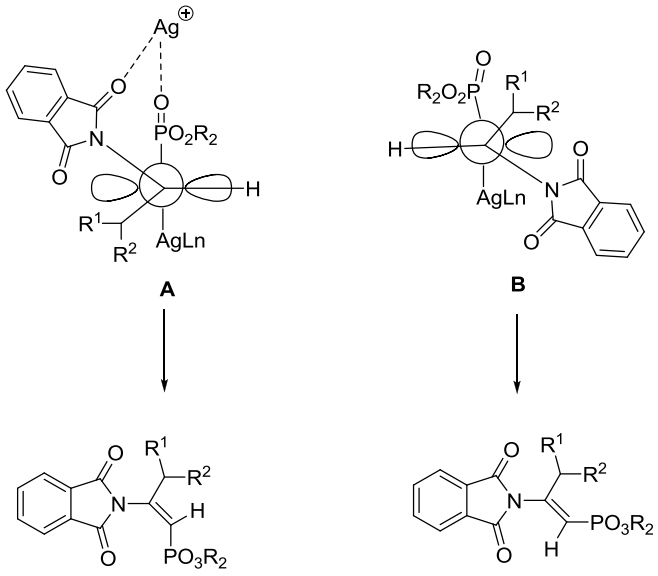


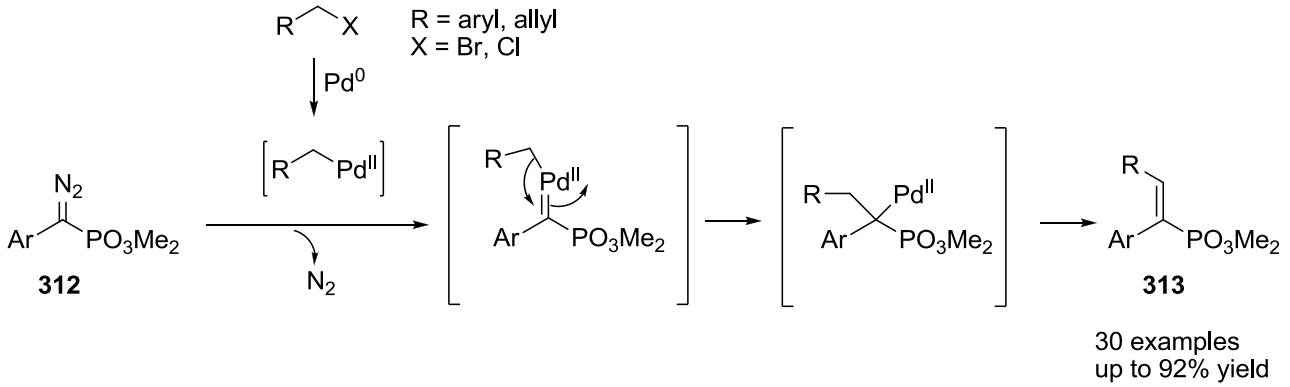

**Figure 7. Conformations Leading to the β-Hydrogen Migration**




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 alkenylphospohonates **313** (Scheme 140).[218]

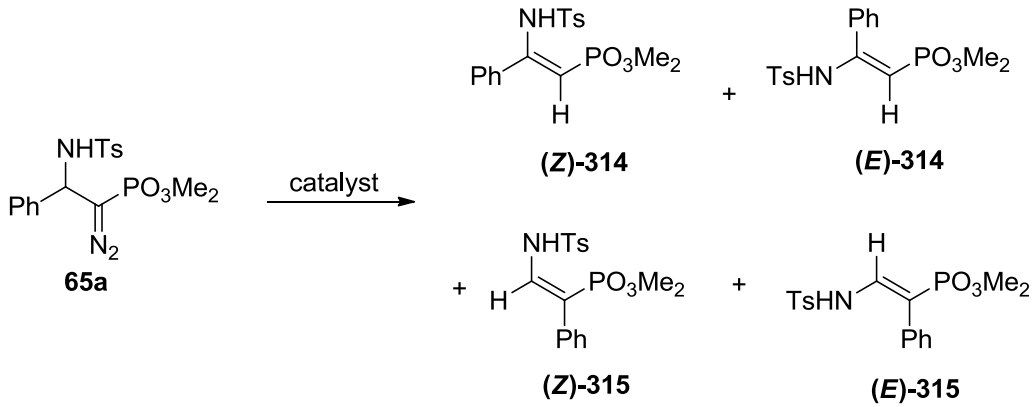
**Scheme 140. Synthesis of Alkenylphosphonates 312 through Palladium Carbene Coupling and 1,2-**

**Hydride Shift Rearrangement**




The competition between 1,2-hydride and 1,2-aryl shift in the decomposition of β-pheny-β-(N-to-syl)amino-α-diazoethylphosphonates **65a** was studied in details by Zhao *et al*.[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**

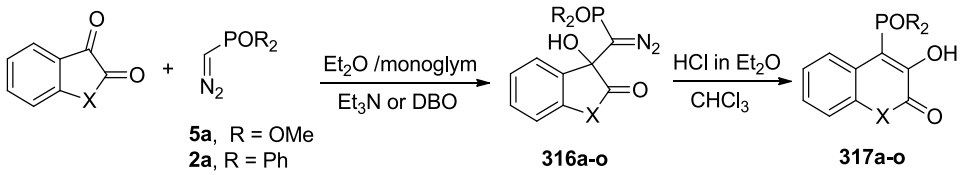



**3.8. Reactions with Aldehydes and Ketones**

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).[219,66,220] Under anhydrous acidic conditions the diazoaldols **316a-o** gave the corresponding ring-enlarged products **317a-o** through the intermediate carbocations.

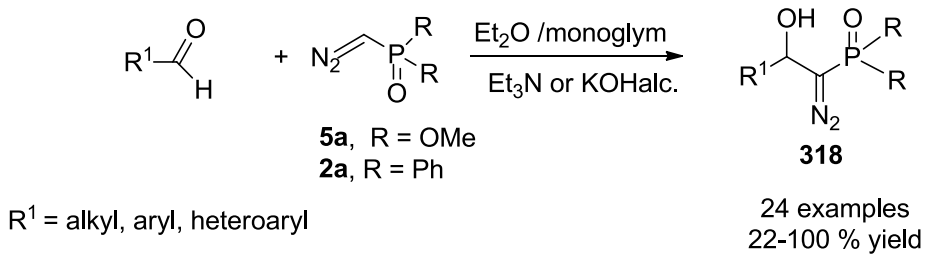
**Scheme 142. Synthesis of β-Hydroxy-PCDCs 316a-o and the Corresponding Ring-Enlarged Products 317a-o**




a: X = $C(CH_3)_2$, R = Ph, 65% (**316**), 86% (**317**); b: X = $C(CH_3)_2$, R = OMe, 74% (**316**), 88% (**317**); c: X = $C(C_6H_5)_2$, R = Ph, 78% (**316**), 84% (**317**); d: X = $C(C_6H_5)_2$, R = OMe, 64% (**316**), 85% (**317**); e: X = NH, R = Ph, 94% (**316**), 95% (**317**); f: X = NH, R = OMe, 90% (**316**), 99% (**317**); g: X = NMe, R = Ph, 80% (**316**), 86% (**317**); h: X = NMe, R = OMe, 81% (**316**), 89% (**317**); i: X = NOH R = Ph, 81% (**316**), 92% (**317**); j: X = NOH R = OMe, 66% (**316**), 82% (**317**); k: X = NOCOMe, R = Ph, 78% (**316**), 86% (**317**); l: X = NOCOMe, R = OMe, 58% (**316**), 65% (**317**); m: X = NCOMe, R = Ph, 93% (**316**), 59% (**317**); n: X = NCOMe, R = OMe, 56% (**316**), 65% (**317**); o: X = O, R = Ph, 38% (**316**), 73% (**317**)

