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Editorial

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This article is part of the Thematic Series "Organophosphorus chemistry"

Guest Editor: P. R. Hanson

Organophosphorus compounds are ubiquitous in nature, and due to their innate chemical properties, serve a fundamental role in a number of important fields. Among the more prominent features that elevate their status as a unique and versatile class of compounds, include variable oxidation states, multivalency, asymmetry and metal-binding properties. Their presence in bioactive natural products, endogenous biomolecules, small molecule therapeutic agents and pro-drugs substantiates their role in modern synthetic chemistry and chemical biology. Moreover, their central use as ligands and effectors in asymmetric catalysis, as well as key functional groups for the development of new synthetic methods, has taken the field to new heights. This Thematic Series highlights and details some of the novel methods that are advancing the field of organophosphorus chemistry.

The Thematic Series covers topics that range from new synthetic methods and phosphorus-based ligands in asymmetric catalysis to bisphosphonates as promising enzyme inhibitors. More specifically, the Thematic Series spans new methods in C–P bond formation, chiral phosphines in nucleophilic organocatalysis, chiral *N*-phosphinyl auxiliaries, cyclic phosphonamide reagents in the total synthesis of natural products, phosphinate-containing heterocycles, new routes to phosphinoyl-indoles and phosphinoyl-isocoumarins and new chemistries of H-phosphonates. The Thematic Series also details work on new metathesis-based reactions of vinyl phosphonates and phosphate tethers, novel phosphorus-based ligands in asymmetric catalysis, novel rasta resin–triphenylphosphine oxides and their use as recyclable heterogeneous reagents, the Atherton–Todd reaction, cyclic phosphonium ionic liquids with distinct properties, photo-removable phosphate protecting groups, new methods of C–H functionalization using phosphoryl-related directing groups, the exciting chemistry of substituted phosphanylidenecarbenes and phosphoryl azides, and bisphosphonate ethers as promising inhibitors of geranylgeranyl diphosphate synthase (GGDPS).

The articles and reviews capture the emerging potential of organophosphorus compounds and exciting opportunities in the field, and hopefully, will inspire and motivate investigators in the field to investigate new chemistry in this area. Taken collectively, organophosphorus chemistry embodies a broad, vibrant and continual growing scientific area with this Thematic Series highlighting recent advances in the field. We are grateful and indebted to the authors for their hard work and exciting contributions to this Thematic Series and look forward to continued contributions in this area.

Paul R. Hanson

Lawrence, July 2014

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# Cyclic phosphonium ionic liquids

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## Abstract

Ionic liquids (ILs) incorporating cyclic phosphonium cations are a novel category of materials. We report here on the synthesis and characterization of four new cyclic phosphonium bis(trifluoromethylsulfonyl)amide ILs with aliphatic and aromatic pendant groups. In addition to the syntheses of these novel materials, we report on a comparison of their properties with their ammonium congeners. These exemplars are slightly less conductive and have slightly smaller self-diffusion coefficients than their cyclic ammonium congeners.

## Introduction

The most widely investigated and commercially available ionic liquids (ILs) are composed primarily of nitrogen-centered (particularly imidazolium, pyridinium, pyrrolidinium, and related quaternary ammonium) cations with a wide range of anions [1]. While a number of these ILs have been applied successfully to commercial processes [1], efforts are continually underway to synthesize ILs with improved properties (such as viscosity, thermal stability, melting point, etc.) to expand their applications into larger scale processes in diverse areas. Along that vein, phosphonium ILs have been observed to have favorable characteristics, including lower costs [2-6], lower viscosity (by ~50%) [7-11], greater thermal stability (by ~100 °C) [10-12], and wider electrochemical windows compared to their ammonium congeners. The family of ILs bearing cyclic cations (pyrrolidinium, piperidinium, and azepanium) [13,14] have been shown to have better transport and physical properties than most acyclic tetraalkylammonium salts. While cyclic phosphonium salts have been noted in patent applications [15], their characteristics have not been reported therein nor in journals, even though the comparisons noted above suggest those properties might be advantageous. To address such questions, we report here on the synthesis and physical characterization of some phosphonium analogues to pyrrolidinium and piperidinium ILs, i.e. phospholanium and phosphinanium ILs respectively.

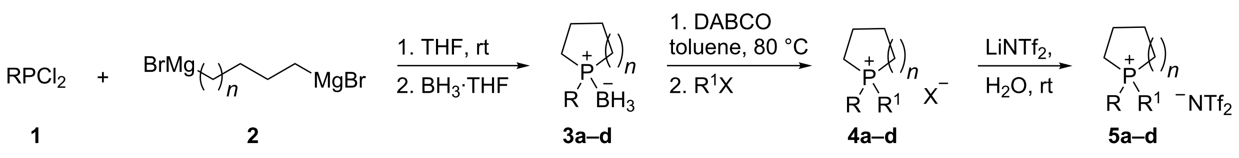
The favorable stability of phosphonium ILs makes them good choices for applications where the IL would be exposed to extreme conditions, such as environmental exposure to high temperatures or exposure to extreme electromagnetic radiation (as in a dye-sensitized solar cell or ionizing radiation as in the recycling of spent nuclear fuel). ILs can play important roles in both of these latter areas [16]. While dialkylimidazolium ILs can be efficient extraction media for nuclear separations [17-19], the imidazolium cation is also a good acceptor of radiolytically produced excess electrons. The resultant radical participates in radiation damage mechanisms that alter the IL's properties [20]. On the other hand, phosphonium ILs, known for their durability and already made in large quantities, can be optimized for extraction of specific species from radioactive spent nuclear fuel. Inclusion of phenyl groups, as in two of the new ILs reported here, can stabilize excess charges (electrons or holes) leading to a more durable extraction system. The question of whether cyclic phosphonium ILs would succeed in solar photoconversion or spent fuel processing depends not only on whether their properties can be tuned to the application, but also whether their reactivity under extreme conditions can be managed.

A major challenge for this work has been the handling of the tertiary phosphine precursors, which are pyrophoric and extremely air sensitive. 1-*n*-Butylphospholane and 1-*n*-butylphosphinane were synthesized by the reaction of *n*-butyldichlorophosphine [21] with the appropriate bis-Grignard reagents, $BrMg(CH_2)_4MgBr$ and $BrMg(CH_2)_5MgBr$ respectively. The resultant cyclic phosphines are air sensitive and therefore were allowed to react with $BH_3$·THF to provide the air-stable 1-*n*-butylphospholane–borane and 1-*n*-butylphosphinane–borane complexes that were purified by silica-gel chromatography. The pure compounds were then treated under nitrogen with 1,4-diazabicyclo[2.2.2]octane (DABCO) at 80 °C to remove the borane, and the resultant mixture was purified in a nitrogen-filled glove box on a short silica-gel column. The pure cyclic phosphines (1-*n*-butylphospholane and 1-*n*-butylphosphinane) were allowed to react immediately with iodomethane at room temperature to produce the 1-*n*-butyl-1-methylphospholanium iodide and 1-*n*-butyl-1-methylphosphinanium iodide, respectively. These materials were each mixed with an equivalent amount of lithium bis(trifluoromethylsulfonyl)amide ($LiNTf_2$) in water at room temperature to produce the water-insoluble salts, 1-*n*-butyl-1-methylphospholanium bis(trifluoromethylsulfonyl)amide and the corresponding 1-*n*-butyl-1-methylphosphinanium bis(trifluoromethylsulfonyl)amide. In a corresponding manner were prepared the 1-phenylphospholane and the 1-phenylphosphinane by the reaction of dichlorophenylphosphine with the appropriate bis-Grignard reagents, $BrMg(CH_2)_4MgBr$ and $BrMg(CH_2)_5MgBr$, respectively. The resulting five-membered cyclic 1-phenylphospholane was isolated in the same manner as was the 1-*n*-butylphospholane: i.e. by conversion with $BH_3$·THF to give the air-stable 1-phenylphospholane–borane complex, followed by silica-gel chromatography and then removal of the borane with DABCO, to give the pure 1-phenylphospholane. The six-membered cyclic phosphine, which appears to be less air sensitive than the 1-butylphosphinane species, was purified in open air using a short column of silica gel. Both cyclic phosphines were each allowed to react with 1-bromobutane at reflux under nitrogen to give the 1-*n*-butyl-1-phenylphospholanium bromide (**4c**) and the 1-*n*-butyl-1-phenylphosphinanium bromide (**4d**), respectively. Each of these salts was then mixed with aqueous $LiNTf_2$ to form the 1-*n*-butyl-1-phenylphospholanium bis(trifluoromethylsulfonyl)amide (**5c**) and the corresponding 1-*n*-butyl-1-phenylphosphinanium bis(trifluoromethylsulfonyl)amide (**5d**). The overall synthetic route is summarized in Scheme 1.

## Results and Discussion

The conductivities, viscosities, self-diffusion coefficients and thermal properties of the phosphonium ILs **5a–d** and their ammonium congeners are given in Table 1.

Comparison of the five-membered cyclic cation ILs $C_4$mPphol $NTf_2$ **5a** and $C_4$mPyrr $NTf_2$ (butylmethylpyrrolidinium $NTf_2$) reveals that the viscosity of the phosphonium salt is one third higher than that of the ammonium salt (101 cP vs 75 cP at 25 °C). For the six-membered rings the phosphonium IL $C_4$mPphin $NTf_2$ **5b** is slightly less viscous than $C_4$mPip $NTf_2$ (butylmethylpiperidinium $NTf_2$), 171 cP vs 183 cP. Interestingly, the cyclic cations do not follow the common trend among



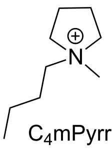
**a**: R = *n*-butyl, $R^1$ = Me, *n* = 1, X = I
(**4a**, **5a** cation: $C_4mPphol^+$, butylmethylphospholanium)
**b**: R = *n*-butyl, $R^1$ = Me, *n* = 2, X = I
(**4b**, **5b** cation: $C_4mPphin^+$, butylmethylphosphinanium)
**c**: R = phenyl, $R^1$ = *n*-butyl, *n* = 1, X = Br
(**4c**, **5c** cation: $C_4PhPphol^+$, butylphenylphospholanium)
**d**: R = phenyl, $R^1$ = *n*-butyl, *n* = 2, X = Br
(**4d**, **5d** cation: $C_4PhPphin^+$, butylphenylphosphinanium)

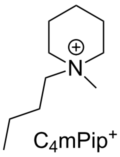
**Scheme 1:** Reaction scheme for the preparation of cyclic phosphonium ionic liquids.

**Table 1:** Physical characteristics of cyclic phosphonium $NTf_2$ ILs.[a]

| Cation[b] | Viscosity cP | Conductivity mS/cm | $D^+$ ($^1H$) $10^{-7}$ cm²/s | $D^-$ ($^{19}F$) $10^{-7}$ cm²/s | $T_g$ °C | $T_m$ °C | $T_d$ °C |
|---|---|---|---|---|---|---|---|
| **5a**: C4mPphol+ | 101 | 2.2 (23 °C) | 1.27 | 1.01 | −85 | 15 | 444 |
| C4mPyrr+ | 75 [22] | 2.8 [22] | 2.2 [23] (30 °C) | 1.8 [23] (30 °C) | −89 | −8 [24] | 431 [22] |
| **5b**: C4mPphin+ | 171 | 0.92 | 0.65 | 0.68 | −78 | 6 | 386 |
| C4mPip+ | 183 [25] | 1.2 [25] | 0.98 [25] | 0.85 [25] | −77 [26] | −25[c] | 400 [25] |
| **5c**: C4PhPphol+ | 223 | – | – | – | −66 | 29 | 422 |
| **5d**: C4PhPphin+ | 48 (75 °C) | 13.3 (76 °C) | 1.56 (75 °C) | 2.47 (75 °C) | −48 | 54 | 387 |

[a] All values are for measurements at 25 °C except where noted. Viscosities are calculated from VFT fits. All glass-transition temperatures ($T_g$) and melting points ($T_m$) are onset temperatures. Water contents of samples ranged from 76–155 ppm. Uncertainties of viscosities, conductivities, diffusion coefficients ($D^+$ and $D^-$) are 1 cP, 7%, 5% and 1 °C respectively. $T_d$ is the thermal decomposition temperature. [b] Abbreviations and structures of ammonium congeners: $NTf_2$ - bis(trifluoromethylsulfonyl)amide anion; $C_4mPphol$ - butylmethylphospholanium; $C_4mPyrr$ - butylmethylpyrrolidinium; $C_4mPphin$ - butylmethylphosphinanium; $C_4mPip$ - butylmethylpiperidinium; $C_4PhPphol$ - butylphenylphospholanium; $C_4PhPphin$ - butylphenylphosphinanium.


$C_4mPyrr^+$


$C_4mPip^+$

[c] Value subject to dispute, either −25 °C [25] or just below 0 °C [27].

the quaternary tetra-*n*-alkylated cations wherein the room temperature viscosities of the phosphonium salts are approximately one-half of those of their ammonium congeners [7-11]. This difference draws attention to the particular role that the cyclic alkyl functionality plays in IL fluid dynamics in contrast to two linear chains. This topic merits further exploration via molecular dynamics simulations [28] and physical studies such as NMR diffusion measurements, nuclear Overhauser effect spectroscopies, and quasi-elastic neutron scattering. As seen for instance for the cyclic ammonium salts, the viscosities of the cyclic phosphonium salts increase with increasing ring size for two of the compounds synthesized. As suggested by the viscosity results, the conductivities of the phosphonium ILs are lower than those for their ammonium congeners, and that for both families they decrease with increasing ring size. The conductivity of $C_4mPphol$ $NTf_2$ (2.2 mS/cm) is slightly smaller than that of the $C_4mPyrr$ (2.8 mS/cm) although not as much as expected from the viscosity difference. The self-diffusion coefficients of the anion ($D^-$) and the cation ($D^+$) are somewhat lower for the phosphonium salts than the ammonium ones. Interestingly, despite its slightly lower viscosity, $C_4mPphin$ IL has lower diffusion coefficients than $C_4mPip$ $NTf_2$.

For the P-versus-N pairs where direct comparisons can be made, the glass-transition temperatures $T_g$ are very close, allowing for experimental differences. In contradiction to the trend for linear tetraalkyl cations, the melting temperatures ($T_m$) for the cyclic phosphonium salts are higher than those of their cyclic ammonium congeners. $C_4mPphol$ $NTf_2$ melts 23 °C higher than does $C_4mPyrr$ $NTf_2$, and $C_4mPphin$ $NTf_2$ melts 31 °C higher than does $C_4mPip$ $NTf_2$. Henderson and Passerini [29] showed that the often-cited $T_m$ of −18 °C for $C_4mPyrr$

$NTf_2$ was due to a metastable crystalline form by using an annealing process. The DSC scan of un-annealed $C_4$mPphol $NTf_2$ shows all the thermal features exhibited by un-annealed $C_4$mPyrr $NTf_2$ (glass transition, cold crystallization, solid–solid transition, and melting). When the recommended annealing method [24] was applied to $C_4$mPphol $NTf_2$ the first three thermal features listed just above were eliminated, but the position of the melting point did not change. The apparent thermal decomposition temperature ($T_d$) of the cyclic phosphonium $NTf_2$ ILs are not particularly different from those of the cyclic ammonium $NTf_2$ ILs, which is similar to the situation of linear alkyl quaternary cation ILs [11]. In some instances where the anion is nucleophilic, such as with dicyanamide [12], or the leaving group is resonance-stabilized, such as a benzyl radical [10], the phosphonium cations have greater thermal stability than the ammonium ones. One trend observed for both cation types is that the ILs with five-membered rings have greater thermal stability than those with six-membered rings. Further work will be required to determine if the observed TGA behaviors are due to actual decomposition or to volatility of the ILs [30].

While developing our synthetic approach to the aliphatic $C_4mPphol^+$ and $C_4mPphin^+$ cations, which requires the use of highly air-sensitive reagents and intermediates as described above, we refined our techniques using less reactive phenylphosphines. The resulting butylphenylphospholanium ($C_4$PhPphol $NTf_2$) and butylphenylphosphinanium ($C_4$PhPphin $NTf_2$) ionic liquids are examples of a rare class of ILs with direct attachment of the aryl group to the cationic center. We were unable to find any information on ILs containing analogous nitrogen-centered cations for comparison, although ILs with aryl groups attached directly to the nitrogen atoms of imidazolium cations are reported [31]. The melting points of the phenylphosphonium ILs are both above room temperature (see Table 1), however $C_4$PhPphol $NTf_2$ is persistently metastable as a supercooled liquid under ambient conditions. The most significant effects observed for the replacement of a methyl group with a phenyl ring in this family of cations are the substantial increases of 19 °C and 30 °C in the glass-transition temperatures for the 5- and 6-membered ring cations respectively. Similar effects on $T_g$ have been reported for other classes of ILs bearing benzyl groups [32]. This family of cations may have the useful attributes for reducing radiation-induced damage of the IL owing to the stabilization of excess charges on the phenyl groups.

## Conclusion

We have successfully prepared a series of new cyclic phosphonium ILs that are representatives of a wide class of potentially useful ILs. These exemplars are slightly less conductive and have slightly smaller self-diffusion coefficients than their cyclic ammonium congeners. Their viscosities are also lower than their ammonium congeners. In other instances, such as the peculiarities in melting point and viscosity trends of the C-2-methylated imidazolium salts [33], ether-substituted ILs [34], and bis(oxalato)borate salts [35], detailed investigation into those intriguing behaviors led to deeper insights into the dynamical workings of ILs that have had important impacts on the field. For this reason we will continue to explore cyclic phosphonium ILs through synthesis of a wider variety of structural types and substituents, variation of anions, and more extensive characterization of their physical, structural, and dynamical properties. In particular, this family of ILs, by comparison with the more familiar cyclic ammonium ILs, should reveal the dynamical effects of cyclic vs linear alkyl chains on the physical properties of ionic liquids.

## Supporting Information

Detailed synthesis and characterization procedures are provided for all compounds synthesized and characterized. NMR spectra are provided for all compounds for which NMR data is reported. DSC thermograms are provided for the bis(trifluoromethylsulfonyl)amide ionic liquids (**5a–5d**).

### Supporting Information File 1

NMR Spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-22-S1.pdf]

### Supporting Information File 2

DSC Thermograms.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-22-S2.pdf]

### Supporting Information File 3

Experimental.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-22-S3.pdf]

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# Phosphinate-containing heterocycles: A mini-review

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Review

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## Abstract

This review provides an overview of recent efforts towards the synthesis of phosphinate heterocycles $R^1R^2P(O)(OR)$. Our laboratory and others' have been involved in this field and as a result new P–C, P–N, and P–O containing heterocyclic motifs are now available through a variety of methods. While developing rapidly, this area is still in its infancy so that biological testing of the compounds has not yet been conducted and applications are rare. The growing availability of synthetic methods will undoubtedly change this situation in the near future.

## Introduction

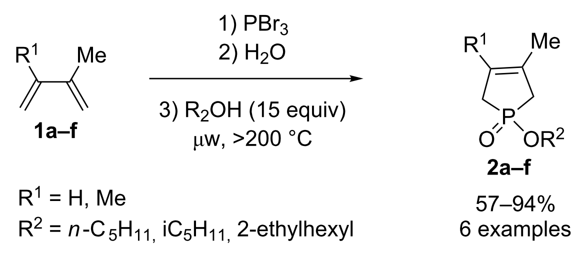
The preparation of P-heterocycles has been the subject of many studies over the years, and the field has been extensively reviewed [1-8]. Typically, accessing *P*-heterocycles involves multistep sequences with low overall yields [1-8]. In the past 20 years, significant effort has been devoted to synthetic and reactivity studies of a particular family of organophosphorus compounds: the phosphinates $R^1R^2P(O)(OR)$ [9]. Because the phosphinic acid moiety P(O)OH can mimic carboxylic acids, its incorporation into heterocycles may offer new opportunities for the discovery of biologically active analogs. However, little or no biological data is available at this time. Selected recent synthetic work by us and others is presented below.

## Review

### Phospholes

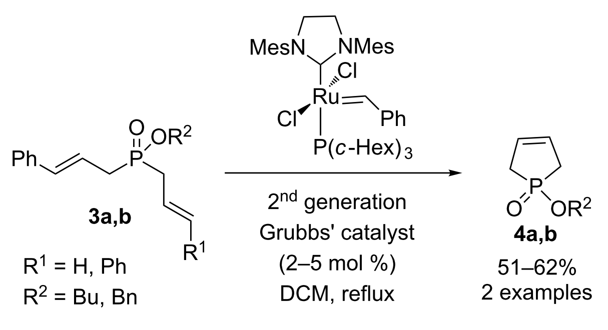
Several compounds have been prepared in this series. Keglevich and coworkers realized the synthesis of phosphole derivatives **2a–f** based on the McCormack reaction [10] followed by microwave-assisted esterification of the phosphinic acid using different alcohols in large excess (Scheme 1) [11,12].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

Montchamp and coworkers have synthesized phospholes **4a,b** by ring closing metathesis using 2 or 5 mol % of 2nd generation Grubbs' catalyst (Scheme 2) [13,14]. Two compounds **4a,b**



**Scheme 1:** McCormack synthesis.

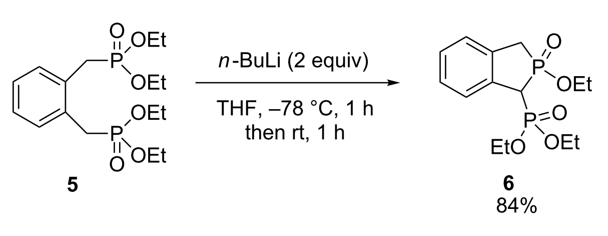
were prepared in 51% and 62% yields. The same approach was reported earlier by Mioskowski and coworkers [15,16] except the starting phosphinates **3a,b** were prepared less efficiently by the sila-Arbuzov reaction of bis(trimethylsiloxy)phosphine $(Me_3SiO)_2PH$.



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

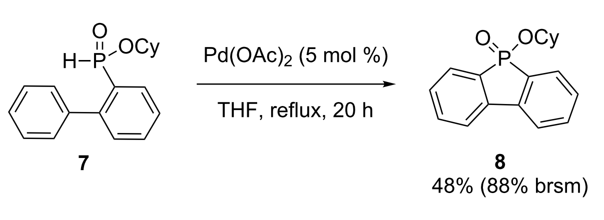
## Phosphindoles

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



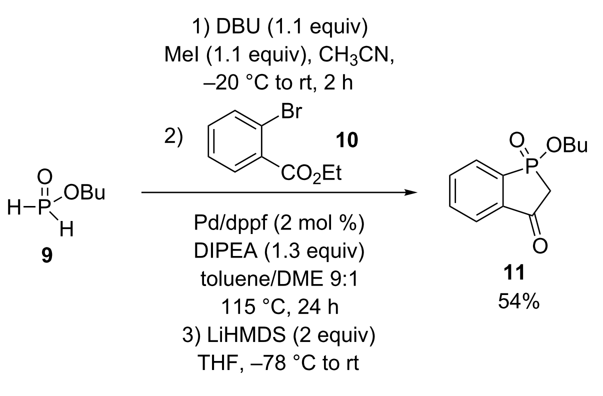
**Scheme 3:** Phospha-Dieckmann condensation.

Cyclohexyl 2-(biphenyl)-*H*-phosphinate **7** was cyclized using 2 mol % of $Pd(OAc)_2$ in refluxing THF to produce another phosphindole **8** in 48% yield (Scheme 4) [18].



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

A phosphindol-3-one **11** was prepared in 54% yield from butylphosphinate **9** by first methylation using DBU and iodomethane followed by a cross-coupling with ethyl 2-bromobenzoate (**10**) and then a Dieckmann-like condensation using LiHMDS (Scheme 5) [19].



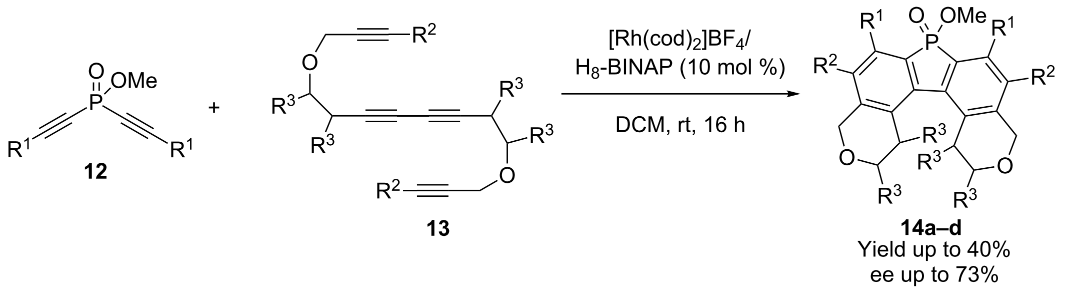
**Scheme 5:** Tandem cross-coupling/Dieckmann condensation.

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

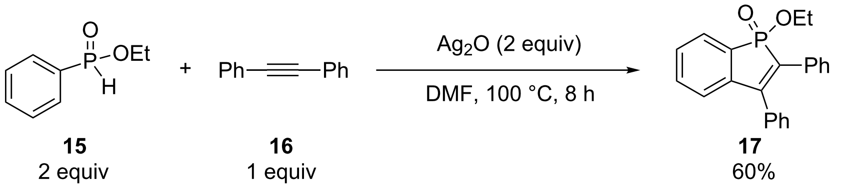
Chen and Duan have synthesized one phosphinoline **17** in 60% yield by the alkyne–arene annulation of ethyl phenyl-*H*-phosphinate (**15**) using 2 equivalents of $Ag_2O$ (Scheme 7) [21]. Miura et al. simultaneously reported the same reaction but with 4 equivalents of AgOAc instead, delivering the heterocycle **17** in 53% yield (Scheme 8) [22]. Both reactions used 4 equivalents of Ag(I) as well as an excess of *H*-phosphinate.

## 1,3-Oxaphospholes

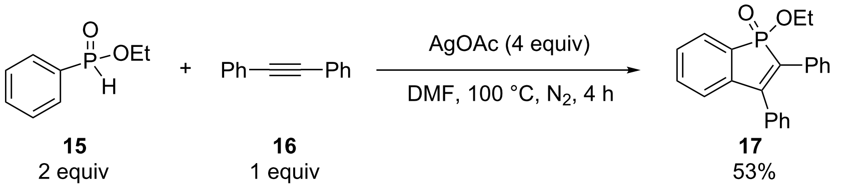
Cristau and coworkers have achieved the direct synthesis of 1,3-oxaphospholes **20a–f** (Scheme 9) by reacting chloroalkylphosphinic or phosphonic chlorides **18** with malonic diester **19** in the



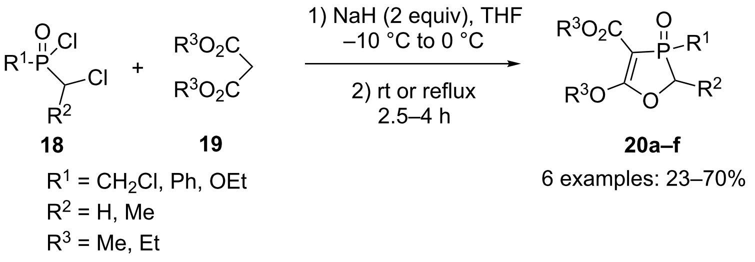
**Scheme 6:** Rhodium-catalyzed double [2 + 2 + 2] cycloaddition.



**Scheme 7:** Silver oxide-mediated alkyne–arene annulation.



**Scheme 8:** Silver acetate-mediated alkyne–arene annulation.



**Scheme 9:** Cyclization through phosphinylation/alkylation of malonate anion.

presence of two equivalents of sodium hydride [23,24]. 1,3-Oxaphospholes **20a–f** were obtained in yields up to 70%.

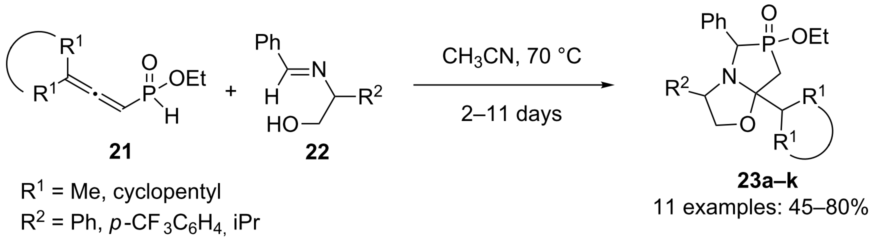
## 1-Aza-3-phospha-6-oxabicyclo[3.3.0]octanes

The synthesis of chiral bicyclic phosphinates **23a–k** by domino hydrophosphinylation/Michael/Michael reaction was realized by Fourgeaud et al. (Scheme 10) [25].

Several 1-oxa-3-aza-6-phosphabicyclo[3.3.0]octanes derivatives **23a–k** were obtained in yields around 70% by reacting allenes **21** with imines **22** derived from (*R*)- or (*S*)-phenylglycinol, (*S*)-2-aminobutanol or ethanolamine. Diastereoisomeric ratios were generally close to 50:50. A model for this reaction's diastereoselectivity was proposed.

## Cyclo-PALA

Montchamp and coworkers have achieved the synthesis of 5- and 6-membered rings "cyclo-PALA" analogs which are 1,3-azaphospholidine and 1,4-azaphosphorine derivatives **26**, **29** [26].

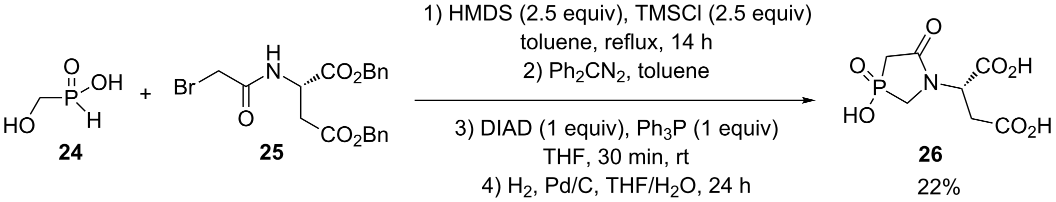


**Scheme 10:** Tandem hydrophosphinylation/Michael/Michael reaction of allenyl-*H*-phosphinates.

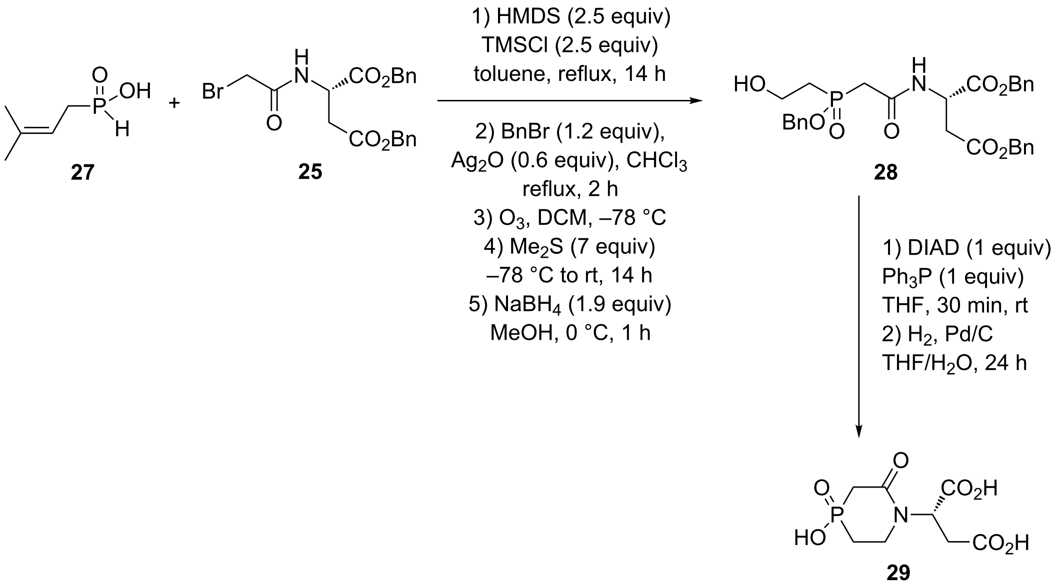
For the 5-membered ring **26**, hydroxymethyl-*H*-phosphinic acid (**24**) underwent a sila-Arbuzov reaction with the bromide **25**, the crude mixture was esterified with diphenyldiazomethane, cyclized using Mitsunobu conditions and then hydrogenolyzed to produce the five-membered amide **26** in 22% overall yield (Scheme 11).

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

In this particular study phosphinates **26** and **29** were tested as inhibitors of aspartate transcarbamoylase (ATCase).



**Scheme 11:** 5-Membered “cyclo-PALA” via intramolecular Mitsunobu reaction.

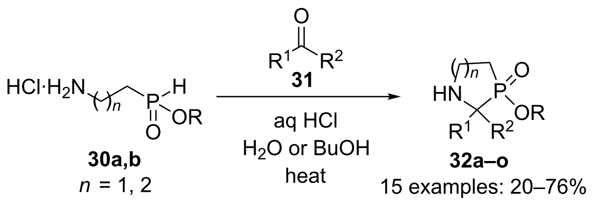


**Scheme 12:** 6-Membered “cyclo-PALA” via intramolecular Mitsunobu reaction.

5-Membered **26** was completely inactive, whereas 6-membered **29** showed modest activity ($K_i$ = 1 µM, 63 times less active than phosphonic acid *N*-phosphonacetyl-L-aspartate PALA, $K_i$ = 16 nM).

## 1,3-Azaphosphorines and 1,3-azaphospholidines

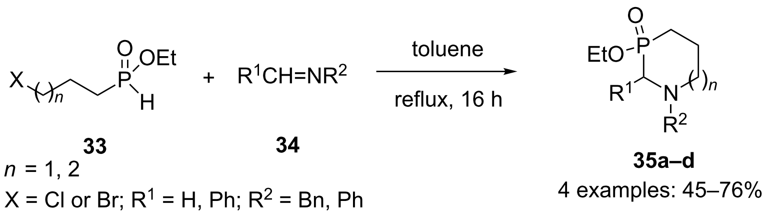
Several 1,3-azaphosphorines and 1,3-azaphospholidines were synthesized by Montchamp and coworkers. The reaction of 2-aminoethyl-*H*-phosphinate **30a** (*n* = 1) with carbonyl compounds **31** in refluxing butanol or concentrated hydrochloric acid took place smoothly to generate seven 1,3-azaphospholidines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



**Scheme 13:** Intramolecular Kabachnik–Fields reaction.

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

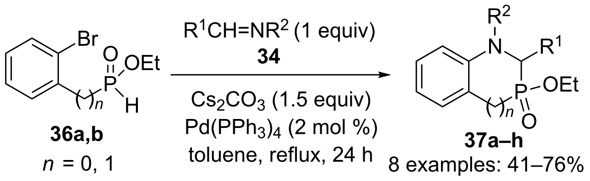
Montchamp and coworkers also prepared two other examples of 1,3-azaphosphorines **35a,b** (*n* = 1) in yields up to 61% by reacting ethyl-3-chloropropyl-*H*-phosphinate **33** with imines **34** in toluene at reflux (Scheme 14) [29].



**Scheme 14:** Tandem Kabachnik–Fields/alkylation reaction.

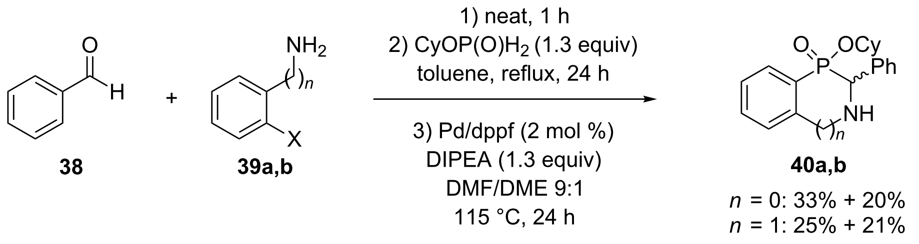
## 1,3-Azaphosphindoles and 1,3-benzazaphosphorines

Several compounds in this series were synthesized by Montchamp and coworkers using two different approaches. The first one is the reaction between an imine **34** and 2-bromophenyl-substituted *H*-phosphinate esters **36** in the presence of $Cs_2CO_3$, and catalytic $Pd(PPh_3)_4$ in refluxing toluene to generate the corresponding cyclized products **37a–h** in yields up to 76% (Scheme 15) [29].



**Scheme 15:** Tandem Kabacknik–Fields/C–N cross-coupling reaction.

The second way is the formation of the imine first by reacting an amine **39a,b** with an aldehyde **38**, then the phosphinate is introduced and the mixture stirred for 24 h at reflux to generate the corresponding *H*-phosphinate esters. Addition of DIPEA and catalytic Pd/dppf in a mixture DMF/DME to the intermediates generated the corresponding cyclized derivatives **40a,b** in yields up to 53% (Scheme 16) [18].



**Scheme 16:** Tandem Kabacknik–Fields/C-P cross-coupling reaction.

For these compounds, the authors were able to separate the different diastereoisomers generated during the reaction by simple column chromatography on silica gel.

## 1,4-Azaphosphorines

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

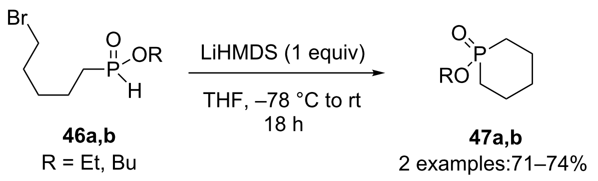
In this example, the amino acid **41** was first cyclized using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (**42**) at pH 5.6 followed by protection of the carboxylic acid and phosphinic acid moieties by diphenylmethyl group using a slight excess of diphenyldiazomethane. The two diastereoisomers obtained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

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

To prepare the required phosphinate **45** a double allylation of $H_3PO_2$ was performed using 2 equivalents of cinnamyl alcohol **44** in the presence of 2 mol % of Pd/Xanthpos followed by an esterification using benzyl bromide. Ozonolysis, and reductive amination using excess benzylamine in the presence of sodium cyanoborohydride completed the synthesis.

## Phosphorines

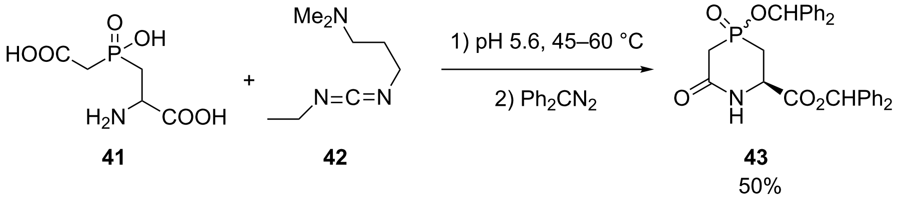
Two phosphorines **47a,b** were obtained by Montchamp and coworkers via the cyclization of 5-bromopentyl-*H*-phosphinate esters **46a,b** in the presence of LiHMDS in 71% and 74% yields for the butyl and ethyl esters respectively (Scheme 19) [28,31].



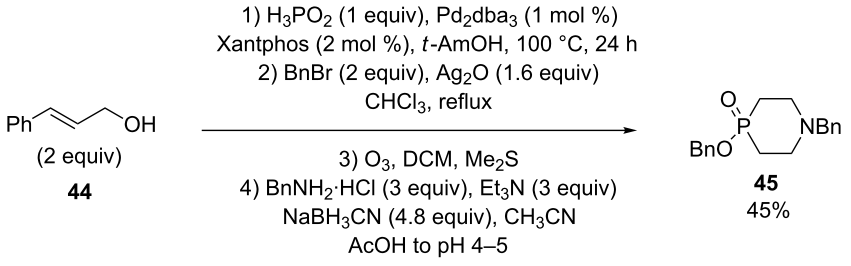
**Scheme 19:** *H*-Phosphinate alkylation.