Shortly after, the application of this reaction to a series of aldehydes was reported (Scheme 143).[221]

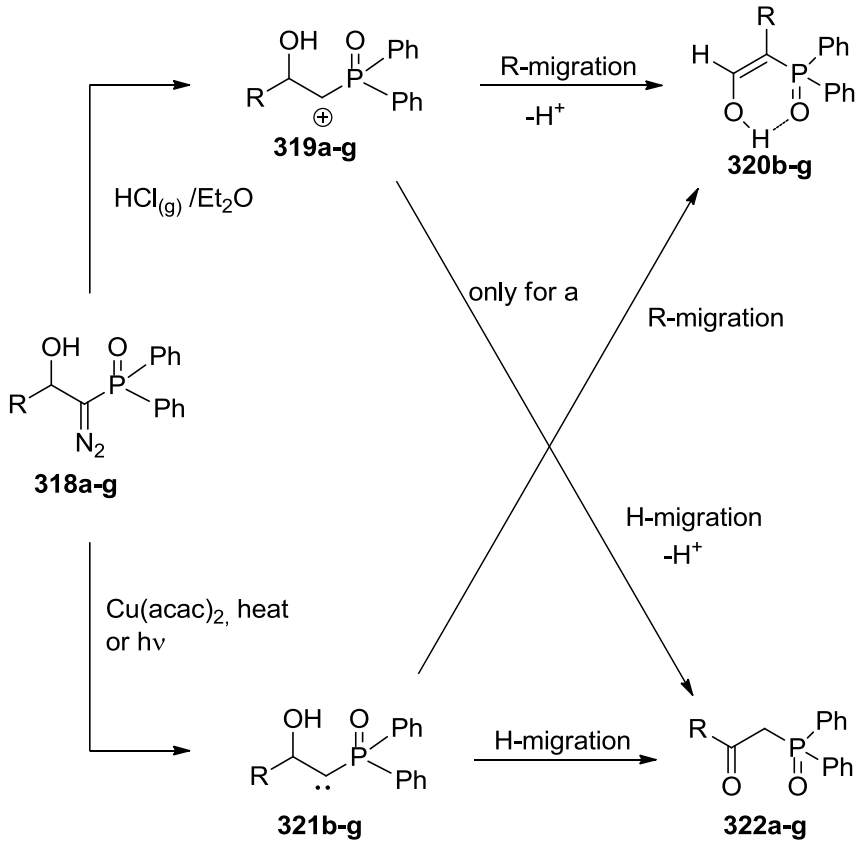
**Scheme 143. Synthesis of β-Hydroxy-PCDCs 318**




$R^1$ = 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**.

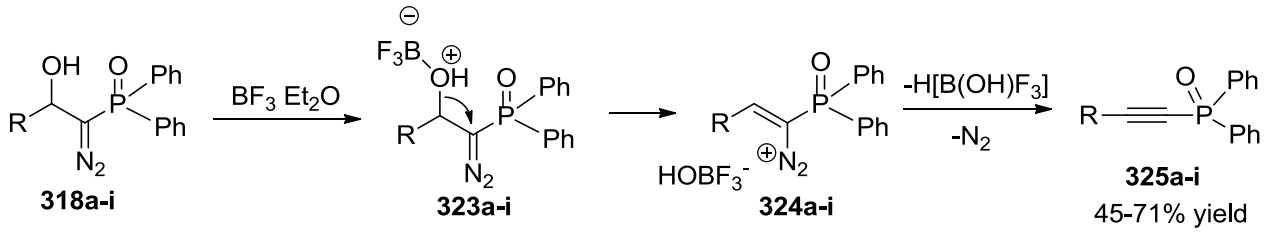
**Scheme 144. Decomposition of β-Hydroxy-α-diazophosphonoxides 318a-g under acidic condition, photolysis and metal catalysis.**




a: R = Me; b: R = 4-Me$C_6H_4$; c: R = Ph; d: R = 4-C$NC_6H_4$; e: R = 2-naphthyl; 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 $BF_3.Et_2O$ afforded the corresponding ethynyldiphenylphosphinoxides **325a-i** in 45-71% yield. The mechanism of the reaction involves the initial formation of the betaines **323a-i**, which by $BF_3OH$ 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**

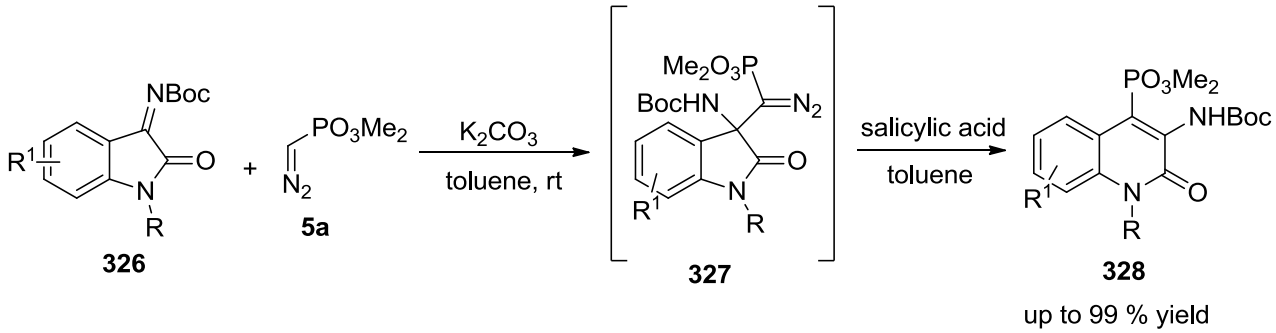



a: R = Me; b: R = 4-$MeC_6H_4$; c: R = Ph; d: R = 4-$CNC_6H_4$; e: R = 2-naphthyl; f: R = 2-thienyl; g: R = CH=C-Ph; h: R = CCPh; i: R = 2-furyl

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-dimethyphosphono-2-**

**quinolinones 328**




R = H, Me, Bn; $R^1$ = H, F, Cl, Br, $NO_2$, OMe

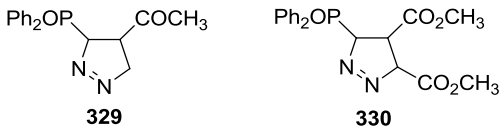
### 3.9. Cycloaddition Reactions

As evidenced in the earlier section dedicated to cyclopropanation reactions, PCDCs are able to partecipate 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 8Error! Reference source not found.), both isolated in 70 % yield, after crystallization of the crudes from methanol.[29]

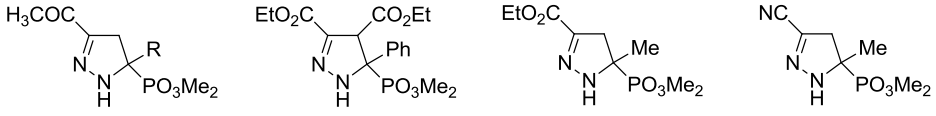
**Figure 8. Phospono-1-Pyrazolines 329 and 330, obtained by Reaction of 2a with Methyl Vinyl Ketone or Dimethyl Maleate**




**329** **330**

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. Phospono-1-Pyrazolines 331-334, obtained by Reaction of PCDCs 11a and 11b with Different Dipolarophiles**




from methyl vinyl ketone **331a,b** | from diethyl maleate **332a,b** | from ethyl acrylate **333a,b** | from acrylonitrile **334a,b**

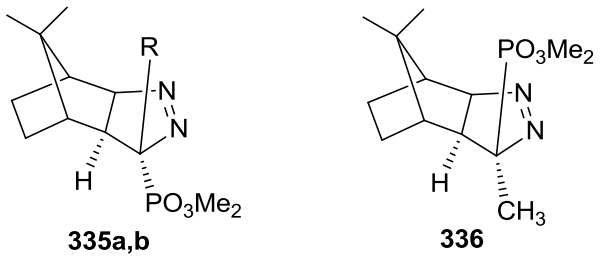
a: R = Ph; b: R = Me

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 $CH_2Cl_2$ 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]

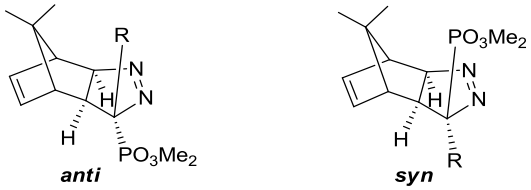
**Figure 10. 3-Phosphono-1-pyrazolines from the Reaction of PCDCs 11a and 11b with Norbornene**




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[225] and the stereospecific vicinal homoallylic $^{5}J_{PH}$ coupling constants.[226] Up to the present Benezra's papers[39,11,223,26] still remain of substantial value in the poor scenario of spectroscopic data on phosphorus-containing compounds.