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

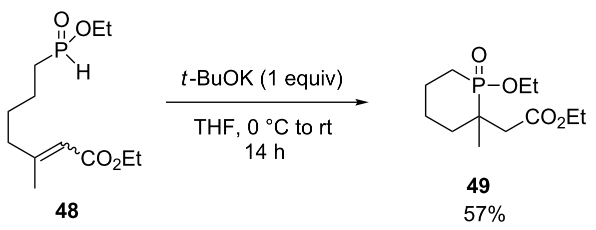
A phosphorino[3’,4’:4,5]furo[2,3-*d*]-1,3-dioxole **51** was synthesized in 36% yield by Tattersall and coworkers by realizing a double Arbuzov-type reaction between bis(trimethylsiloxy)phosphine and the dibromide **50** followed by the esterification of the phosphinic acid using diazomethane (Scheme 21)



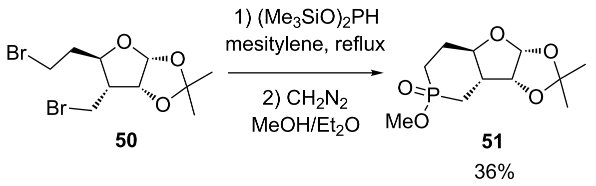
**Scheme 17:** Heterocyclization via amide formation.



**Scheme 18:** Cyclization via reductive amination.



**Scheme 20:** Cyclization through intramolecular Michael addition.



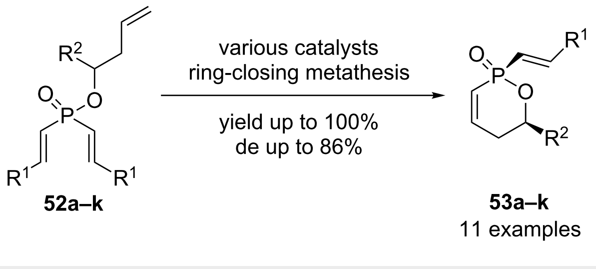
**Scheme 21:** Double Arbuzov reaction of bis(trimethylsiloxy)phosphine.

[32]. The heterocyclization step followed methodology initially introduced by Frost et al [33].

Compound **51** was subsequently converted into the corresponding analog of cyclic AMP, but no biological activity was reported.

## 1,2-Oxaphosphorines

Gouverneur and coworkers have realized the synthesis of several 1,2-oxaphosphorine derivatives **53a–k** using diastereoselective ring closing metathesis with 2 to 4 mol % of various catalysts (Scheme 22) [34].

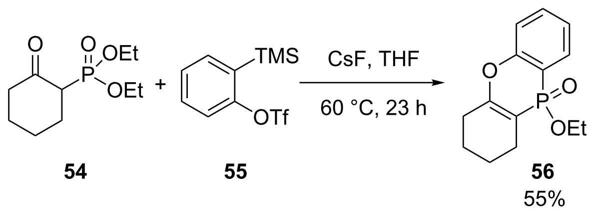


**Scheme 22:** Diastereoselective ring-closing metathesis.

During this work, they obtained 11 different compounds in yields up to 100% and diastereomeric excesses up to 86%. The starting phosphinates **52a–k** were prepared using classical chemistry involving Grignard addition to $EtOP(O)Cl_2$.

## Phenoxaphosphine

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



**Scheme 23:** 2-Ketophosphonate/benzene annulation.

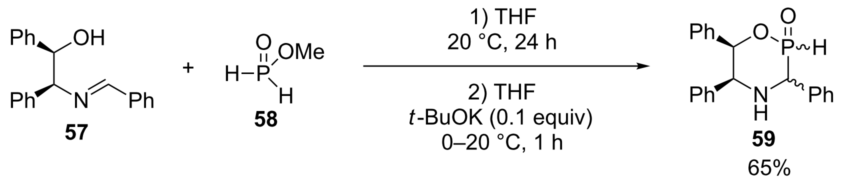
## 1,4,2-Oxazaphosphinane

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

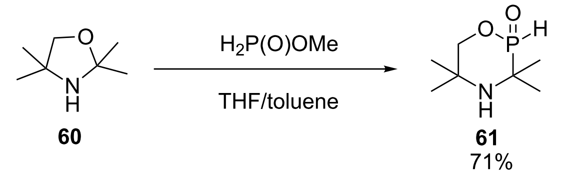
This versatile intermediate **59** was reacted with aldehydes, imines, olefins and aryl bromides or aryl iodides to generate a wide range of phosphinates.

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

This oxazaphosphinane **61** was synthesized in two steps at room temperature, first, by a nucleophilic attack of methyl hypophosphite on oxazolidine **60** followed by an intramolecular cyclization, this time without base catalyzed transesterification. The authors explained this difference of reactivity by the



**Scheme 24:** Tandem Kabachnik–Fields/transesterification reaction.



**Scheme 25:** Tandem Kabachnik–Fields/transesterification reaction with oxazolidine.

Thorpe–Ingold effect [38]. Indeed, the presence of four methyl groups allows the hydroxy function to be spatially closer to the reactive phosphinate, facilitating the intramolecular cyclization of this product.

## Conclusion

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

## Acknowledgements

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## License and Terms

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# Synthesis of fluorescent (benzyloxycarbonylamino)(aryl)methylphosphonates

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Full Research Paper

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## Abstract

The synthesis of a library of structurally variable aromatic esters of (benzyloxycarbonylamino)(aryl)methylphosphonic acids is described by means of the Oleksyszyn reaction. The library was enlarged by the application of a Suzuki–Miayra approach and by preparation of mixed esters.

## Introduction

Screening of the activity of large libraries of fluorogenic substrates of chosen enzymes is an emerging approach to determine their substrate preferences and thus to provide a set of data useful for the preparation of their selective inhibitors [1-5]. Such fluorogenic probes have been also used for profiling the proteolytic secretomes with the obtained profiles being useful as diagnostic tools [6-8]. Also conjugates of drugs with fluorescent probes have been used as so called theranostics (combination of therapeutics and diagnostics) [9,10].

Diaryl esters of α-aminoalkanephosphonic acids and their short peptides are a class of well-established inhibitors of serine proteases [11,12]. Their mechanism of action involves phosphonylation of the active-site of these enzymes with simultaneous release of the appropriate phenol [13,14]. Therefore, the synthesis of such inhibitors carrying fluorescent probes in their side chains or in the ester phosphonate moieties might find an application in constructing fluorescent probes for studying structural requirements of enzymes having serine in their active sites (proteinases and phosphatases) or to study their elevated level in various tissues. Thus, their libraries may serve for the construction of diagnostic tools. A similar approach has been recently patented as a mean to differentiate lipases and esterases [15].

The objective of this paper is to evaluate the utility of a popular three component reaction of triaryl phosphites with aldehydes and benzyl carbamates (the so called Oleksyszyn reaction) for the synthesis of fluorescent (benzyloxycarbonylamino)-(aryl)methylphosphonates.

## Results and Discussion

### Synthesis of diaryl (benzyloxycarbonylamino)(phenyl)methylphosphonates

Diaryl esters of Z-protected aminobenzylphosphonic acid were obtained by using the classical three-component amidoalkylation procedure described by Oleksyszyn et al. (Scheme 1) [14].

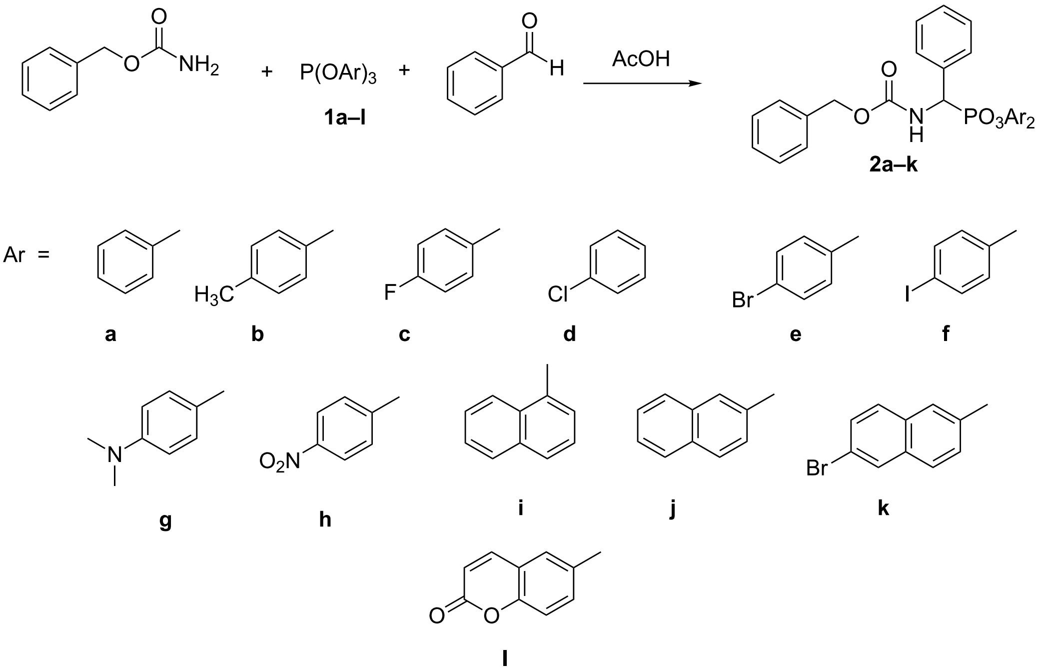
First, appropriate triaryl phosphites have to be synthesized. They were obtained by refluxing stoichiometric quantities of phosphorus trichloride with the appropriate phenol (molar ratio 1:3) in acetonitrile [16,17]. The desired phosphites deposited from acetonitrile as solids or oils and did not require further purification. Corresponding reactions carried out in different solvents (toluene, benzene or diethyl ether in the presence of butyllithium in hexane) or with phosphorus tribromides gave far less satisfactory results because the obtained crude products were difficult to purify.

The obtained phosphites were reacted with benzaldehyde and benzyl carbamate, according to literature [18-20], providing the desired diaryl (benzyloxycarbonylamino)(phenyl)methylphosphonates (Scheme 1) with good yields (59–86%). Unfortunately, the reaction of phosphite obtained from 7-hydroxycoumarine failed, since it appeared to be unstable upon harsh reaction conditions and underwent decomposition as seen by $^{31}$P NMR. Therefore, we have decided to apply a more delicate procedure described recently by Goldeman and Soroka [21]. According to this procedure the reaction was carried out in dry chloroform in the presence of catalytic amounts of tetrafluoroboric acid. Unfortunately, tri(7-hydroxycoumaric) phosphite also underwent decomposition under these conditions.

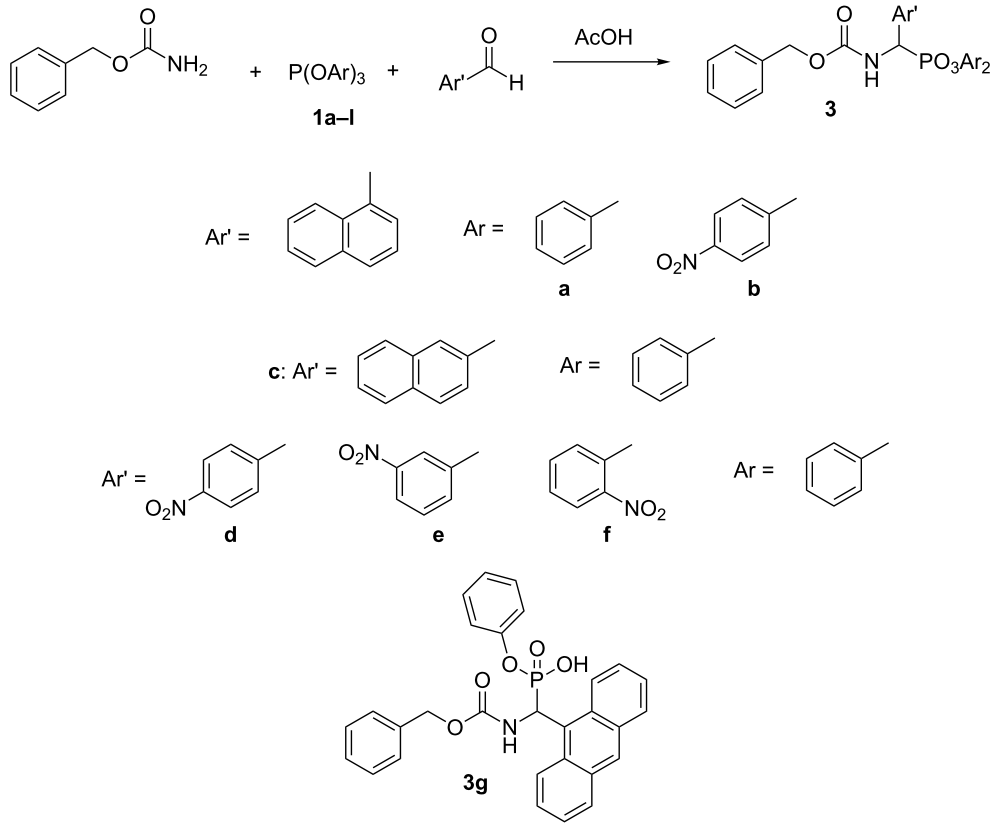
The diaryl esters **2** exhibit restricted rotation around the C–N bound of their carbamate group. As a consequence, they exist in solution in *cis*- and *trans*-forms, with the equilibrium strongly shifted towards the formation of *trans*-isomers [22].

### Synthesis of diaryl (benzyloxycarbonylamino)(aryl)methylphosphonates

By applying the same procedure we have synthesized a small library of diaryl esters of aromatic Z-aminophosphonates (Scheme 2). They were obtained in satisfactory yields



**Scheme 1:** Diaryl (benzyloxycarbonylamino)(phenyl)methylphosphonates.



**Scheme 2:** Diaryl (benzyloxycarbonylamino)(aryl)methylphosphonates.

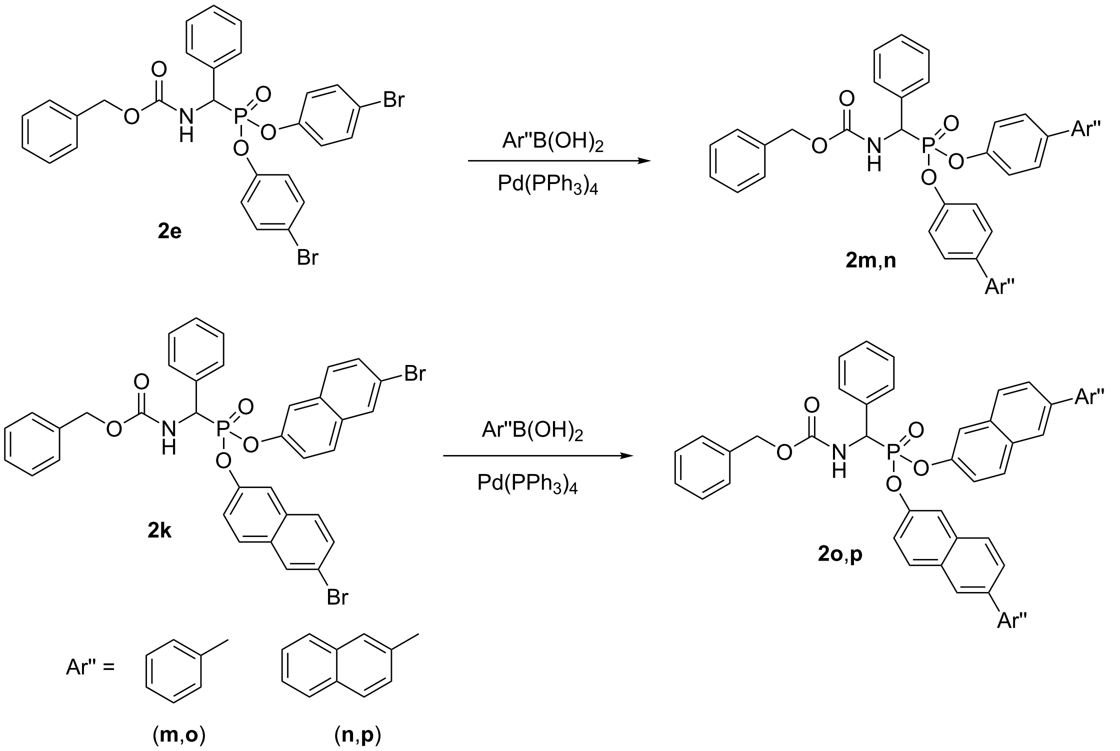
(55–84%). When using 5-anthracenylaldehyde a complex mixture of products was obtained and the product was isolated by column chromatography in a low yield of 1% as the monophenyl ester.

This library was enlarged by application of the Suzuki–Miyaura approach with compounds **2e** and **2k** being chosen as substrates (Scheme 3) [23,24]. Despite the enormous number of data considering application of this reaction, according to the best of our knowledge, there is no report on its application to synthesize phosphorus esters. After dissolving the substrates the catalyst was added to the reaction mixture and it was carried under reflux for 6 h. Optimization of the reaction conditions revealed that a mixture of dioxane and water (out of: dioxane, acetonitrile, chloroform and acetonitrile/water mixture) appeared to be the best solvent with 5% of $Pd(PPh_3)_4$ serving as optimal catalyst.

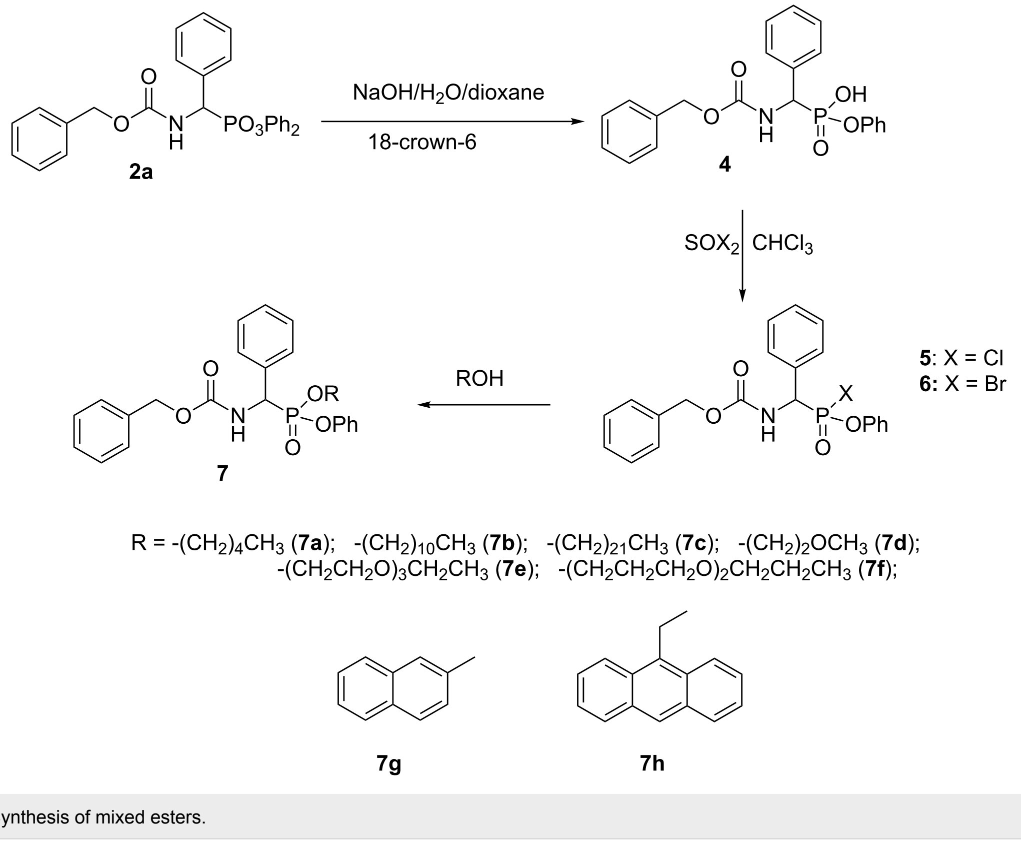
## Synthesis of mixed esters of (benzyloxycarbonylamino)(aryl)methylphosphonates

Also a small library of mixed esters was obtained. Using the procedures worked out in our laboratory diphenyl (benzyloxycarbonylamino)(phenyl)methylphosphonate (**2a**) was converted into the monoester by hydrolysis with aqueous potassium hydroxide in the presence of 18-crown-6 [25,26]. The obtained monoester **4** was transformed into chloride **5** or bromide **6**, which were used in the next step of the synthesis without purification (Scheme 4). Upon halogen introduction a new chirality center is formed at the phosphorus atom and the products **5** and **6** were obtained as unequimolar mixtures of diastereoisomers (45:55 and 42:58 respectively). Upon reaction with an excess of aliphatic alcohol mixed esters of reversed configuration were obtained, as indicated by the reversed order of the $^{31}P$ NMR peaks. This is in agreement with the mechanism of this reaction, which proceeds with inversion of the configuration at the phosphorus atom. Upon purification of the obtained compounds **7**, either by crystallization or column chromatography, a significant enrichment in one of the diastereomers had been observed. For example, compound **7b** obtained as a 55:45 molar mixture of stereoisomers after purification by means of chromatography was obtained as 85:15 molar mixture.