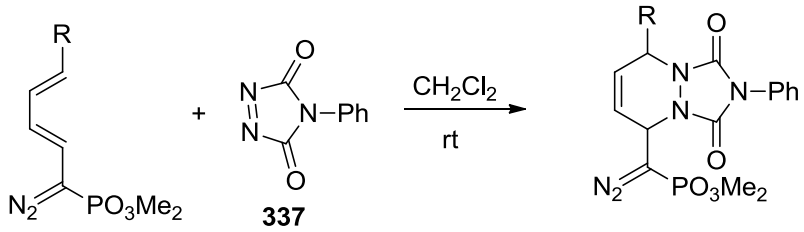
**Figure 11. Steric Course of the Cycloaddition Reaction of PCDCs with Norbornadiene**




R = 4-MeOC$_6$H$_4$, 95 (anti), 5 (syn); R = 4-MeOC$_6$H$_4$, 90 (anti), 10 (syn); R =4-BrC$_6$H$_4$, 90 (anti), 10 (syn); R = C$_6$H$_5$, 95(anti), 5 (syn); R = 4-NO$_2$C$_6$H$_4$, 93(anti), 7(syn); R = 4-MeOCOC$_6$H$_4$, 91 (anti), 9 (syn); R = 2-MeOC$_6$H$_4$, anti only; R = 1-naphthyl, anti only; R = 2-naphthyl, 90 (anti), 10 (syn); R = Me, 75 (anti), 25 (syn); R = Et, 60 (anti), 40 (syn); R = *i*Pr, 50 (anti), 50 (syn); R = *t*Bu, syn only; R = benzyl, 55(anti), 45 (syn)

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-3*H*-1,2,4-triazole-3,5(4*H*)-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**

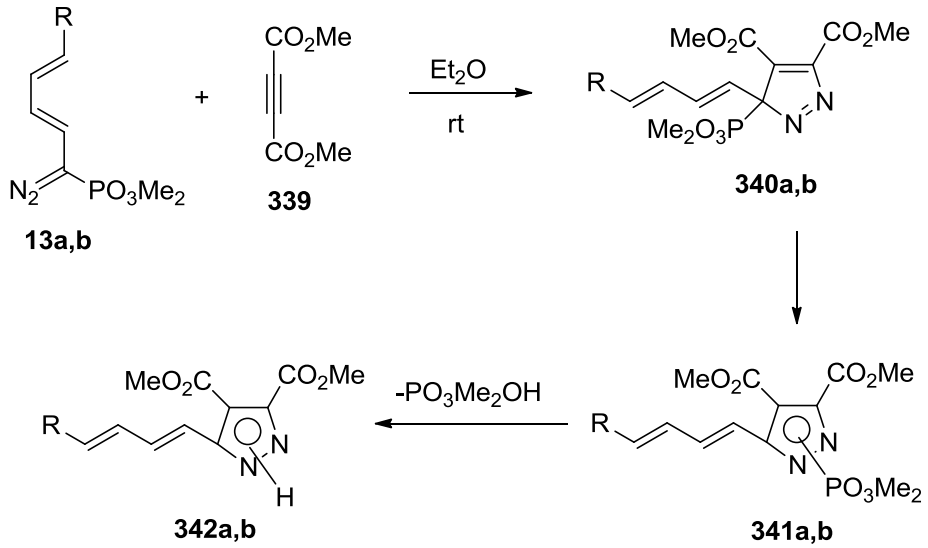



a: R = Ph; b: R = Me

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 3*H*-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**, 3*H*-pyrazole **340** resulted so stable as to be isolated in 66% yield by stopping the reaction after 24 h.

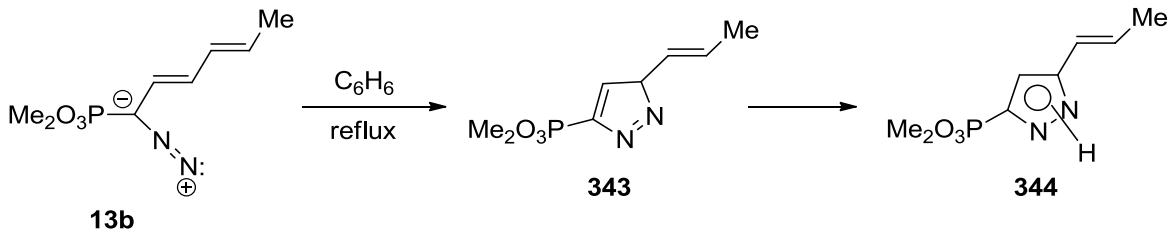
**Scheme 148. Cycloaddition Reactions of PCDCs 13a,b with Dimethyl Acetylendicarboxylate (339)**




a: R = Ph; b: R = Me

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).[41] Theis's paper represents another valuable source of spectroscopic data.

**Scheme 149. Intramolecular Cycloaddition of PCDC 13b**

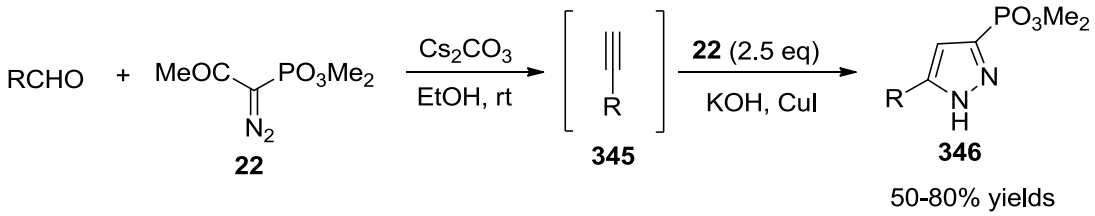



Under basic conditions, BOR (**22**) undergoes 1,3-dipolar cycloaddition reactions with double bonds conjugated with nitro,[227,228] carbonyl,[229,230] and nitrile[231] groups thus affording the corresponding differently substituted phosphonopyrazoles. This research topic has been very prosperous and has

been recently reviewed.[232] For this reason, only the work published after 2012 will be described here.

Kumar *et al*.[233] 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 $Cs_2CO_3$ in ethanol to generate a terminal acetylene **345**. 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 phosphonylpyrazoles **346** 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.[41]

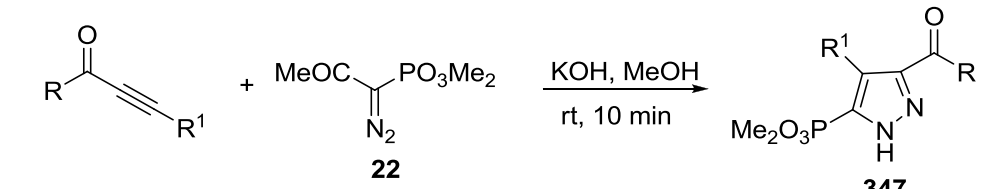
**Scheme 150. One-pot, Telescoped Transformation of Aldehydes into 3-Phosphonopyrazoles 346**




R = aryl, heteroaryl

Later on Pramanik *et al*.[234] extensively investigated the reactivity of **22** with a variety of ynones, as dipolarophiles, obtaining 3-carbonylpyrazole-3-phosphonates **347** (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.

**Scheme 151. Cycloaddition Reaction of Ynones and BOR (22)**

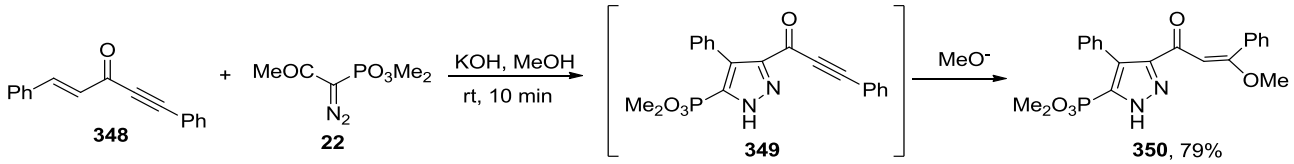



R = alkyl, cycloalkyl
aryl. heteroaryl
$R^1$ = aryl, TMS

79-90% yields

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**

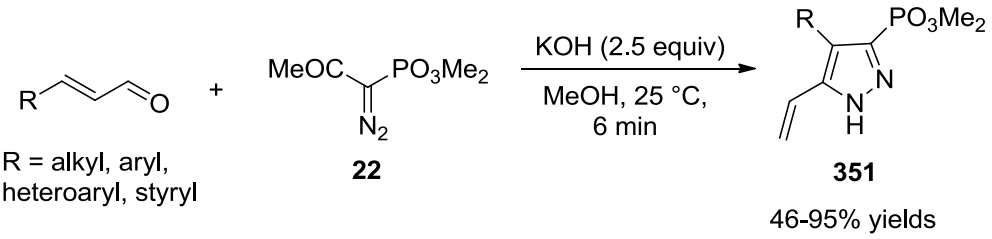



BOR cycloaddition occurred exclusively at the double bond, whereas Michael addition of the methoxide ion is the preferred reaction on the triple bond.

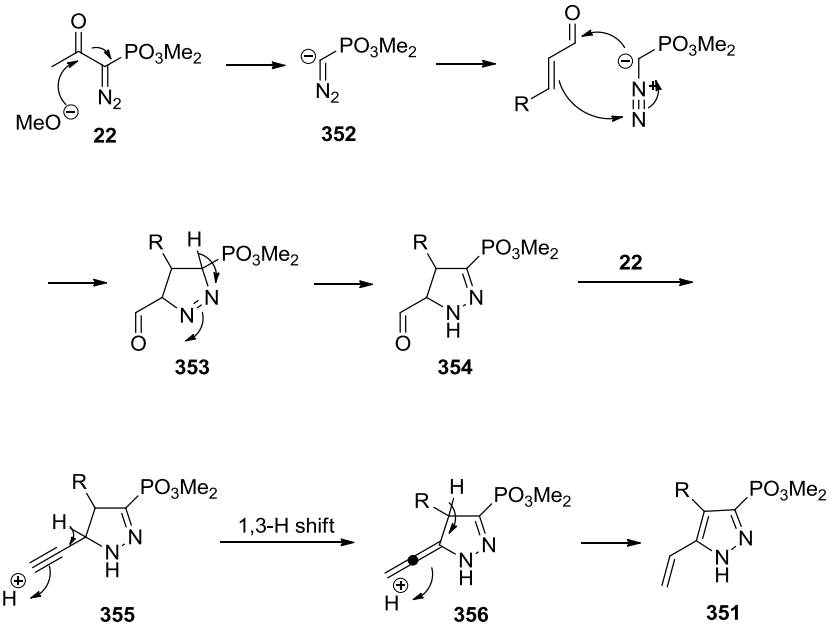
Continuing along this path, Ahmad *et al*.[235] proposed a domino process involving the reaction of α,β-unsatured aldehydes with an excess of BOR (**22**) in the presence of KOH in methanol, for obtaining in one-step and very short reaction time the corresponding 4-sustituted-5-vinyl-3-phosphonopyrazoles **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

**353**. 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-unsatured aldehydes and BOR (22)**

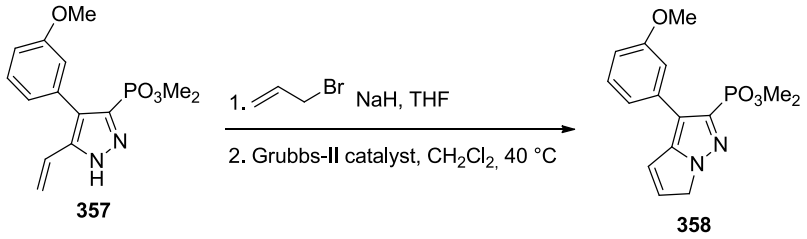



**Scheme 154. Proposed Mechanism of the Domino Reaction of α,β-Unsatured Aldehydes and BOR (22)**



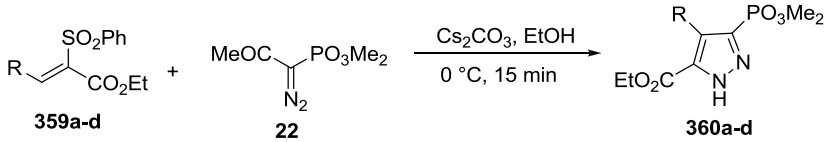

The potential synthetic application of this methodology was explored by synthesizing **358**, a phosphorous-containing analog of the alkaloid whitasomnine. In particular, the phosphonopyrazole **357**, obtained from 3-methoxycinnamaldehyde, was first *N*-allylated and then treated with Grubbs-II catalyst 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]

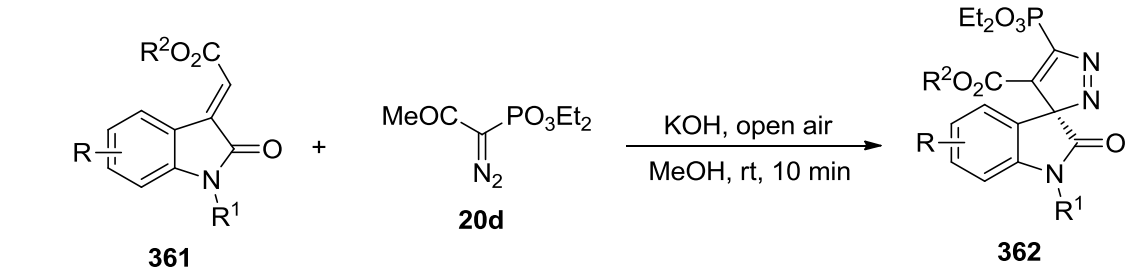
**Scheme 156. Synthesis of Phosphonopyrazoles 360a-d *via* Cycloaddition of BOR (22) to Vinyl Sulfonyl Carboxylates 359a-d**




a: R = 4-OMe$C_6H_4$,72%; b: R = benzo[d][1,3]dioxole,74%; **c:** R = 3-Br$C_6H_4$, 70%;
d: R = cyclohexyl, 67%

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-oxopropylphosphonate (**20d**) and substituted methyleneindolinones **361** (Scheme 157).[237]

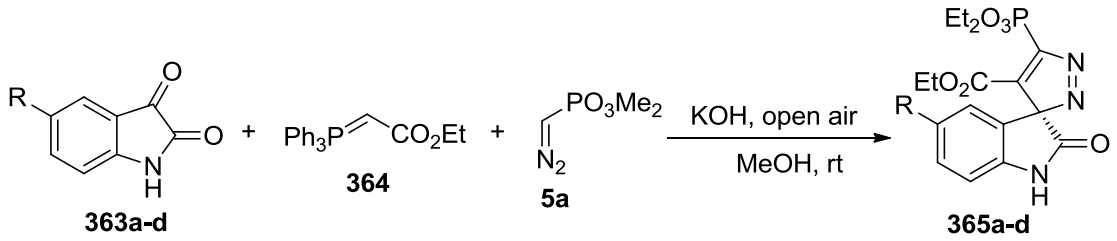
**Scheme 157.1,3-Cycloaddition Reaction between Methyleneindolinones 361 and PCDC 20d**




R = H, 5-Br, 5-Cl, 5-F, 5-OMe,
5-$OCF_3$, 5-$NO_2$, 4-Cl, 6-Br
$R^1$ = H, Bn, Me, Boc
$R^2$ = Me, Et

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).