The approach to obtain mixed esters bearing two aromatic moieties is far more difficult as shown by reaction of chloride **5** with 2-naphthol providing compound **7g**. This reaction was carried out in chloroform in the presence of triethylamine.



**Scheme 3:** Diaryl (benzyloxycarbonylamino)(aryl)methylphosphonates obtained by Miyaura–Suzuki approach.



R = $-(CH_2)_4CH_3$ (**7a**); $-(CH_2)_{10}CH_3$ (**7b**); $-(CH_2)_{21}CH_3$ (**7c**); $-(CH_2)_2OCH_3$ (**7d**);
$-(CH_2CH_2O)_3CH_2CH_3$ (**7e**); $-(CH_2CH_2CH_2O)_2CH_2CH_2CH_3$ (**7f**);

**Scheme 4:** Synthesis of mixed esters.

## Fluorescence

Fluorescence of the representative examples of the obtained compounds was measured upon irradiation of two wavelengths of 254 and 366 nm. Compounds **2n** and **3g** exhibited strong fluorescence under both conditions. The remaining phosphonates either show a weak (**2h**, **3b**, **3d** and **3e**) fluorescence when irradiated with 254 nm or exhibited the lack of fluorescence (**2f**, **2k**, **2m**, **2o**, **3a**, **3c**, **4**, **7a**, **7d**, **7e**, **7g**).

## Supporting Information

### Supporting Information File 1

Experimental procedures and analytical data and NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-68-S1.pdf]

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## License and Terms

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# Group-assisted purification (GAP) chemistry for the synthesis of Velcade via asymmetric borylation of *N*-phosphinylimines

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Letter

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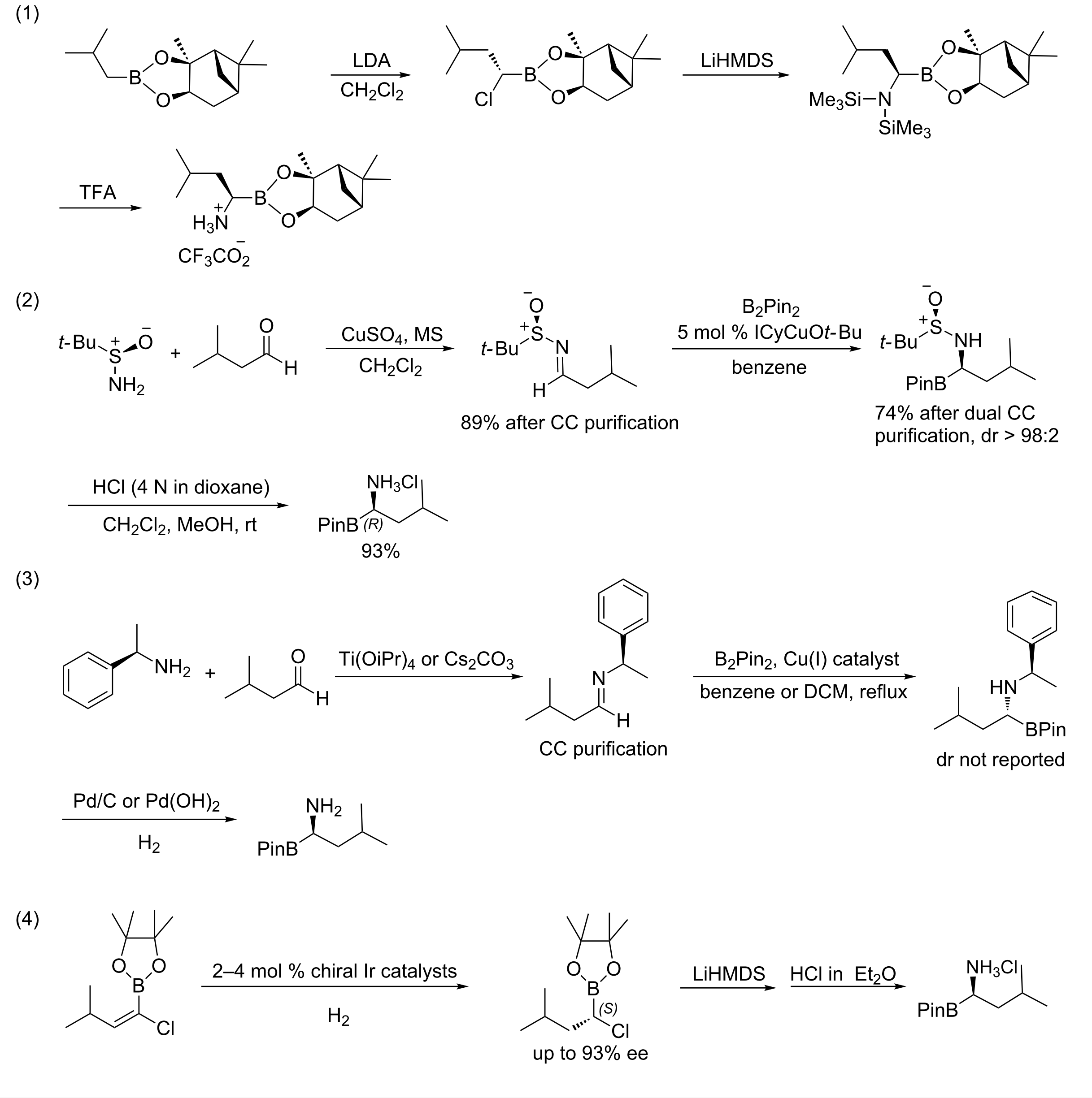
## Abstract

A new approach to the anticancer drug Velcade was developed by performing asymmetric borylation of an imine anchored with a chiral *N*-phosphinyl auxiliary. Throughout the 7-step synthesis, especially in the imine's synthesis and in the asymmetric borylation reactions, operations and work-up were conducted in simple and easy ways without any column chromatographic purification, which defines the GAP (group-assisted purification) chemistry concept. It was found that the optically pure isomer (dr > 99:1) can be readily obtained by washing the crude mixture of the asymmetric borylation reaction with hexane; the chiral *N*-phosphinyl auxiliary can be easily recovered after deprotection is finished. Several other *N*-phosphinylimines were also investigated for the asymmetric borylation reaction. The absolute configuration of the borylation product was confirmed by single crystal X-ray diffraction analysis.

## Introduction

The synthesis of chiral α-aminoboronic acids and their derivatives has attracted much attention in the organic and medicinal chemistry communities because of their importance for drug discovery and biological research [1-8]. In the past several years, asymmetric catalysis and auxiliary-directed asymmetric synthesis has been conducted for assembling adjacent chiral centers of boronic aicds [9-13], but only a few methods for generating chiral α-aminoboronic acids have been reported so far [14-20]. Among the resulting products from the above methods, (*R*)-(1-amino-3-methylbutyl)boronic acid served as the key mechanism-based pharmacophore in the anticancer drug Velcade, which was the first FDA approved proteasome inhibitor, and has been in clinical use for the treatment of multiple myeloma and mantle cell lymphoma [21]. This product is usually synthesized in three representative processes: (1) to use (1*S*,2*S*,3*R*,5*S*)-(+)-2,3-pinanediol as the chiral auxiliary for the addition reaction followed by chlorination and amination [14,15]; (2) to perform copper-catalyzed borylation of the imine anchored with chiral auxiliaries [16,17]; (3) to conduct asymmetric catalytic hydrogenation as the key step to control the chiral center of boronic aicd [18]. As anticipated, the above known syntheses required traditional purification methods using column chromatography or recrystallization (Scheme 1).

Recently, our group has established a concept called GAP (group-assisted purification) chemistry for greener synthesis [22-25]. This concept describes a process where special functional groups are attached onto reaction substrates, facilitating purification of crude products by avoiding traditional purification methods such as chromatography or recrystallization. The pure products, often pure stereoisomers, can be easily obtained by washing the crude products with common solvents or co-solvents [22-25]. Our GAP concept was attributed to the study of a series of new compounds containing achiral/chiral *N*-phosphonyl and chiral *N*-phosphinylimines, and the reactions of these compounds.



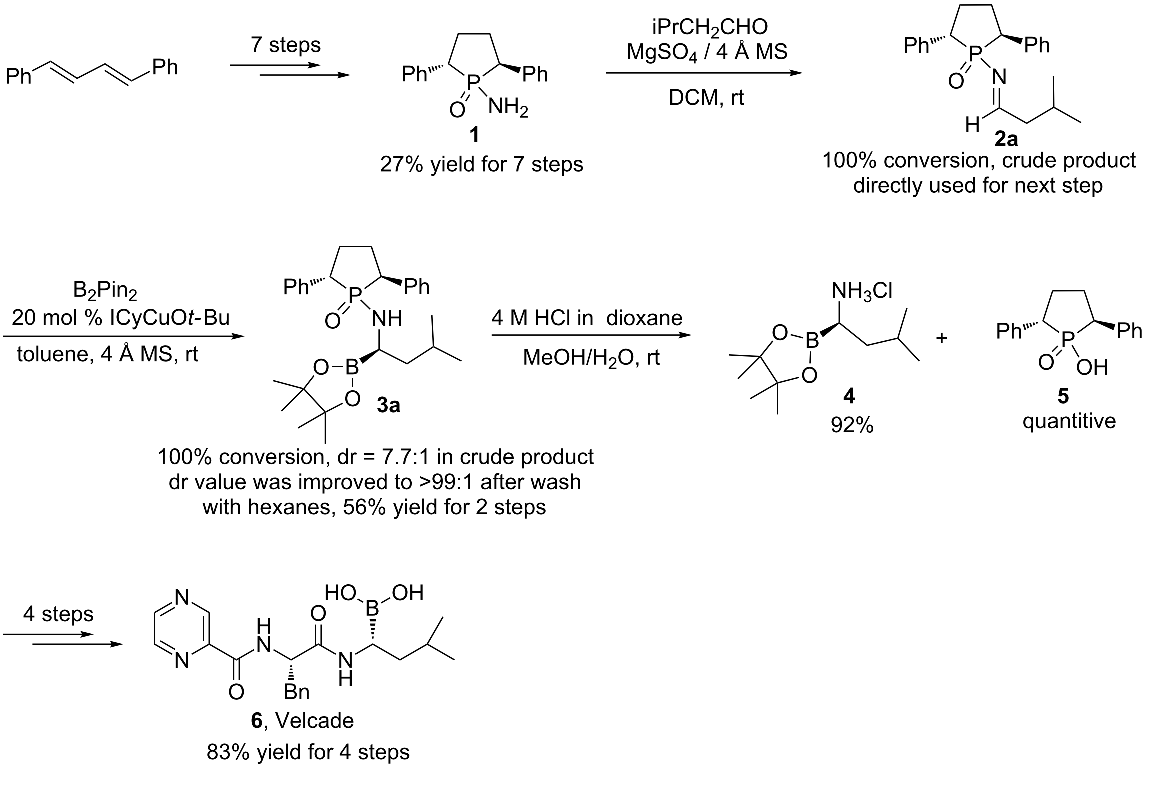
**Scheme 1:** Previous work for (*R*)-(1-amino-3-methylbutyl)boronic acid synthesis.

The requirements of GAP chemistry are shown by the fact that the functional groups of the reactants should generate products of adequate solubility. The GAP products should be soluble in some solvents such as THF and DCM for further reactions. However, they should have poor solubility in other solvents such as petroleum ether, hexanes, and their co-solvents with EtOAc. The GAP requirements should include adequate chemical reactivity of GAP compounds towards many reactants and species. If GAP groups are chiral, they should control asymmetric additions efficiently. Our GAP functional groups have also showed the flexibility for structural modifications in order to control the solubility of products and also to control the chemical tolerance towards various reactions under different conditions. Moreover, the GAP auxiliaries have been proven to be easily deprotected under several conditions for re-use.

Herein, we report the synthesis of the anticancer drug Velcade and its derivatives of chiral α-aminoboronic esters via GAP chemistry. Simple operations are needed during purification without the need for column chromatography; GAP washing can lead to a single isomeric product, which was deprotected with quantitative recovery of the phosphinic acid as shown in Scheme 2.

## Results and Discussion

We started our synthesis with (2*S*,5*S*)-1-amino-2,5-diphenylphospholane 1-oxide (**1**), which was synthesized according to the literature and our previous work in 7 steps from (1*E*,3*E*)-1,4-diphenylbuta-1,3-diene with an overall high yield (27% for 7 steps) [25,26]. With the optically pure amide **1** in hand, we screened the condensation conditions to generate the imine **2a**. Titanates, such as $Ti(OiPr)_4$ and $Ti(OEt)_4$, resulted in the complete conversion of the aliphatic aldehyde in two days, but the hemiaminal was obtained as the main product [27], which can slowly decompose to release the desired imine **2a**. Anhydrous $CuSO_4$, which was used as a mild condensation reagent by Ellman's group, was found to be not suitable for this condensation reaction. This lack of suitability can probably be attributed to the strong coordination tendency of the imine to a copper ionic center. $TiCl_4$ was proven to be an efficient reagent and lead to complete condensation within 2 hours to give 90% conversion to imine according to crude $^{31}P$ NMR. We also found that when the crude imine product was purified by column chromatography, isomerization of **2a** to enamine was observed; this observation became more obvious when the solvents used for chromatography contained a higher water content. Eventually, $MgSO_4$ or $CaSO_4$ was chosen as the dehy-



**Scheme 2:** Synthesis of (*R*)-**4** and Velcade.

dration reagent together with molecular sieves for imine formation. Under these conditions, complete conversion can be reached after 5 days to give the chiral *N*-phosphinylimine, which can be directly used for the following asymmetric borylation reaction without further purification.

$B_2Pin_2$ and ICyCuO*t*-Bu were utilized as the electrophilic addition reagent and catalyst, respectively, for the borylation reaction as previously reported [16,28]. Unlike the previous system, in which benzene was employed as the solvent, we used the much less toxic solvent toluene to successfully replace benzene. We achieved full conversion with 2 equiv of $B_2Pin_2$ in the presence of 20 mol % of ICyCuO*t*-Bu catalyst after 3 days to afford a dr value of 7.7:1 as revealed by crude $^{31}P$ NMR analysis. After simple work-up and washing with hexanes, the dr value was improved to a single isomer (Scheme 2) in 56% yield for two steps. The absolute configuration of product **3a** was unambiguously determined by X-ray analysis [29] to be in the (*S*,*S*,*R*)-configuration (Figure 1). As shown in Figure 1, H-bonds exist between the molecules, which would further help the formation of the solid.

To hydrolyze the resulting aminoboronic ester, the known method [16] was followed first by treating the ester with one equivalent of HCl in co-solvents of methanol and dioxane. A mixture of products was generated indicating a poor yield according to the crude $^{31}P$ and $^{1}H$ NMR analysis. Another co-solvent system consisting of $H_2O$ and MeOH (2:1) was examined. It was found that treatment of the aminoboronic ester with 1.5 equiv of HCl for 16 hours resulted in complete deprotection; work-up consisted of extraction with DCM followed by concentration to give product **4** as a white solid in 92% yield. Pure phosphinic acid **5** was recovered by simple filtration in quantitative yield. The final product, Velcade **6**, was synthesized according to the literature procedure [16] in 83% yield after 4 steps (Scheme 2). $^{1}H$ NMR and $^{13}C$ NMR spectra of the product were proven to be identical to the literature data.

To expand the substrate scope for the borylation reaction, several other new *N*-phosphinyl imines were synthesized for examination (Scheme 3). $Ti(OiPr)_4$ was chosen as the general condensation reagent. When aliphatic aldehydes were subjected to the condensation reaction, the main products were generated either as hemiaminals **7** or as a mixture of imine and hemiaminal after purification by column chromatography. The hemiaminals were slowly transferred to the corresponding *N*-phosphinylimine as revealed by NMR analysis. The aliphatic imines are found to be unstable even in the presence of a trace amount of moisture, and can easily isomerize to form the enamine. Therefore, we directly subjected the mixture of imine and hemiaminal to the borylation reaction. The borylation reactions went smoothly with full conversion after stirring the reaction mixture at room temperature for 3 days. Although moderate diastereoselectivities were obtained for all the three aliphatic *N*-phosphinylimines, the diastereopurities can be easily improved by GAP washing with hexane. For example, the original dr value for **3b** of 75:25 can be enhanced to a single isomer (dr > 99:1) in 26% yield over two steps (calculated from amide **1**). When aromatic aldehydes were employed, the yields of *N*-phosphinylimine formations were quantitative; the crude products were almost pure according to crude $^{31}P$ NMR spectra. After simple work-up to remove most of the titanate, the crude products were used directly for the next step without further purification. For the aromatic cases (entries 4 and 5, Table 1),

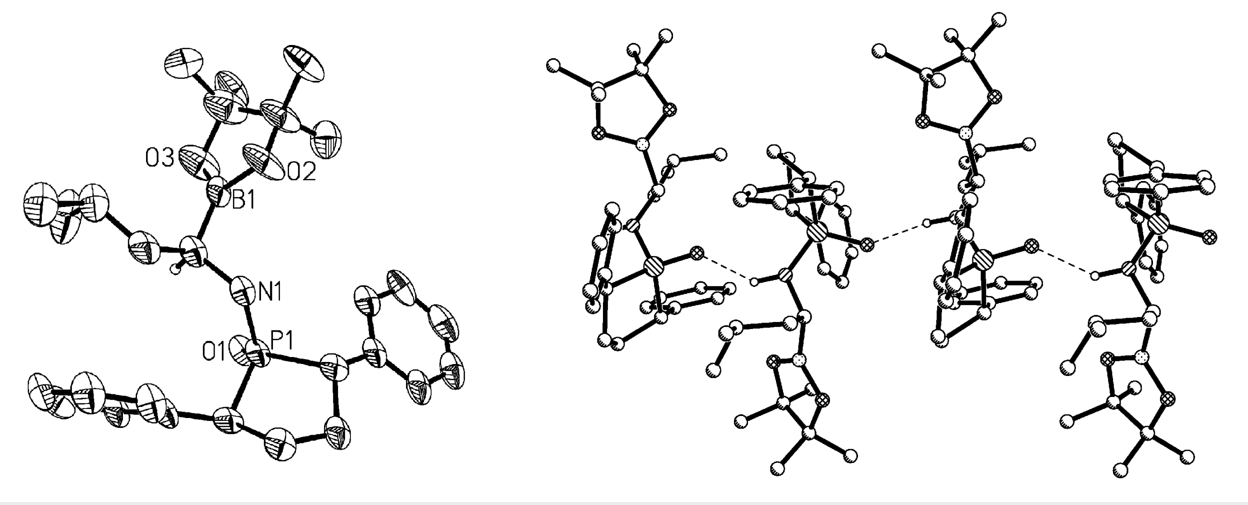
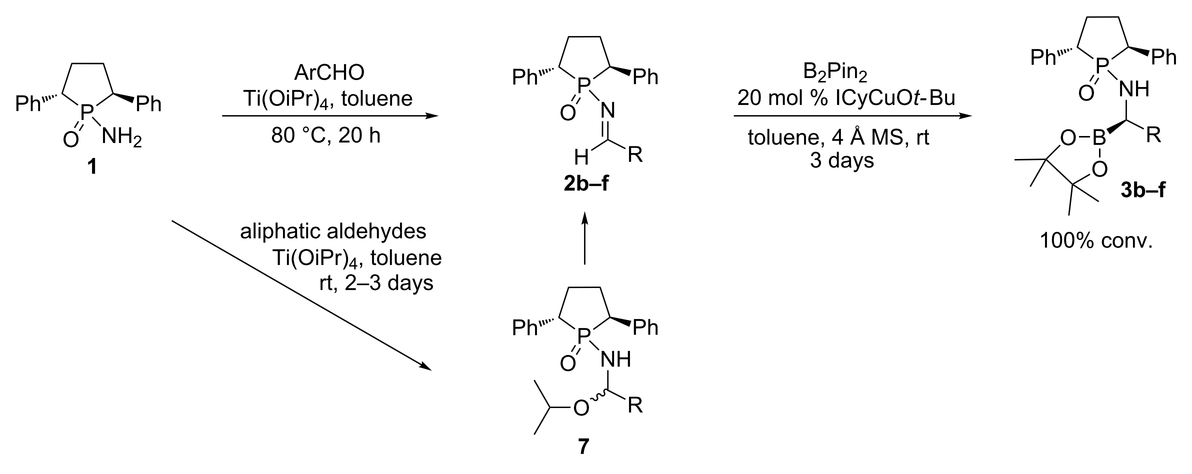


**Figure 1:** ORTEP diagram of (*S*,*S*,*R*)-**3a** (left, most of the hydrogen atoms were omitted except the one on the chiral center connected to boron) and the H-bonds between the molecules (right). Selected bond lengths [Å] and angle [°]: P1–O1 1.505, P1–N1 1.613, N1–H1, 0.957, B1–O2 1.368, the H-bond O1···H2 1.990; the angle of H bond N1–H1···O4 142.79.