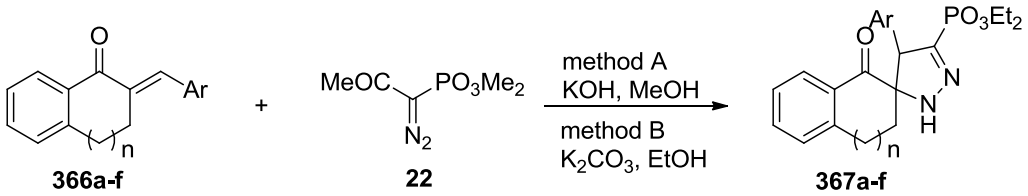
**Scheme 158. Sequential Multicomponent Reaction of Isatin, Phosphonium Ylide and 5a**




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 ($K_2CO_3$ in EtOH; method B) led to a substantial yield improvement. In all cases the resulting phosphonopyrazolines **367a-f** were formed as a single diastereoisomer.

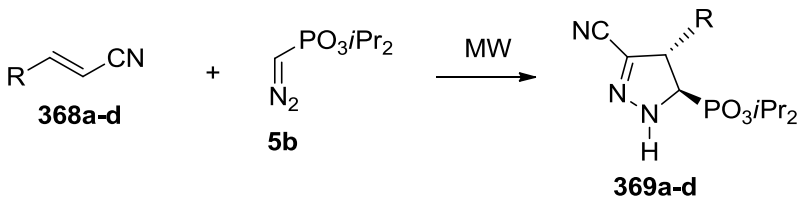
**Table 4. Synthesis of Spiropyrazolynes 367a-f from Trisubstitited Enones 366a-f and BOR (22)**




| Compound | n | Ar | Yield (%) Method A | Yield (%) Method B |
|---|---|---|---|---|
| **a** | 1 | Ph | 61 | 72 |
| **b** | 1 | 4-OMe-Ph | 56 | 76 |
| **c** | 1 | 4-Cl-Ph | 75 | 91 |
| **d** | 1 | 2-thienyl | 51 | 70 |
| **e** | 0 | Ph | 50 | 72 |
| **f** | 0 | 4-Cl-Ph | 52 | 74 |

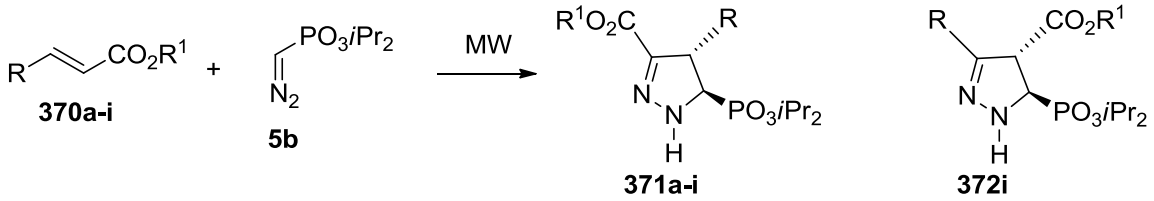
A more general method for the synthesis of functionalized phosphonopyrazolines was recently reported by Marinozzi *et al*.[34] The procedure involves the microwave-assisted cycloaddition of diisopropyl diazomethylphosphonate (**5b**) to electron deficient alkenes, such as α,β-unsaturated nitriles **368a-d** (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.

**Scheme 159. Microwave-Assisted Cycloaddition of α,β-Unstured Nitriles 368a-d and 5b**




a: R = H, 82%; b: R = Me, 76%; c: R = Et, 82%; d: R = Ph, 73%

**Scheme 160. Microwave-Assisted Cycloaddition of α,β-Unstured Esters 370a-h and 5b**

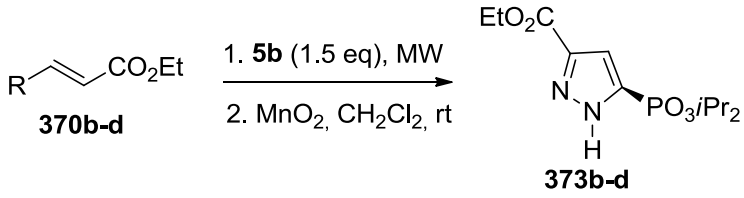



a: R = H, $R^1$ = Et, 80% (**371**); b: R = Me, $R^1$ = Et, 68% (**371**); c: R = *n*Pr, $R^1$ = Et, 68% (**371**); d: R = Ph, $R^1$ = Et, 54% (**371**); e: R = $CH_2Br$, $R^1$ = Et, 79% (**371**); f: R = (*E*)-$CO_2Me$, $R^1$ = Me, 91% (**371**); g: R = (*Z*)-$CO_2Me$, $R^1$ = Me, 87% (**371**); h: R = (*E*)-$CO_2t$Bu, $R^1$ = Et, 86% (**372**); i: R = COPh, $R^1$ = Me, 55% (**371**), 34% (**372**)

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 substituents, from which two regioisomeric phosphonopyrazolines **371i** and **372i** were obtained. A peculiarity 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 fulfilling 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**

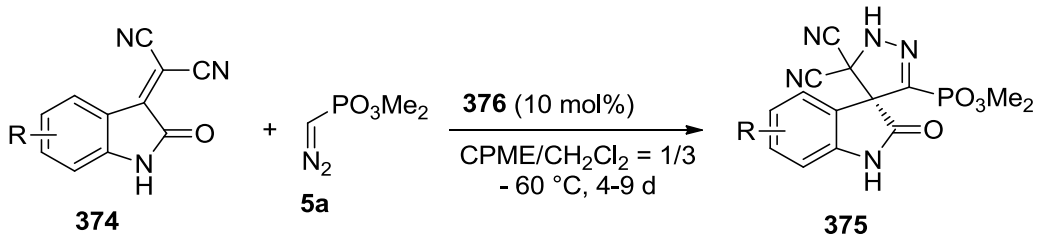



b: R = Me, 85%; c: R = Et, 82%; d: R = Ph, 72%

In 2015, the first example of organocatalytic enantioselective 1,3-cycloaddition with a PCDC was reported.[238] 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.

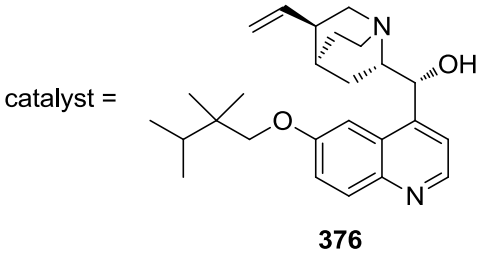
**Scheme 162**. **Organocatalytic Enantioselective 1,3-Cycloaddition between 5a and Isatylidene**

**Malononitriles 374**



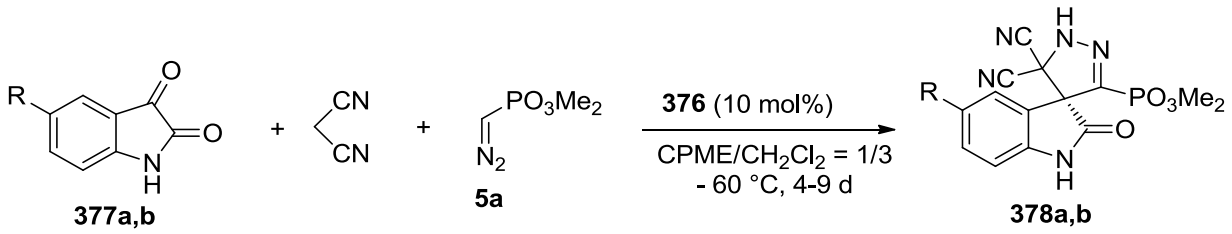

R = H, 5-Cl, 5-Me, 5-Br, 5-F, 5-I, 5-OMe, 5-Br 7-Me, 4-Cl, 4-Br, 6-Cl, 6-Br

75-99% yields
up to99% ee




**376**

**Scheme 163**. **Three-component Reaction based on a Domino Knoevenagel Condensation/1,3-Dipolar Cycloaddition Sequence**



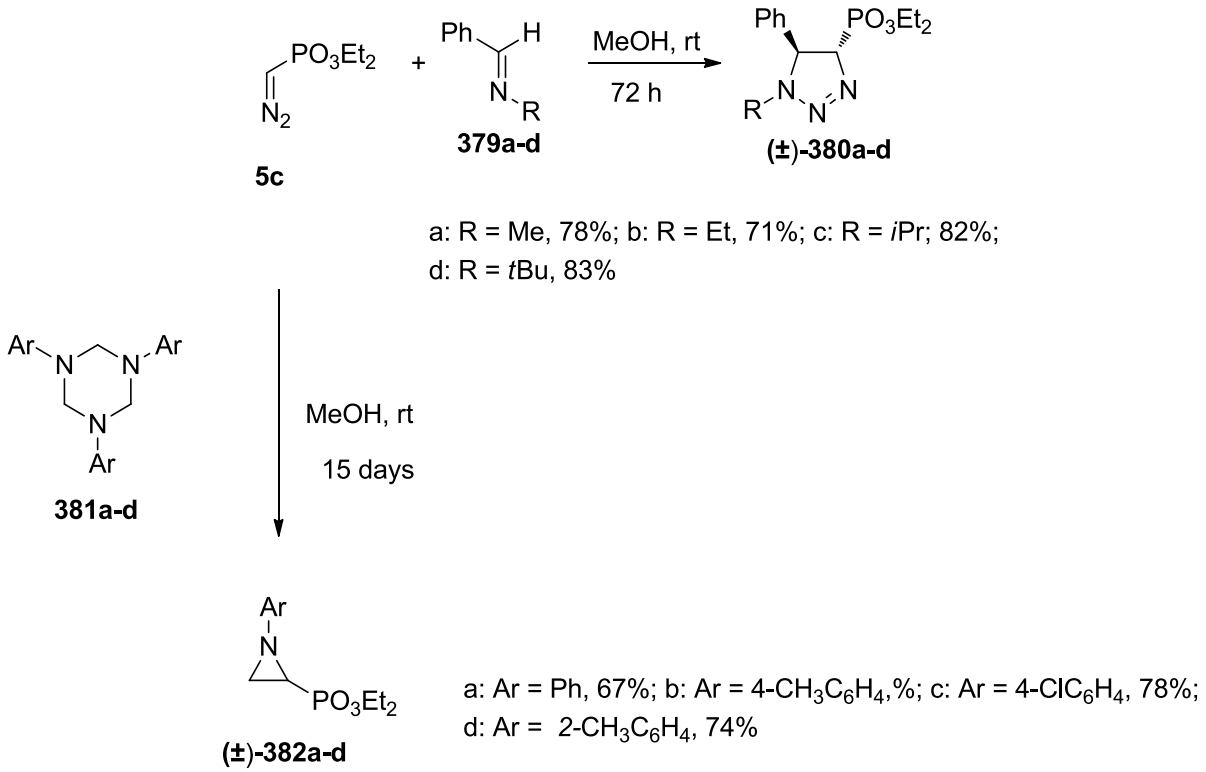

a: R = H, 75%, 93% *ee*; b: R = F, 88%, 97% *ee*

### 3.9.2. Cycloaddition Involving Carbon-Nitrogen Double Bond

The cycloaddition of diethyl diazomethylphosphonate (**5c**) to a carbon-nitrogen double bond was first reported by Bartnik *et al*.,[239] who exploited this reaction for the preparation of $\Delta^2$-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-1*H*-[1,2,3]triazol-4-yl)phosphonic acid diethyl ester (**380a**) in 77% yield, as single diastereoisomer

(Scheme 164). 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).

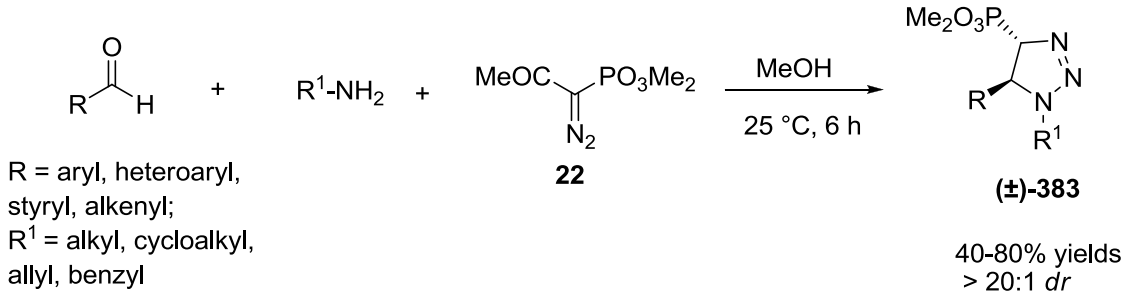
**Scheme 164**. **Synthesis of Δ²-1,2,3-Triazolinyl-4-phosphonates 380a-d, and Aziridinyl-2-phosphonates 382a-d**




In January 2016, Ahamad *et al*.[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

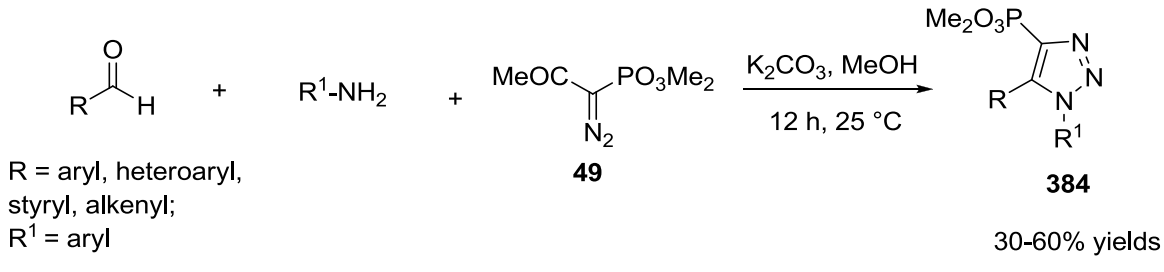
amine, and BOR (**22**), in methanol at room temperature the corresponding *trans*-1,4,5-trisubstituted 1,2,3-triazoline **383** are obtained as almost exclusive single diastereoisomer.

**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 $K_2CO_3$, was necessary to get the products in reasonable yields. The generality of this strategy was also explored.