**Scheme 3:** Synthesis of phosphinylimines and their borylation products.

**Table 1:** Results of borylation reactions[a].

| Entry | Imines | R | Products | dr (crude)[b] | dr (GAP)[b] | Yield[c] |
|---|---|---|---|---|---|---|
| 1 | **2b** | iPr | **3b** | 75:25 | >99:1 | 26% |
| 2 | **2c** | cyclohexyl | **3c** | 78:22 | 99:1 | 40% |
| 3 | **2d** | $PhCH_2CH_2$ | **3d** | 84:16 | 98:2 | 45% |
| 4 | **2e** | Ph | **3e** | 97:3 | – | 51% |
| 5 | **2f** | 4-MeOPh | **3f** | >99:1 | – | 44% |

[a]Reaction conditions: 0.74 mmol scale, [substrate] = 1.8 M, 2.0 equiv $B_2Pin_2$, 20 mol % ICyCuO*t*-Bu, toluene (4 mL), room temperature, 3 days. [b]Determined by $^{31}$P NMR analysis. [c]Calculated from the starting amide **1**, isolated yields with GAP washing (for **3e** and **3f**, GAP washing was not conducted).

excellent diastereoselectivities, dr = 97:3 and >99:1, respectively, were achieved according to the $^{31}$P NMR analysis of crude products. Pure products **3e** and **3f** were obtained via flash column chromatography since GAP washing led to some decomposition in these two cases.

## Conclusion

We have successfully demonstrated that *N*-phosphinylimines can undergo electrophilic borylation reactions, and that this reaction can be applied in the synthesis of the anticancer drug Velcade. The *N*-phosphinyl auxiliary displayed good to excellent asymmetric induction and great stability in the catalytic borylation and deprotection reactions. GAP washing is found to enhance the diastereopurity of the borylation products in most cases. The absolute configuration of the borylation product in Velcade's synthesis has been confirmed by single crystal X-ray diffraction analysis.

## Experimental

Standard operations for catalytic borylation and GAP: A 10 mL Schlenk tube was charged with crude imine **2**, $B_2Pin_2$ (375 mg, 2 equiv), catalyst ICyCuO*t*-Bu (54 mg, 20 mol %) and 4 Å molecular sieves (~500 mg). The mixture was protected with argon atmosphere, followed by toluene (4 mL) addition via syringe. The reaction mixture was stirred vigorously for 3 days, and the resulting slurry was filtered through Celite and washed with EtOAc 5 times. The filtrate was then concentrated and checked by $^{31}$P NMR to determine the % conversion and the crude dr value. GAP operations: 1) **Method A**: The filtrate was re-dissolved in EtOAc and washed with 1 N HCl, water, and brine successively, then dried over anhydrous $Na_2SO_4$. The crude product was obtained by filtration and concentration, followed by addition of 5 mL of hexanes to triturate the crude product. After 30 minutes, the solvent was decanted and another 5 mL hexanes were added. The resulting slurry was then filtered and the solid was washed with another 2 mL hexanes. The solid product was collected and dried in vacuo. The yield was calculated and the dr value and purity were checked by $^{31}$P NMR and $^{1}$H NMR. 2) **Method B**: The filtrate was re-dissolved in EtOAc/hexanes (20 mL, v/v = 1:1), and then filtered through Celite. The filtrate was concentrated and triturated with hexanes (5 mL). After 30 minutes, the solvent was decanted and another

5 mL hexanes was added. The resulting slurry was then filtered and the solid was washed with another 2 mL hexanes. The solid product was collected and dried in vacuo. The yield was calculated from the starting amide **1**. The dr value and purity were checked by $^{31}$P NMR and $^{1}$H NMR.

## Supporting Information

### Supporting Information File 1

Experimental details, characterization data of all products, and copies of NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-69-S1.pdf]

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29. For the details of the crystal, see CCDC number 937895.

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# Addition of *H*-phosphonates to quinine-derived carbonyl compounds. An unexpected C9 phosphonate–phosphate rearrangement and tandem intramolecular piperidine elimination

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Full Research Paper

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## Abstract

The Abramov reaction, a base-catalyzed nucleophilic addition of dialkyl *H*-phosphonates (phosphites) to carbonyl compounds, was performed with oxidized quinine derivatives as the substrates. Homologous aldehydes obtained from the vinyl group reacted in a typical way which led to α-hydroxyphosphonates, first reported compounds containing a direct P–C bond between the quinine carbon skeleton and a phosphorus atom. For the C9 ketones a phosphonate–phosphate rearrangement, associated with a tandem elimination of the piperidine fragment, was evidenced.

## Introduction

Medicinal, organocatalytic and stereoselective properties of quinine make it the most prominent representative of *Cinchona* alkaloids [1], a group of natural compounds of a unique three-dimensional structure. The structure involves a particular arrangement of two rigid heterocyclic fragments: aromatic quinoline and chiral aliphatic quinuclidine, and a hydroxy function on the stereogenic carbon atom. Such an architecture combined with the presence of nucleophilic and electrophilic centers buried in a hydrophobic environment predestinates the molecule to asymmetric applications, such as: chiral catalysis, transition metal complexing, molecular recognition, chromatographic separation and analysis of enantiomers [2-5].

Synthetic modifications of the basic structure, motivated by an improved stereoselectivity potential of quinine, are an issue of ongoing trials [6-9]. Surprisingly, phosphorus compounds chemistry, particularity that avoiding an expansion of the core carbon skeleton [10-13], is poorly recognized and mainly involves esterification of different phosphorus acids with the *O*-9-hydroxy group [14-21]. These phosphorus esters were consecutively applied in organo- and metal-assisted catalysis [14,17-20] and NMR-monitored enantiodiscrimination [21]. According to our knowledge no example of formation of a direct C–P linkage between the quinine backbone and a phosphorus atom has been reported in the literature. Stimulated by this challenge we planned to envisage a nucleophilic addition of dialkyl phosphites to quinine-based carbonyl compounds and obtain 1-hydroxyalkylphosphonate derivatives (Abramov reaction, phospha-aldol reaction [22,23]). The scope, stereochemistry and side-reactions of the addition are described.

## Results and Discussion

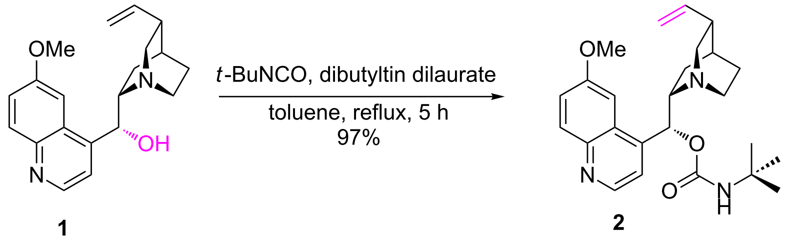
Quinine-based carbonyl compounds were obtained by oxidation of either the secondary C9 hydroxy group to the corresponding ketone or the vinyl group to homologous aldehydes. The last-mentioned alternative demanded a protection of the OH function. This was performed via carbamoylation of quinine (**1**) with *t*-butyl isocyanate as described elsewhere (Scheme 1) [24]. A higher scale of reaction improved the yield if compared to the literature data.

### Vinyl group modifications

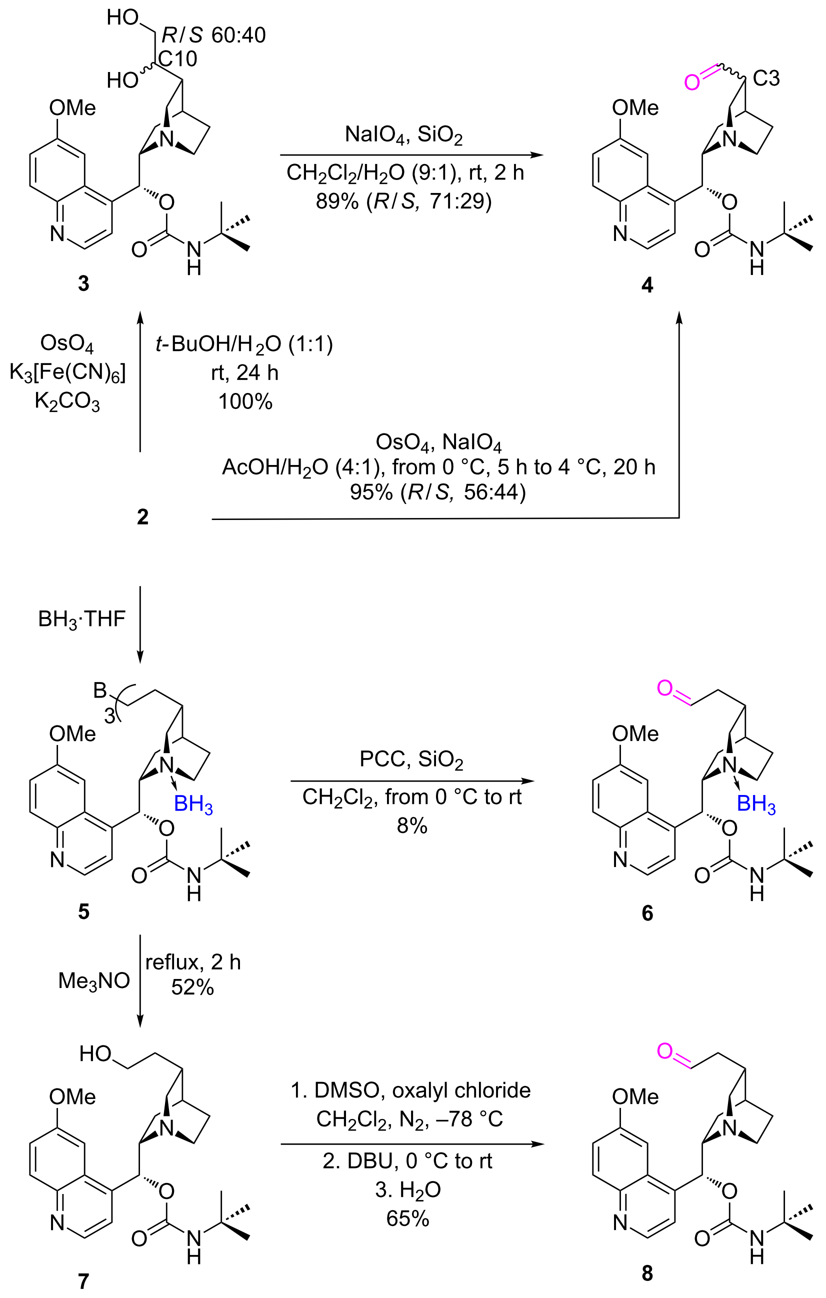
Oxidation of the vinyl group of quinine can be carried out in two different manners to give homologous aldehydes. The one-carbon atom-shortened aldehyde **4** is the product of osmium tetroxide/periodate oxidation [25]. Depending on the reaction conditions a variable ratio of epimers at the neighboring C3 carbon atom was obtained (Scheme 2). A single-step oxidation process was not selective and produced equal amounts of diastereoisomers, 56:44 (C3 *R*/*S*, yield 95%), which was comparable to the literature data reported as 50:50 (C3 *R*/*S*, 95%) by Waddell [25] and 55:45 (C3 *R*/*S*, 80%) by Braje [26]. The two-step procedure initially involved the use of a co-oxidizer other than periodate, e.g., potassium hexacyanoferrate with catalytic amounts of osmium tetroxide to obtain the vicinal diol **3** [27]. This intermediate was preparatively separated as a 60:40 (*R*/*S*) mixture of epimers at C10. The diol compound was subsequently oxidized with $NaIO_4$ to the aldehyde **4** with simultaneous C–C bond breakage. According to the literature an oxidative cleavage on silica in a two-phase system led predominantly to the C3 epimer of the *R* configuration 90:10 (yield 93%) in a short reaction time [27]. In our case, when the reaction time was prolonged to 2 hours, the overall yield remained at the same level while the diastereoselectivity was reduced to 71:29 (*R*/*S*).

The homologous aldehyde can be prepared by oxidation of the double bond in a hydroboration–oxidation sequence, however, the presence of the nitrogen atoms, particularly that of the tertiary amino group of quinuclidine, may be troubleshooting [28,29]. Borane complexes with heteroaromatic and aliphatic amines are considered inconveniently stable in protic solvents (water, alcohols) and dissociate only at an elevated temperature [30]. Most probably, in our case the formation of the amine–borane complex proceeded faster than the hydroboration of the vinyl group. When compound **2** was reacted with the $BH_3$·THF complex and then oxidized with pyridinium chlorochromate (recommended PCC on $SiO_2$ [26]) a complicated mixture of products (50% of conversion) was obtained. The mixture contained the target aldehyde **6** (minority, Scheme 2) and the corresponding alcohol (majority, ratio 1:5), both in their complexed forms (borane-tertiary amino group). Again, step-by-step approach and separation of the intermediate appeared more profitable. First, the alcohol **7** was synthesized by hydroboration of the substrate with $BH_3$·THF under an inert atmosphere followed by oxidation of the intermediate borane **5** complex with trimethylamine oxide [31]. As the oxide also released the borane–quinuclidine complex at elevated temperature the free alcohol was obtained in a satisfactory yield. This alcohol was subjected to Swern oxidation, recommended for multifunctional compounds [32], to produce the target aldehyde **8** in 65% yield.

The obtained aldehydes **4**, **6**, and **8** were reacted with 1.1 equiv of diethyl phosphite. The presence of the tertiary amino group of quinuclidine was expected to be a sufficient catalytic base for the addition reaction, and furthermore to induce a diastereoselectivity. However, the expected hydroxyphosphonates were not formed, neither at room temperature after 24 hours, nor upon



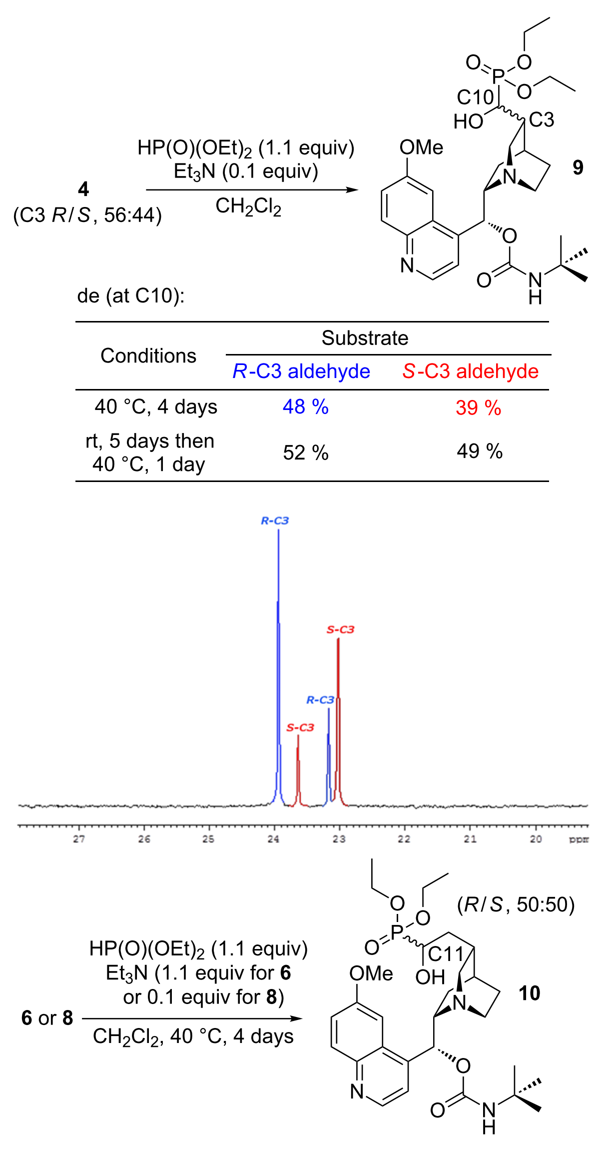
**Scheme 1:** Quinine (**1**) and *O*-9-*t*-butylcarbamoylquinine (**2**) as the substrates for oxidation of the C9 hydroxy and the vinyl group, respectively.



**Scheme 2:** Oxidation of the vinyl group of 9-*O*-*tert*-butylcarbamoylquinine to homologous aldehydes.

increasing the temperature to 40 °C within additional 48 hours. Addition of 0.1 equiv of $Et_3N$ initiated the reaction of **4** and **8** (Scheme 3) [33], in the case of borane complex **6** a stoichiometric amount of triethylamine (1.1 equiv) was applied.

Crude reaction mixtures were analyzed by NMR. To achieve complete separation of the $^{31}P$ NMR signals and reliable assessment of the diastereomeric composition addition of 10 equiv of acetic acid was demanded. Despite the long reaction time (up to 4 days at 40 °C) the starting aldehydes were not fully consumed. Partially stereoselective addition was observed for the shorter homolog **4**. The diastereomeric excess of the newly appearing stereogenic center at C10 of α-hydroxyphosphonate **9** slightly depended on the reaction conditions and the C3 absolute configuration of the substrate, and varied in the range of 40–50% (Scheme 3). The *R*-C3 epimer gave rise to somewhat more pronounced induction. The $^{31}P$ NMR resonances of the predominating forms of the hydroxyphosphonate are shifted



| Conditions | Substrate | |
|---|---|---|
| | *R*-C3 aldehyde | *S*-C3 aldehyde |
| 40 °C, 4 days | 48 % | 39 % |
| rt, 5 days then 40 °C, 1 day | 52 % | 49 % |

**Scheme 3:** Addition of diethyl phosphite to aldehydes obtained in oxidation of the vinyl group.

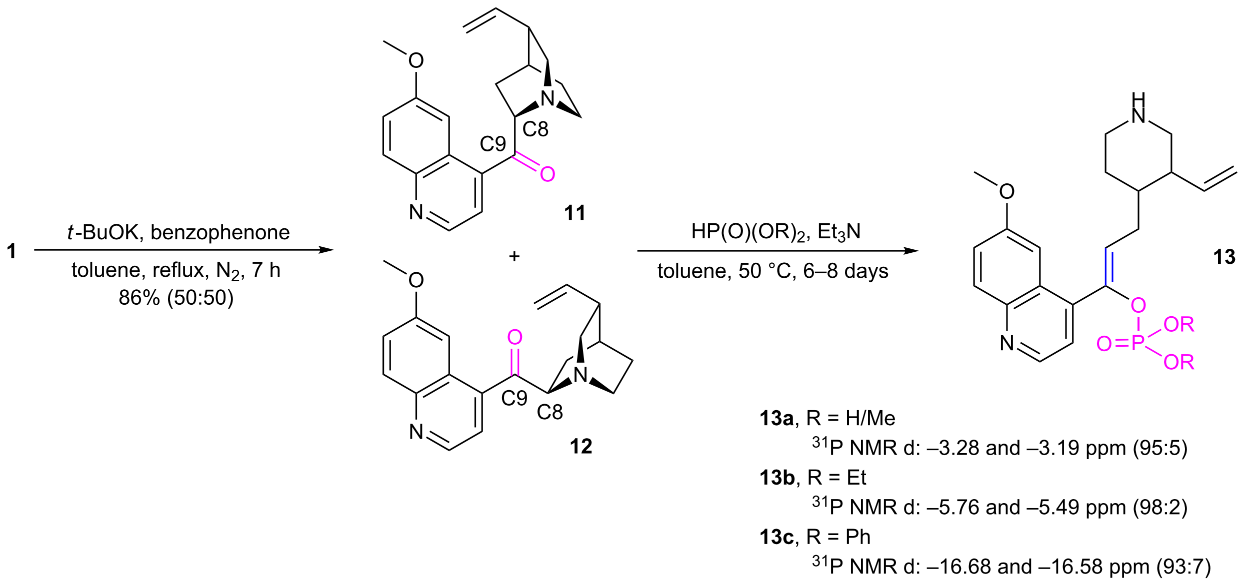
apart by approximately 1.0 ppm. We speculate that this means a diastereomeric relationship of their C3–C10 fragment (being the result of induction of the same C10 configuration, see the inserted spectrum in Scheme 3). Thus, general stereo-controlling properties of quinine predominate and do not cooperate (no match–mismatch effect visible) with the absolute configuration of the starting aldehyde epimers. The hydroxyphosphonates derived from the longer homologs were completely racemic at C11. Two diastereoisomers of the hydroxyphosphonate **10** were formed in a ratio of 1:1, irrespectively of the substrate amino group state: either free (**8**) or complexed with borane (**6**). Elevated temperature and the presence of 1.1 equiv of Et$_3$N caused entire decomposition of the quinuclidine–borane complex in the case of substrate **6**. Final α-hydroxyphosphonate esters **9** and **10** were purified by column chromatography and characterized (for **9** two fractions, each containing two individuals, were refined by preparative thin-layer chromatography, for details see Supporting Information File 1).