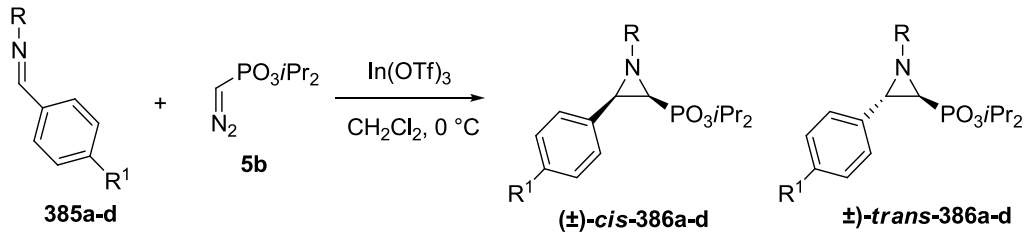
**Scheme 166**. **Synthesis of Dimethyl 1,2,3-Triazole-4-phosphonates 384**




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**.

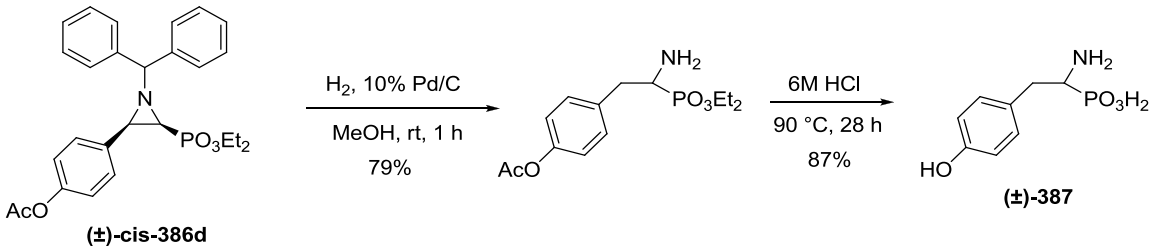
**Scheme 167**. **Synthesis of *cis*- and *trans*-3-Substituted-Aziridine-2-Phosphonates 386a-d**




a: R = Ph, $R^1$ = H, *cis* only, 40%; b: R = $CHPh_2$, $R^1$ = H, 4/1 *cis*/*trans* only, 58% (cis), 19% (trans); c: R = $CHPh_2$, $R^1$ = Me, 4/1 *cis*/*trans*, 40% (cis), 16% (trans); d: R = $CHPh_2$, $R^1$ = AcO, 4/1 *cis*/*trans*, 68% (cis), 18% (trans); e: R = $CHPh_2$, $R^1$ = Cl, 6/1 *cis*/*trans*, 79% (cis), 12% (trans); f: R = $CHPh_2$, $R^1$ = $CF_3$, 2/1 *cis*/*trans*, 54% (cis), 28% (trans); g; R = $CHPh_2$, $R^1$ = $NO_2$, 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).

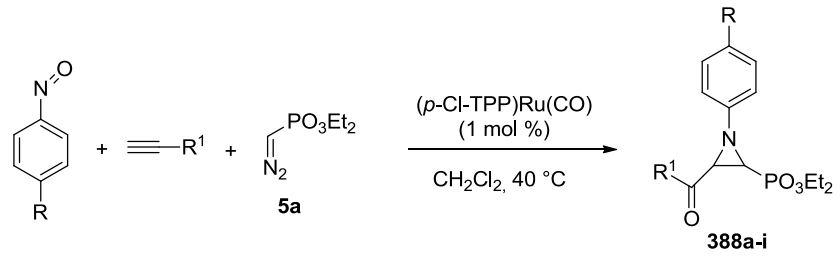
**Scheme 168**. **Synthesis of [1-Amino-2-(4-hydroxyphenyl)ethyl]phosphonic Acid Hydrochloride (±)-387**




The synthesis of 3-acylaziridine-2-phosphonates was recently realized via ruthenium-catalyzed three-component reaction involving dimethyl α-diazomethylphosphonate (**5a**), a nitrosoarene and

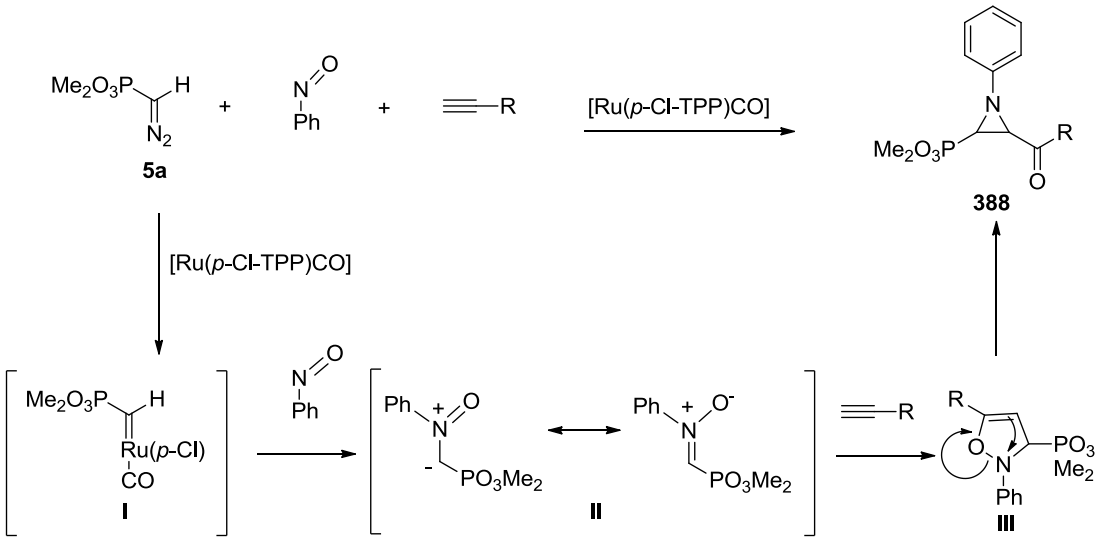
an alkyne (Scheme 169).[242] The optimization of the reaction conditions, already performed in analogous reactions with diazocarbonyl reagents, had evidenced [Ru(*p*-Cl-TPP)CO] ($H_2$-*p*-Cl-TPP = *meso*-tetrakis(4-chlorophenyl)porphyrin] as the best catalyst in terms of yield and diastereoselectivity. 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 *trans* isomer was always observed. The mechanistic hypothesis as reported by the authors is depicted in the Scheme 170**:** the nitrone intermediate **II**, generated by the trapping of ruthenium-carbene complex **I** by nitrosoarene, undergoes 1,3-dipolar cycloaddition with alkyne to give isoxazoline **III**, which rapidly rearranges to the corresponding aziridine **388**.

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




a: R = H, $R^1$ = $C(CH_3)_2OH$, 98%, 91:9 *dr*; b: R = H, $R^1$ = $CH_2OH$, 95%, 90:10 *dr*; c: R = H, $R^1$ = $CH_2Cl$, 87%, 92:8 *dr*; d: R = H, $R^1$ = $CH_2Br$, 85%, 92:9 *dr*; e: R = H, $R^1$ = $Si(CH_3)_3$, 45%, >99:1 *dr*; f: R = H, $R^1$ = $(CH_2)_3CH_3$, 77%, >99:1 *dr*; g: R = H, $R^1$ = $C_5H_9$, 78%, >99:1 *dr*; h: R = Cl, $R^1$ = $C(CH_3)_2OH$, 85%, 90:10 *dr*; i: R = $CH_3$, $R^1$ = $C(CH_3)_2OH$, 94%, 90:10 *dr*

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

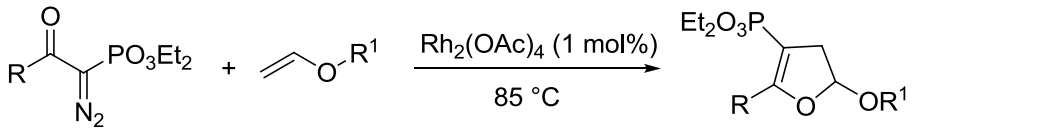


### 3.9.3. Other 1,3-Dipolar Cycloaddition Involving Loss of the Diazo Nitrogen Moiety

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**.[72]

**Scheme 171**. **Synthesis of Diethyl 2,5-Disustituted-2,3-dihydrofuran-3-phosphonates 389a-g**




**20d,e**
**59**

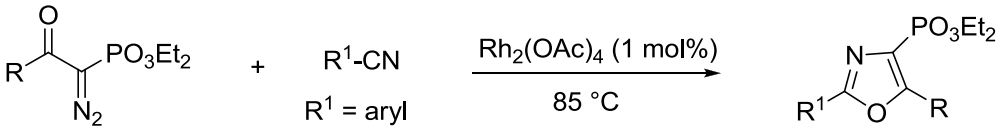
**389a-g**

**20d**: R = Me
**20e**: R = Ph
**59**: R = $CF_3$

**a**: R = Me, $R^1$ = Et, 76% yield
**b**: R = Me, $R^1$ = *n*Bu, 83% yield
**c**: R = Me, $R^1$ = *i*Bu, 85% yield
**d**: R = Ph, $R^1$ = *n*Bu, 40% yield
**e**: R = Ph, $R^1$ = *i*Bu, 35% yield
**f**: R = $CF_3$, $R^1$ =*n*Bu, 88% yield
**g**: R = $CF_3$ $R^1$ = *i*Bu, 90% yield

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-Disustituted-1,3-Oxazol-4-Phosphonates 391a-g**




**20d-f**
**390**

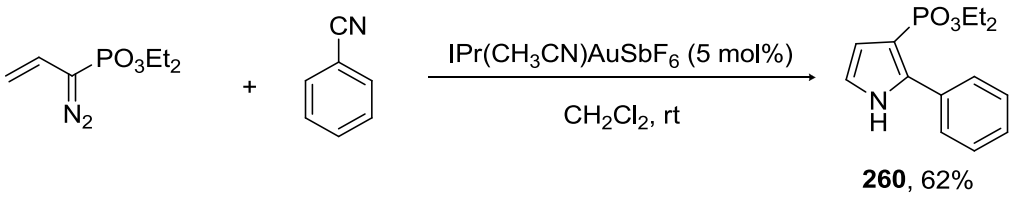
**391a-g**

**20d**: R = Me
**20e**: R = Ph
**20f**: R = OEt
**390**: R = OMe

**a**: R = Me, $R^1$ = Ph, 83% yield
**b**: R = Me, $R^1$ = *o*$CH_3C_6H_4$, 55% yield
**c**: R = Me, $R^1$ = *m*$CH_3C_6H_4$, 85% yield
**d**: R = Ph, $R^1$ = Ph, 37% yield
**e**: R = Ph, $R^1$ = *m*$CH_3C_6H_4$, 31% yield
**f**: R = OMe, $R^1$ = Ph, 61% yield
**g**: R = OEt, $R^1$ = Ph, 70% yield

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-1*H*-pyrrol-3-yl)phosphonate (**392**), (Scheme 173).[244]

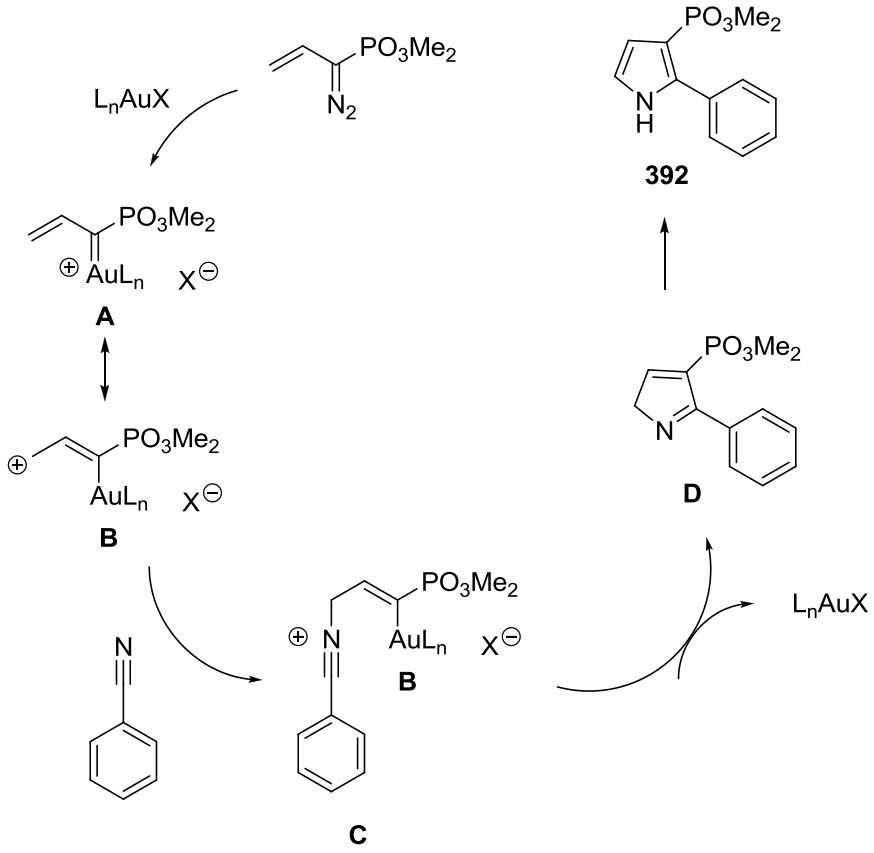
**Scheme 173. Synthesis of Diethyl (2-Phenyl-1*H*-pyrrol-3-yl)phosphonate (392).**




**260**, 62%

The result of the [3+2]cycloaddition was razionalized 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.

**AUTHOR INFORMATION**

Corresponding Author

*E-mail: maura.marinozzi@unipg.it

**Notes**

The Authors declare no competing financial interest

**Biographies**

**Maura Marinozzi** graduated in Pharmaceutical Chemistry and Technology in 1986 and received her PhD in Rational Design and Synthesis of Drugs in 1990 from University of Perugia. She is currently Associate Professor of Medicinal Chemistry at the Department of Pharmaceutical Sciences of University of Perugia. Since Ph.D studies she has focused her research interest on the application of diazo compounds for the synthesis of biologically active derivatives. Her other research fields include the design and synthesis of steroidal and non-steroidal modulators of metabolic nuclear receptors, and modulators of the kynurenine pathway of tryptophan metabolism, and the development of more environmentally-friendly synthetic stategies for the preparation of desired building blocks. She is author/coauthor of several scientific publications in the field of medicinal, as well as organic chemistry.

**Fabrizio Pertusati** received is 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.

**Michaela Serpi** graduated in Medicinal Chemistry in 1998. She received her Ph.D. in Medicinal Chemistry in 2005 from the University of Perugia (Italy), under the supervision of Professor Roberto Pellicciari, with a work on constrained analogues of L-AP4, as ligands at group III metabotropic

glutamate receptors. After her Ph.D., she joined the medicinal chemistry group of Professor Chris McGuigan at Cardiff University. She worked from January 2008 to January 2011 as a Post Doctoral Fellow funded by NIH at the University of Southern California in the Group of Professor Charles E. Mckenna. Her research interests include the design, synthesis, and biological evaluation of nucleoside analogues as antitumoral, antinfective, and antibacterial agents. She is currently a Senior Scientist in the School of Pharmacy of Cardiff University.

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**ABBREVIATIONS**

| | |
|---|---|
| acac | acetylacetonate |
| BARF | tetrakis[3,5-bis(trifluoromethyl)phenyl]borate |
| biTISP | (2*S*,2'*S*),(5*R*,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 | α, α, α', α'-tetramethyl-1,3-benzenedipropionate |
| GC-MS | gas chromatography- mass spectrometry |
| hfba | heptafluorobutyramide |
| 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*-acetamidobenzenesulfonyl 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-Iodo-*p*-toluenesolfonamide |

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