## C9 position modification, phosphonate–phosphate rearrangement

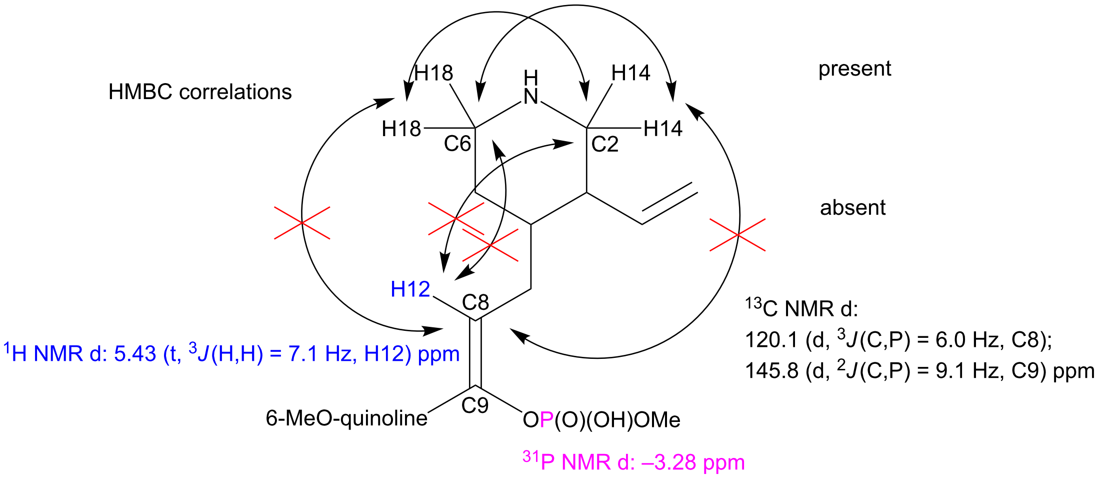
Oxidation of the C9 hydroxy group of quinine to the corresponding ketone, quininone, was performed with potassium *tert*-butoxide and benzophenone (Scheme 4) [34]. Using toluene as the solvent, instead of benzene, the reaction time was shortened to 7 hours while maintaining the same yield [35]. Epimerization, that occurred at the neighboring C8 atom, resulted in formation of two diastereomeric products: quininone **11** and quinidinone **12** in a 50:50 ratio.

The mixture of ketones **11** and **12** was treated with diethyl phosphite and heated in toluene at 50 °C for a week with addition of a catalytic amount of triethylamine (Scheme 4). The reaction mixture was purified by column chromatography. Formation of four diastereomeric compounds, derivatives of epiquinidine (8*R*,9*R*), quinidine (8*R*,9*S*), quinine (8*S*,9R) and epiquinine (8*S*,9*S*), was expected under non or partially stereoselective conditions. However, spectroscopic characterization revealed the presence of only two species (one present in an overwhelming excess) which exhibited the $^{31}$P NMR chemical shifts not expected for phosphonates but typical for phosphates, **13b**: −5.76 and −5.49 ppm. Apparently, they were products of the phosphonate–phosphate rearrangement of intermediate hydroxyphosphonates [36-38]. Treatment of ketones **11** and **12** with dimethyl- and diphenyl phosphite brought quite similar results. The expected product, diphenyl hydroxyphosphonate was not obtained, intead the quinotoxin enol diphenyl phosphate **13c** appeared, and it was separated chromatographically whereas methyl monodealkylated derivative **13a** precipitated directly from the reaction mixture. The selective hydrolysis of the phosphorus esters is not surprising as triethylamine and quinuclidine are bases strong enough to release the methyl ester.

The additional structural modifications of the quinine skeleton of **13a** were indicated with the $^{1}$H,$^{13}$C-HMBC correlation spectra. The C2–H18 and C6–H14 interactions were present, whereas correlations C2–H12, C6–H12, C8–H14 and C8–H18 were not visible (Scheme 5), what demonstrated a degradation of the bicyclic fragment of quinuclidine to a piperidine skeleton. In addition, the characteristic signal of the H11 proton was absent and the H12 resonance was shifted to the lower field (5.43 ppm), between the H20 and H21 vinyl protons. The C8 resonance signal was consequently shifted from 60 ppm to approximately 120 ppm. The aromatic system remained intact. These data suggest formation of the C8=C9 double bond in a

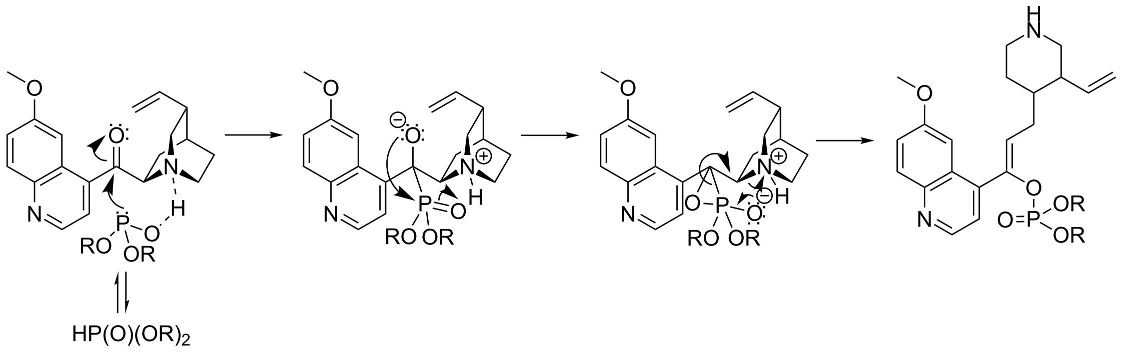


**Scheme 4:** Oxidation of quinine to quininone and quinidinone and addition of phosphites to the ketones yielding the rearrangement products.



**Scheme 5:** Spectroscopic features that confirmed the structure of the phosphate ester product of rearrangement and intramolecular elimination.

cascade process with concomitant cleavage of the C–N bond that follows the phosphonate–phosphate rearrangement (Scheme 6). Two $^{31}$P NMR signals are related to the *E*/*Z* diastereoisomerism. Configuration of the predominating form can be assigned as *Z*. First, this is indicated by the nuclear Overhauser effect – irradiation of the H12 proton caused the most significant cross-relaxation changes in intensity of the H3’ and H5’ protons of the quinoline system. This proximity is achievable only in the case of location of vinyl and quinoline protons at the same side of the double bond. Theoretical prediction of the H12 NMR chemical shift provided an additional confirmation [39]. The δ calculated for the *Z* arrangement (geminal alkyl, *cis* aromatic and *trans* dialkyl phosphoryl, whose estimated influence corresponds to the acetoxy group [40]) is 5.4–5.5 ppm and well matches with the observed values (5.43–5.49). The chemical shift calculation performed for the opposite configuration remains in worse agreement (5.2–5.3 ppm).



**Scheme 6:** Tentative mechanism of the phosphonate–phosphate rearrangement associated with tandem quinuclidine degradation.

The observed reactivity seemed to be general as formation of compound **13b** was evidenced (to a different extent) in other variants of the catalytical addition of diethyl phosphite to quininone/quinidinone, with catalytic systems such as: KF/$Al_2O_3$, $NH_3$/EtOH and DBU/EtOH or toluene. Independent of the catalyst and conditions applied α-hydroxyphosphonates were not detected in the crude reaction mixture, and the rearranged compound was the only appearing product. The enol phosphates **13** were not stable and underwent slow decomposition to give four to five signals in the $^{31}$P NMR spectra after a month.

This is a novel contribution to the reactivity of quinine although similar eliminations of piperidine in *Cinchona* alkaloids have been reported in the literature. Accordingly, heating of quinine or derivatives in acids provided either quino-/cinchotoxine ketones or their tautomeric enol esters, depending on the substrate structure and the reaction conditions [41-43]. The corresponding compounds were also suggested as the products of a base-catalyzed Hofmann elimination of quaternary quinuclidinium salts studied as chiral catalysts [44,45]. These unwanted rearrangement negatively influenced the stereoselective properties of the alkaloids [44,45]. An elimination associated with the phosphonate–phosphate rearrangement was also reported for other 1-hydroxyphosphonate systems [46-48].

## Conclusion

An intriguing chemical behavior of C-9 quinine-derived ketones was demonstrated in the Abramov (phospha-aldol) reaction. These carbonyl compounds reacted with dialkyl and diphenyl phosphites producing quinotoxin enol phosphates that resulted from a tandem phosphonate–phosphate rearrangement and an intramolecular piperidine elimination. It can be hypothesized that the driving force of the structural changes is the proximity of the tertiary amine nucleophilic center. Based on this supposition, a mechanism of the rearrangement was suggested. The homologous C10 and C11 aldehydes obtained by oxidation of the vinyl group reacted in a typical manner to yield α-hydroxyphosphonates, the first described quinine-derived C–P compounds.

## Supporting Information

### Supporting Information File 1

Experimental and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-85-S1.pdf]

## Dedication

The contribution is dedicated to Prof. Roman Tyka on his 90th anniversary.

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# Allenylphosphine oxides as simple scaffolds for phosphinoylindoles and phosphinoylisocoumarins

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## Abstract

A range of phosphinoylindoles was prepared in one-pot from functionalized propargyl alcohols and a suitable P(III) precursor via a base-mediated reaction. The reaction proceeds via the intermediacy of allenylphosphine oxides. Similarly, phosphinoylisocoumarins were prepared from allenylphosphine oxides in a trifluoroacetic acid-mediated reaction; the latter also acts as a solvent. Interestingly, in the presence of wet trifluoroacetic acid, in addition to phosphinoylisocoumarins, phosphorus-free isocoumarins were also obtained. Key products were characterized by single crystal X-ray crystallography.

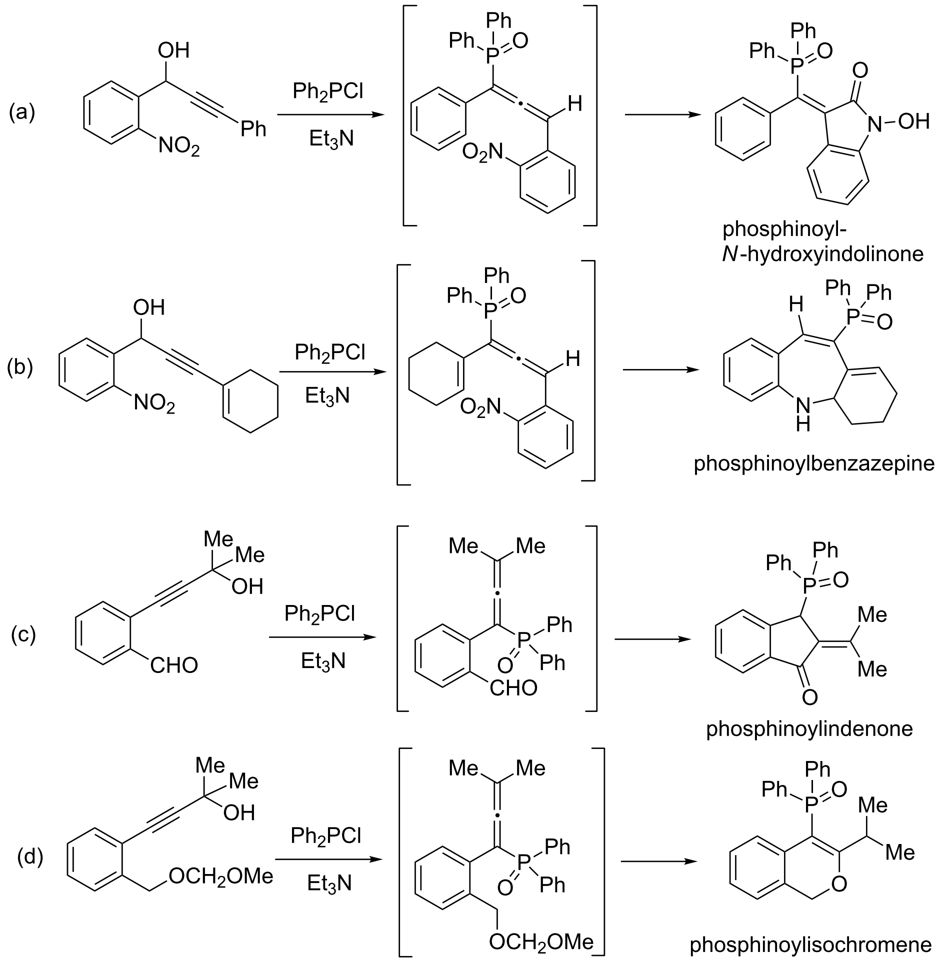
## Introduction

Allenes, by virtue of cumulative double bonds that facilitate reactions with diverse classes of substrates, are versatile building blocks from a synthetic perspective [1,2]. They are also found in many natural products, pharmaceuticals [3] and molecular materials [4]. Thus, over the last decade, allenes have attained a prominent position in organic transformations like cycloaddition, cycloisomerization, base or metal-catalyzed reactions [5-7]. In particular, cyclization reaction of allenes has emerged as a valuable tool in developing different methods leading to various carbo-/heterocycles [8-14]. Allenylphosphonates and allenylphosphine oxides, as a subclass of allenes, have also been utlized in several novel transformations [15-17]. It may also be noted that organophosphonates in addition have wide applications in medicinal chemistry [3,18,19] and as reagents in organic synthesis [20]. In our previous reports, we described the utility of phosphorus-based allenes in various cyclization reactions involving heteroatoms that could lead to phosphono/phosphinoyl hetero-/carbocycles [21-30]. The reported series include phosphonobenzofurans/indenones [21,22], -pyrazoles [23], -chromenes/thiochromenes [24,25], -pyrroles [26], multiply substituted furans [27], indolopyran-1-ones [28], *N*-hydroxyindolinones [29], and oxindoles [30]. In the reaction shown in Scheme 1a, for the formation of the phosphinoylindolinone, one of the oxygen atoms of the nitro group has been moved to a carbon [29]. The reaction shown in Scheme 1b led to rather previously unsuspected and unexpected benzazepines as products. After the elimination of a $CO_2$ molecule, this reaction also features an unprecedented rearrangement involving the interemdiate allene [29]. Many other unusual transformations have also been reported recently [31]. In another reaction leading to phosphinoylindenone depicted in Scheme 1c, an intramolecular *ene*-reaction is possibly involved and in Scheme 1d the reaction led to phosphinoylisochromenes via deprotection of an allene intermediate under Lewis acid mediation [22]. In this context it was of interest to see, in a reaction like that shown in Scheme 1c, whether the introduction of an amide or a carboxylate ester in place of the –CHO group could lead to phosphinoyl-subtstituted indoles/isocoumarins via allenic intermediates or not. It is pertinent to note that indoles and isocoumarins are core structures found in many natural and pharmacological products [32-34]. Thus in this paper, we wish to report simple synthetic routes to phosphinoylindoles, and -isocoumarins utilizing functionalized allenylphosphine oxides/allenylphosphonates.

## Results and Discussion

In order to achieve the anticipated phosphinoylindoles/isocoumarins, we prepared a variety of functionalized propargyl alcohols **1a–m** and **2a–j** containing an acetamide, benzamide or an ester group at the *ortho* position (Figure 1) [35-37]. Some of the propargyl alcohols **1a–c**, **1m** and **2a–j** were transformed to allenylphosphine oxides **3a–c**, **3m** and **4a–j** (Scheme 2) by following known methods [38,39].

After having several functionalized allenes in hand, initially we chose allenes **3a** and **3m** to achieve intramolecular cyclization. These were treated with 0.5 mol equivalents of base ($K_3PO_4$) since the substrates contain active hydrogen. This reaction afforded the *N*-substituted phosphinoylindoles **5** and **7**, **8**. Essentially a single isomer **5** (a dihydroindole), in which the

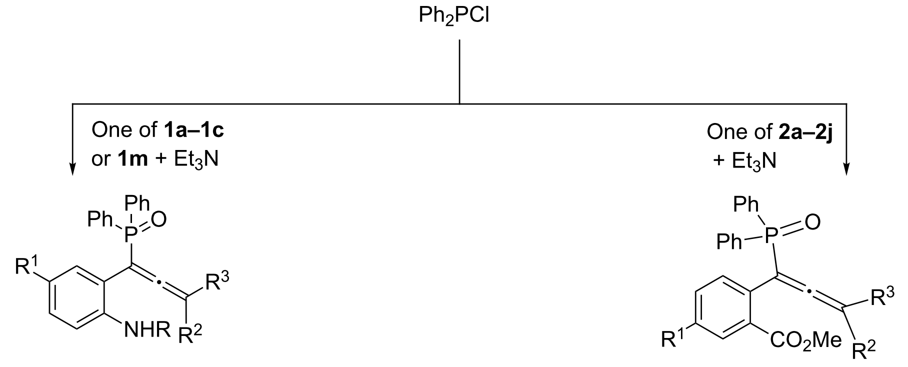


**Scheme 1:** Reaction of P(III)-Cl precursors with propargyl alcohols leading to phosphorus based (a) *N*-hydroxyindolinone, (b) benzazepine, (c) indenone and (d) isochromene via allenic intermediates.

R = Ac
R$^1$ = H, R$^2$ = R$^3$ = Me (**1a**)
R$^1$ = H, R$^2$ = H, R$^3$ = Me (**1b**)
R$^1$ = H, R$^2$ = Me, R$^3$ = Ph (**1c**)
R$^1$ = H, R$^2$ = R$^3$ = H (**1d**)
R$^1$ = H, R$^2$ = Me, R$^3$ = Et (**1e**)
R$^1$ = H, R$^2$ = H, R$^3$ = Ph (**1f**)
R$^1$ = H, (R$^2$ R$^3$) = -(CH$_2$)$_5$- (**1g**)
R$^1$ = Me, R$^2$ = R$^3$ = H (**1h**)
R$^1$ = Me, R$^2$ = H, R$^3$ = Me (**1i**)
R$^1$ = Me, R$^2$ = H, R$^3$ = Ph (**1j**)
R$^1$ = Me, R$^2$ = R$^3$ = Me (**1k**)
R$^1$ = Me, R$^2$ = Me, R$^3$ = Ph (**1l**)
R = Bz, R$^1$ = R$^2$ = H, R$^3$ = Me (**1m**)

R$^1$ = R$^2$ = R$^3$ = H (**2a**)
R$^1$ = R$^2$ = H, R$^3$ = Me (**2b**)
R$^1$ = H, R$^2$ = R$^3$ = Me (**2c**)
R$^1$ = H, (R$^2$ R$^3$) = -(CH$_2$)$_5$- (**2d**)
R$^1$ = R$^2$ = H, R$^3$ = Ph (**2e**)
R$^1$ = H, R$^2$ = Me, R$^3$ = Et (**2f**)
R$^1$ = Br, R$^2$ = R$^3$ = H (**2g**)
R$^1$ = Br, R$^2$ = H, R$^3$ = Me (**2h**)
R$^1$ = Br, R$^2$ = R$^3$ = Me (**2i**)
R$^1$ = Br, (R$^2$ R$^3$) = -(CH$_2$)$_5$- (**2j**)

**Figure 1:** Functionalized propargyl alcohols **1a–m** and **2a–j** used in the present study.

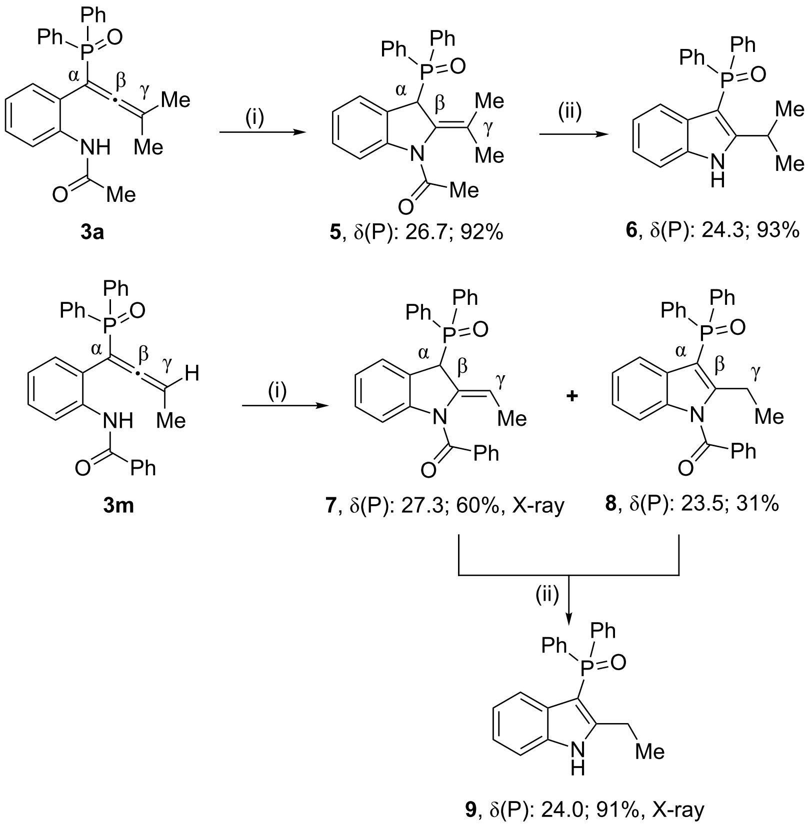


R = -C(O)Me, R$^1$ = H
R$^2$ = R$^3$ = Me **3a**, δ(P): 35.2; 87%
R$^2$ = H, R$^3$ = Me **3b**, δ(P): 34.1; 78%
R$^2$ = Me, R$^3$ = Ph **3c**, δ(P): 34.5; 92%
R = -C(O)Ph, R$^1$ = H
R$^2$ = H, R$^3$ = Me **3m**, δ(P): 34.3; 75%

R$^1$ = R$^2$ = R$^3$ = H **4a**, δ(P): 27.7; 85%
R$^1$ = R$^2$ = H, R$^3$ = Me **4b**, δ(P): 28.8; 79%
R$^1$ = H, R$^2$ = R$^3$ = Me **4c**, δ(P): 29.8; 88%
R$^1$ = H, (R$^2$ R$^3$) = -(CH$_2$)$_5$- **4d**, δ(P): 29.5; 90%
R$^1$ = R$^2$ = H, R$^3$ = Ph **4e**, δ(P): 27.5; 85%
R$^1$ = H, R$^2$ = Me, R$^3$ = Et **4f**, δ(P): 29.2; 82%
R$^1$ = Br, R$^2$ = R$^3$ = H **4g**, δ(P): 27.6; 86%
R$^1$ = Br, R$^2$ = H, R$^3$ = Me **4h**, δ(P): 28.7; 84%
R$^1$ = Br, R$^2$ = R$^3$ = Me **4i**, δ(P): 29.8; 91%
R$^1$ = Br, (R$^2$ R$^3$) = -(CH$_2$)$_5$- **4j**, δ(P): 29.5; 74%

**Scheme 2:** Synthesis of functionalized allenes **3a–c**, **3m** and **4a–j**.

N–H proton moves only to the α-carbon resulting in an exocyclic double bond, was formed (Scheme 3). The presence of a doublet for P*C*H carbon at δ 48.3 with a $^1J$(P–C) value of 62.0 Hz reveals that the phosphorus moiety is attached to an sp$^3$-hybridized carbon. On the other hand, in the reaction using the =CHMe allene **3m**, two isomers in which the N–H proton moves to either the α-carbon (**7**) or the γ-carbon (**8**), are obtained. These two isomers can be readily distinguished by the corresponding δ and $^1J$ values for the P–C carbon (for **7**, δ 47.3 and $J$ = 62.0 Hz; for **8**, δ 106.5 and $J$ = 120.0 Hz). Overall, the



**Scheme 3:** Reaction of functionalized allenes **3a** and **3m** leading to phosphinoylindoles. Conditions: (i) $K_3PO_4$ (0.5 equiv), THF, 80 °C, 12 h, (ii) NaOH (2 equiv), EtOH/$H_2O$ (4:1), 80 °C, 8 h.

yields of the isolated products were excellent in both cases. The structure of compound **7** was further confirmed by X-ray crystallography (Figure 2). The *C*=*C*HMe distance of 1.317(2) Å clearly indicates a double bond between these two carbon atoms. The other stereoisomer in which the methyl group is *trans* to the nitrogen was not observed. Interestingly though, the removal of the acyl/benzoyl group on the nitrogen in compounds **5** or **7**, **8** in aq NaOH afforded the 2,3-disubstituted N*H*-indoles **6** or **9**, respectively, in excellent yields. The NH band (3156 $cm^{-1}$) in the IR spectrum and a doublet for PC carbon at δ 98.4 ($^1J$(PC) = 128.0 Hz) reveal the identity of compound **9**. Its structure was further confirmed by X-ray crystallography (Figure 3).

Subsequently, we used aq sodium hydroxide as the base instead of $K_3PO_4$ (cf. conditions (ii) in Scheme 3) to perform the reaction on allene **3a**. To our delight, only phosphinoyl-N*H*-indole **6** was the sole product with not even traces of **5** (Scheme 4). This shows that a strong base like sodium hydroxide effectively performs both deprotection and cyclization in a single step.

With the above conditions in hand, we then performed the reaction in one pot starting from propargyl alcohol **1a** without

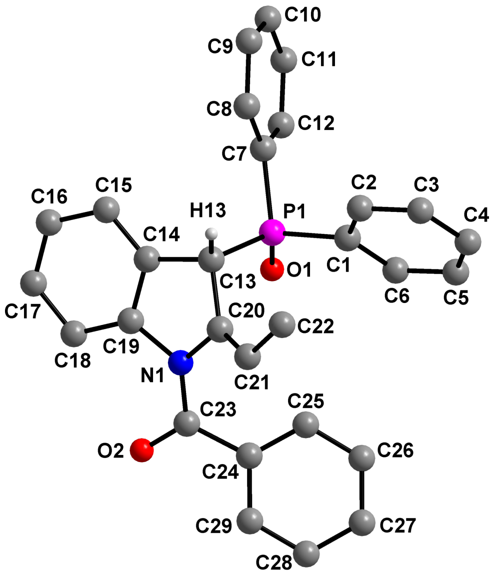


**Figure 2:** Molecular structure of compound **7**. Hydrogen atoms (except PCH) are omitted for clarity. Selected bond distances (Å): P1–C13 1.8402(15), C13–C20 1.5161(19), C13–C14 1.512(2), C20–N1 1.4508(18), C20–C21 1.317(2).

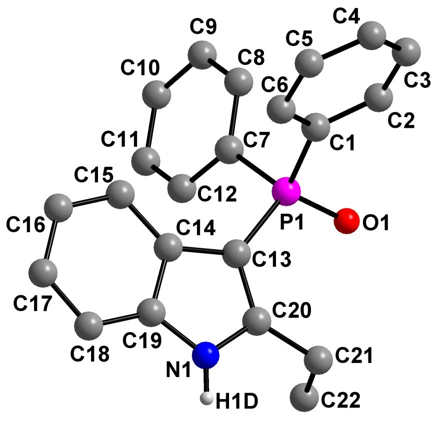
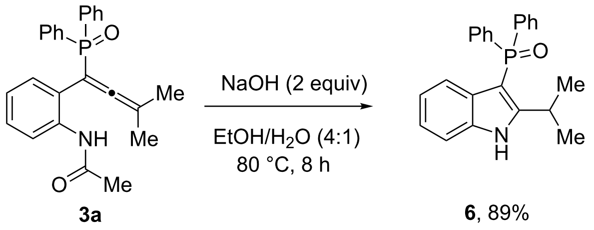
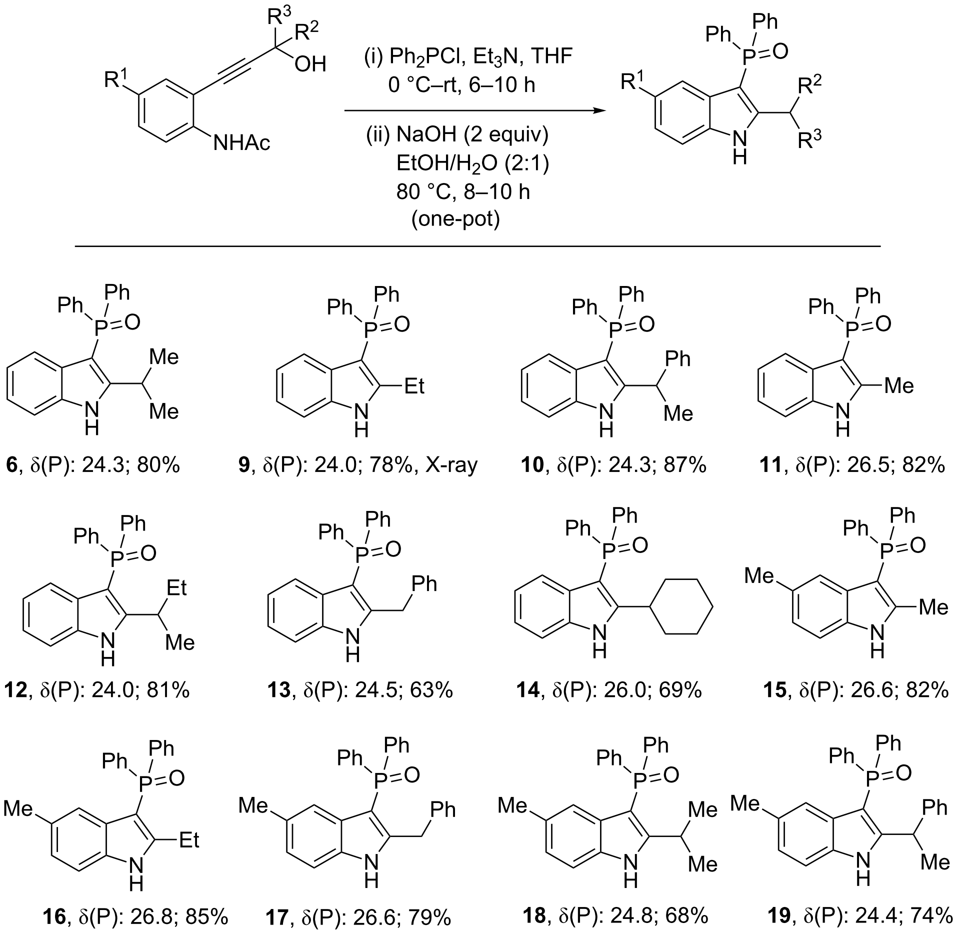


**Figure 3:** Molecular structure of compound **9**. Hydrogen atoms (except NH) are omitted for clarity. Selected bond distances (Å): P1–C13 1.771(2), C13–C20 1.385(3), C13–C14 1.450(3), C20–N1 1.360(3), C20–C21 1.489(3).



**Scheme 4:** Synthesis of phosphinoylindole from allene **3a** in a single step.

isolating the intermediate allenylphosphine oxide **3a**. Gratifyingly, the method furnished the desired product **6** in 80% yield. Inspired by this, functionalized propargyl alcohols **1b–l** were also subjected to the same one-pot conditions (Scheme 5). This one-pot strategy furnished the desired phosphinoylindoles **9–19** in good to excellent yields without any difficulty in isolation. Analogous products could also be isolated using the P(III) precursor $(OCH_2CMe_2CH_2O)PCl$ (see Supporting Information



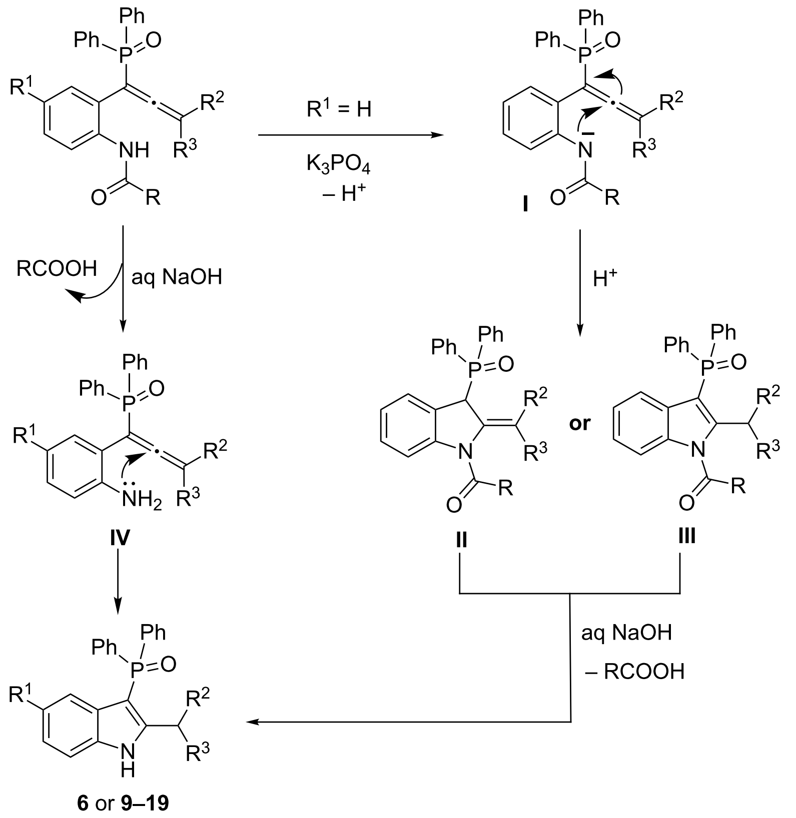
**Scheme 5:** One-pot preparation of substituted phosphinoylindoles **6** and **9–19** from functionalized alcohols.

File 1 for details). In our attmept to obtain phosphorus-free 2-alkylindole from **17** in the presence of triflic acid (as a solvent; 100 °C) led to a mixture of products in which the benzyl group also was cleaved (NMR evidence). Such a reductive cleavage of the P–C bond from phosphinoyl indoles is a reaction that we are still exploring.

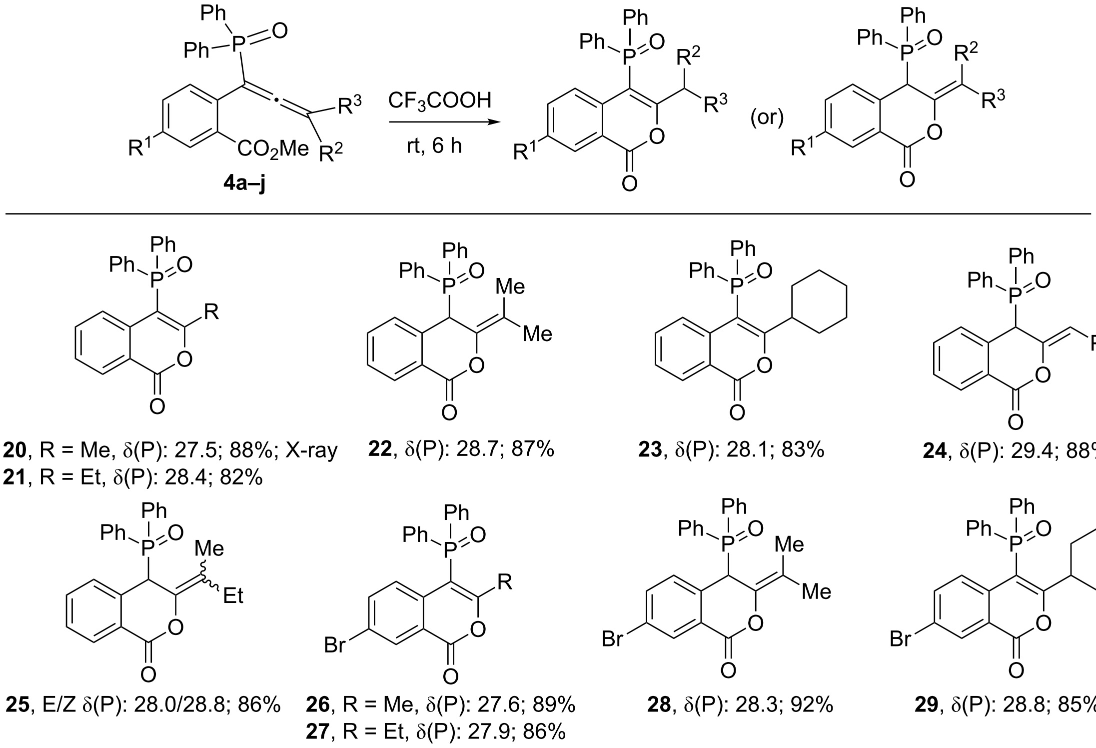
A plausible pathway for the formation of phosphinoylindoles **6** and **9–19** is shown in Scheme 6. As depicted above in Scheme 2, the normal reaction of propargyl alcohol with chlorodiphenylphosphine is expected to lead to the allenylphosphine oxide. We believe that there is a subtle difference between the use of $K_3PO_4$ and aq NaOH. $K_3PO_4$ abstracts the NH proton from allenylphosphine oxide leading to intermediate **I** which is followed by attack of the nitrogen lone pair on the β-carbon [24] of the allene forming addition product **II** or **III**. This upon treating with aq NaOH leads to the deacylated/debenzoylated phosphinoylindoles. In the one-pot reaction, though, the in situ generated allenylphosphine oxide first undergoes deacylation/debenzoylation with aq NaOH resulting in $-NH_2$ functionalized allene **IV**; the lone pair on nitrogen will then attack the β-carbon of the allene intramolecularly leading to phosphinoylindoles **6** or **9–19**.

After succeeding in generating phosphinoylindoles, we then concentrated on synthesizing phosphinoylisocoumarins. To achieve this, we treated the functionalized allene precursors **4a–j** that are tethered with a methyl ester group, with an excess of trifluoroacetic acid at room temperature for 6 h. Gratifyingly, this readily leds to the phosphinoylisocoumarins **20–29** (Scheme 7) in good yields. In the case of compound **25**, as expected, both the *E* and *Z* isomers are present in a ratio of 1:0.65 (close $R_f$ values). Very subtle energy differences seem to be prevalent between the dihydroisocoumains **22**, **24, 25**, **28**, **29** and the normal isocoumarins **20**, **21**, **23**, **26, 27**. The former set shows a doublet in the $^1$H NMR spectra at δ ~ 4.78 ($^2J$(P–H) = 18.0 Hz, PC*H*) which is absent in the latter set; the difference in the value of $^1J$(P–C) in the two sets is also consistent with the hybridization at the corresponding α-carbon (to phosphorus). Finally, the X-ray structure was determined for **20** (Figure 4).

The above reaction is believed to proceed by the initial interaction of $H^+$ with the α,β-allenic double bond to lead to **V** (Scheme 8) which on subsequent attack of oxygen of the ester group onto the β-position of allene forms **VI**. Intermediate **VI** on demethylation leads to phosphinoylisocoumarin **VII**. This product **VII** further involves the double bond isomerization to



**Scheme 6:** Possible pathway for the formation of phosphinoyl indoles **6** and **9–19**.



**Scheme 7:** Synthesis of phosphinoylisocoumarins from functionalized allenes.

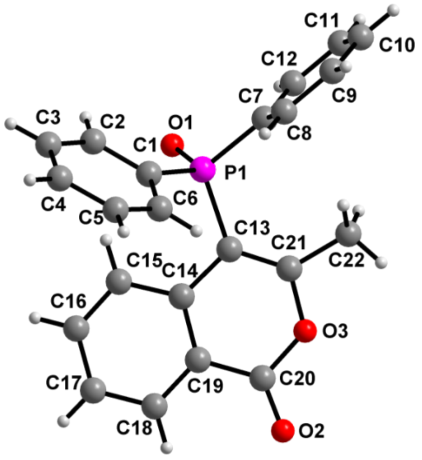


**Figure 4:** Molecular structure of **20**. Selected bond lengths [Å] with estimated standard deviations are given in parentheses: O3–C21 1.386(2), C21–C22 1.486(3).

lead to phosphinoyl isocoumarins **20**, **21**, **23**, **26** and **27**. The isomerization is not observed in the case of **22**, **24**, **25**, **28** and **29**. Alternatively, the cyclization may also proceed after the hydrolysis of ester group to –COOH due to the presence of adventitious moisture in trifluoroacetic acid.

When the above reaction was performed in wet trifluoroacetic acid (TFA/$H_2O$ = 20:1) at 70 °C, phosphinoylisocoumarins were formed in all cases, but additionally, phosphorus-free isocoumarins **30–35** (Scheme 9) [37] are also formed in the reaction using terminally substituted allenes **4b–d** and **4h–j**. We have also determined the X-ray structure of compound **33** (Figure 5) for final confirmation. It is possible that isocoumarins **30–35** are formed via the intermediates **VIII–IX** (Scheme 10) [40]. The phosphorus moiety of **IX** may then be cleaved as $Ph_2POOH$ to form the phosphorus-free isocoumarins. Since this was not the interest in the present study, we did not proceed further.

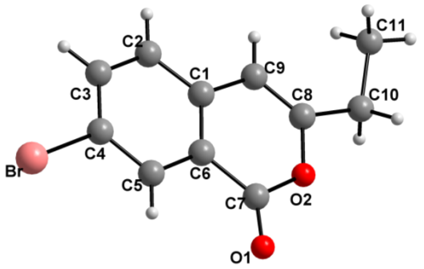
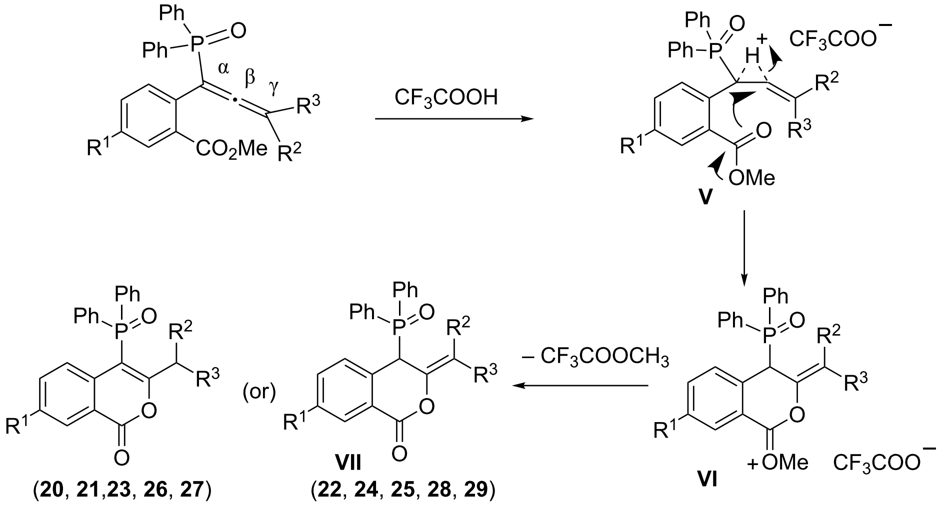
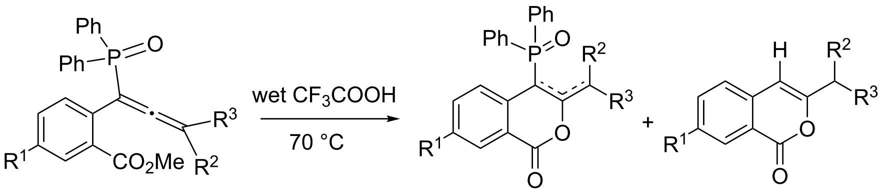


**Figure 5:** Molecular structure of **33**. Selected bond lengths [Å] with estimated standard deviations are given in parentheses: O2–C8 1.377(6), C8–C10 1.492(6).



**Scheme 8:** Possible pathway for the formation of phosphinoylisocoumarins.



**4b–d** and **4h–j**

| | | | |
|---|---|---|---|
| $R^1$ = H, $R^2$ = H, $R^3$ = Me | **21** (52%) | + | **30** (32%) |
| $R^1$ = H, $R^2$ = $R^3$ = Me | **22** (46%) | + | **31** (41%) |
| $R^1$ = H, ($R^2$ $R^3$) = -$(CH_2)_5$- | **23** (49%) | + | **32** (38%) |
| $R^1$ = Br, $R^2$ = H, $R^3$ = Me | **27** (50%) | + | **33** (38%; X-ray) |
| $R^1$ = Br, $R^2$ = $R^3$ = Me | **28** (55%) | + | **34** (35%) |
| $R^1$ = Br, ($R^2$ $R^3$) = -$(CH_2)_5$- | **29** (45%) | + | **35** (42%) |

**Scheme 9:** Reaction of allenes in wet trifluoroacetic acid.

## Conclusion

A fairly simple route to phosphinoylindoles and phosphinoylisocoumarins starting from functionalized propargyl alcohols via allenyl phosphine oxide is developed. The first reaction involves base-mediated deprotection and cyclization while the latter methodology involves acid mediation in which trifluoroacetic acid acts as the reagent as well as the solvent.

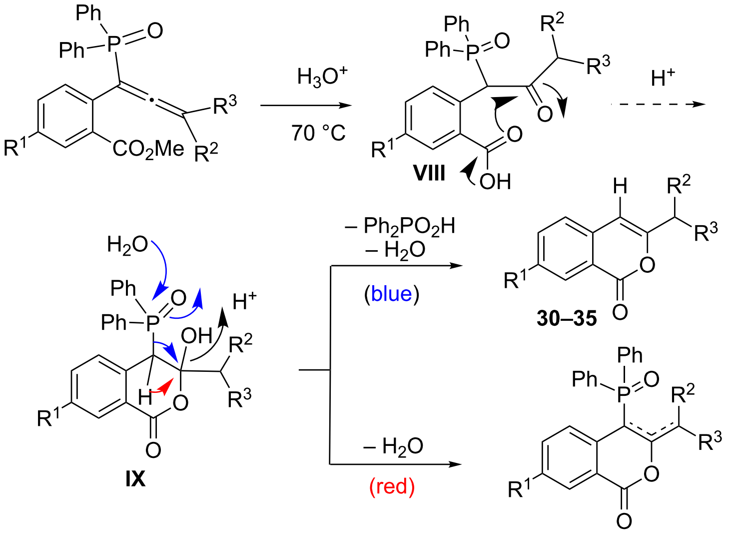
## Experimental

Details on the synthesis of the compounds **1a**–**1m**, **2a**–**2j**, **3a**–**3c**, **3m**, **4a**–**4j** and **5**–**35** are given in Supporing Information File 1.

Crystallographic data for the structures of **7**, **9**, **20** and **33** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 981067-981070. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk]. The structures were solved and refined by standard methods [41-43].

**7**: Colorless block, $C_{29}H_{24}NO_2P$, $M$ = 449.46, monoclinic, space group $P2_1/c$, $a$ = 9.9427(15), $b$ = 16.894(3), $c$ = 14.819(2) Å, α = 90.00, β = 109.195(2), γ = 90.00°, $V$ = 2350.8(6) Å$^3$, $Z$ = 4, μ = 0.143 mm$^{-1}$, data/restrains/parameters: 4141/0/299, R indices (I> 2σ(I)): R1 = 0.0408, $w$R2 (all data) = 0.1101. CCDC no. 981067.

**9**: Colorless block, $C_{22}H_{20}NOP$, $M$ = 345.36, orthorhombic, space group $Pccn$, $a$ = 11.2497(6), $b$ = 21.1287(9), $c$ = 15.2880(6) Å, α = 90, β = 90, γ = 90°, $V$ = 3633.8(3) Å$^3$, $Z$ = 8,



**Scheme 10:** Possible pathway for the formation of isocoumarins **30–35** (along with **21–23** and **27–29**).

μ = 0.160 $mm^{-1}$, data/restrains/parameters: 3205/0/231, R indices (I> 2σ(I)): R1 = 0.0430, *w*R2 (all data) = 0.1076. CCDC no. 981068.

**20**: Colorless block, $C_{22}H_{17}O_3P$, *M* = 360.33, triclinic, space group *P*1̄, *a* = 9.7440(19), *b* = 9.9918(17), *c* = 10.2864(18) Å, α = 84.229(14), β = 76.556(16), γ = 66.323(18)°, *V* = 892.0(3) $Å^3$, *Z* = 2, μ = 0.173 $mm^{-1}$, data/restrains/parameters: 3647/0/236, R indices (I> 2σ(I)): R1 = 0.0455, *w*R2 (all data) = 0.1114. CCDC no. 981069.

**33**: Colorless needles, $C_{11}H_9BrO_2$, *M* = 253.09, triclinic, space group *P*1̄, *a* = 7.9413(19), *b* = 7.9674(19), *c* = 9.746(2) Å, α = 66.05(2), β = 79.379(19), γ = 62.93(2)°, *V* = 501.8(2) $Å^3$, *Z* = 2, μ = 4.064 $mm^{-1}$, data/restrains/parameters: 1354/0/128, R indices (I> 2σ(I)): R1 = 0.0425, *w*R2 (all data) = 0.1021. CCDC no. 981070.

## Supporting Information

### Supporting Information File 1

Details on the synthesis and characterization of the compounds **1a–1m**, **2a–2j**, **3a–3c**, **3m**, **4a–4j** and **5–35** and $^1H/^{13}C$ NMR spectra of new compounds (including **A–B**). [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-99-S1.pdf]

### Supporting Information File 2

CIF file for the compounds **7**, **9**, **20** and **33**. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-99-S2.cif]

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## License and Terms

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# Theoretical studies on the intramolecular cyclization of 2,4,6-$t$-$Bu_3C_6H_2P$=C: and effects of conjugation between the P=C and aromatic moieties

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Full Research Paper

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3,4-dihydro-1-phosphanaphthalene; intramolecular cyclization; organophosphorus; phosphanylidenecarbene; steric protection; theoretical calculation

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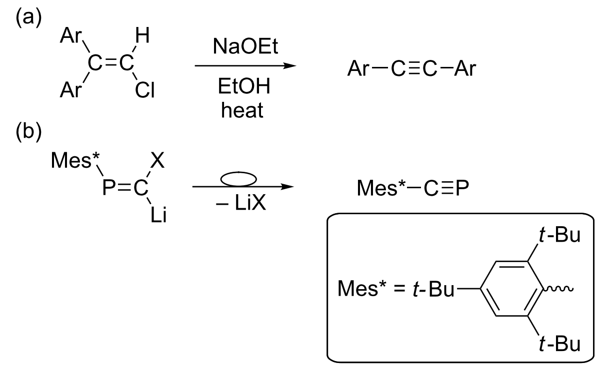
## Abstract

The intramolecular C–H insertion of the Mes*-substituted phosphanylidenecarbene [Mes*P=C:] (Mes* = 2,4,6-$t$-$Bu_3C_6H_2$) and physicochemical properties of the cyclized product, 6,8-di-*tert*-butyl-3,4-dihydro-4,4-dimethyl-1-phosphanaphthalene were studied based on ab initio calculations. Whereas the alternative Fritsch–Buttenberg–Wiechell-type rearrangement requires almost no activation energy, the intramolecular cyclization needs an activation energy of 12.3 kcal/mol at the MP2(full)/6-31G(d) condition. DFT calculations supported that the optimized structure of the cyclization product of Mes*P=C: suggests remarkable conjugation effects between the nearly coplanar P=C skeleton and the aryl moiety.

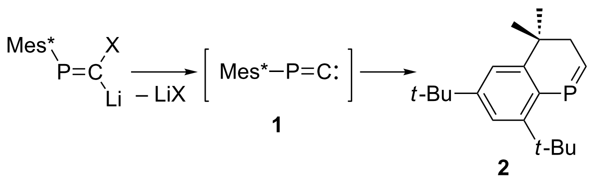
## Introduction

Sterically demanding groups on the phosphorus atom play an important role in the chemistry of low-coordinate phosphorus compounds and the supermesityl (Mes* = 2,4,6-tri-*tert*-butylphenyl) group was successfully applied to stabilize and characterize a diphosphene (Mes*P=PMes*) for the first time [1]. The effect of the Mes* group on the stabilization of various kinds of unusual phosphorus compounds has been clarified so far [2-4]. Phosphanylidenecarbene [RP=C:], a heavier congener of alkylidenecarbene (phosphaisonitrile) has been an intriguing reaction intermediate containing a low-coordinated phosphorus atom, and afforded a number of unique organophosphorus compounds [5,6]. The phosphorus version of Fritsch–Buttenberg–Wiechell (FBW) reaction [7-10] of Mes*P=C(X)Li (X = halogen, Mes* = 2,4,6-$t$-$Bu_3C_6H_2$) affording an air-stable phosphaalkyne Mes*C≡P is a typical example for understanding the chemistry of a phosphanylidenecarbenoid (Scheme 1) [11-13]. The phosphorus version of FBW rearrangement showed considerable stereospecificity in affording phosphaalkyne, which could be explicable by plausible reaction mechanisms including formation of the phosphavinyl anion intermediate without generation of phosphanylidenecarbene [10,14].



**Scheme 1:** (a) The original FBW rearrangement reaction and (b) the phosphorus version of FBW rearrangement.

As an alternative reaction of phosphanylidenecarbenoid, we have previously found the intramolecular cyclization reaction affording 6,8-di-*tert*-butyl-3,4-dihydro-4,4-dimethyl-1-phosphanaphthalene (**2**) putatively through formation of phosphanylidenecarbene **1** generated from Mes*P=C(Br)Li (Scheme 2) [15]. In contrast to the selective formation of Mes*C≡P from (*E*)-Mes*P=C(Cl)Li [11,12], facile removal of the bromide ion in Mes*P=C(Br)Li might be critical for the C–H insertion. The C–H insertion of carbene has been studied well [16], and thus intensive studies on the intramolecular cyclization of **1** would be necessary to develop the chemistry of reactive intermediates containing low-coordinated heavier main group elements [17]. Additionally, the structure of **2** is expected to be quite unique as the P=C π-system is nearly coplanar with the aromatic ring. In our previous paper, unique photo-absorption properties of **2** were discussed in comparison with the Mes*-substituted phosphaalkenes where the P=C and the Mes* aryl moieties are almost perpendicular [14].



**Scheme 2:** Intramolecular C–H insertion of phosphanylidenecarbene.

## Results and Discussion

In this paper we discuss the intramolecular cyclization of **1** and the structural aspects of **2** based on theoretical calculation data. Ab initio and DFT calculations were carried out with the Gaussian 09 program package [18].

Structures of **1** in the singlet state and **2** were optimized at the MP2(Full)/6-31G(d) level, and subsequently employed for calculation of the transition state. DFT methods were avoided in this calculation, as the Mes*–P–C angle was considerably bent at the level, such as B3LYP/6-31G(d) [14]. The bent structure optimized by the DFT method might reflect overestimation of the sp$^2$-type hybridization of the phosphorus atom because of the sterically encumbered Mes* group [19]. Figure 1 displays the DFT-optimized structure of the transition state (TS), and Figure 2 shows the energy profile of the cyclization process. Considerable elongation of the C–H bond of the corresponding methyl group has been characterized, whereas the P=C length was found comparable to that in **1** (vide infra). The optimized activation energy ($\Delta E_a$) was 12.3 kcal/mol, and the Gibbs free energy $\Delta G$ was estimated as 11.6 kcal/mol. Such energy profile indicates a sharp contrast to the modeled FBW rearrangement of phosphanylidenecarbene requiring no activation energy [20], and would be partially explicable for the experimental result that the phosphanylidenecarbenoid [Mes*P=C(Br)Li] afforded both phosphaalkyne [Mes*C≡P] and **2** [15]. The single imaginary frequency was optimized for the transition state (Figure 3).

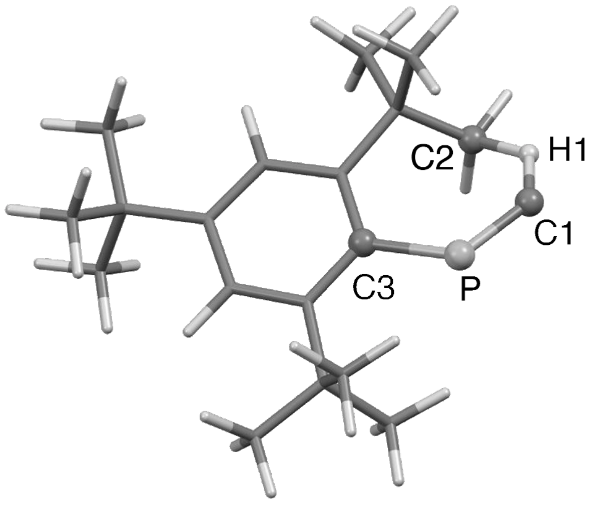


**Figure 1:** Optimized structure of the transition state (TS) for the intramolecular C–H insertion of **1** [MP2(Full)/6-31G(d)]. Bond lengths (Å): P–C1 1.660, C1–H1 1.228, C2–H1 1.281, P–C3 1.865.

Figure 4 displays the optimized structure of **2** [MP2(full)/6-31G(d)]. Relative energy ($E_{\mathrm{rel}}$) and Gibbs free energy ($G$) of **2** to **1** were determined as 95.0 kcal/mol and 91.5 kcal/mol, respectively. Whereas the P1–C1 distance is typical for phosphaalkenes [21], dihedral angle of the P=C and almost planar benzene ring is close to co-planar due to the fused 6-membered

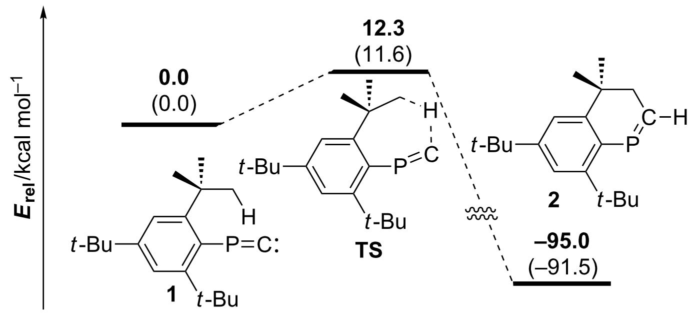


**Figure 2:** Computationally characterized cyclization procedures of **1** affording **2** [MP2(full)/6-31G(d)]. Values in boldface correspond to relative energies (kcal/mol). Values in parentheses display Gibbs free energies (*G*, kcal/mol at 298.15 K).

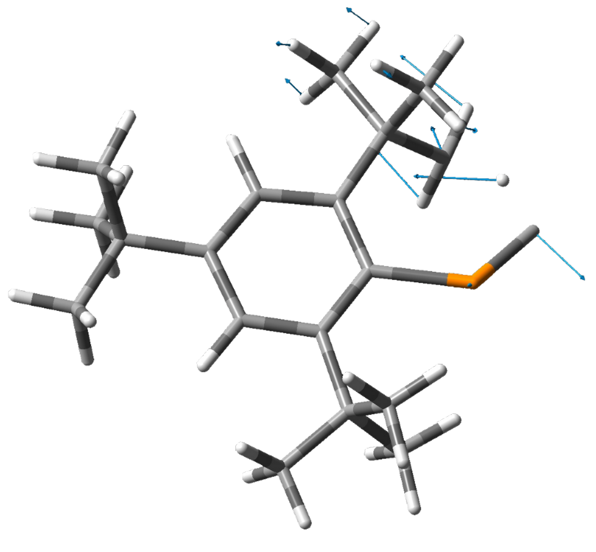


**Figure 3:** Displacement vectors of the transition state (ν = 216.93 *i* cm$^{-1}$).

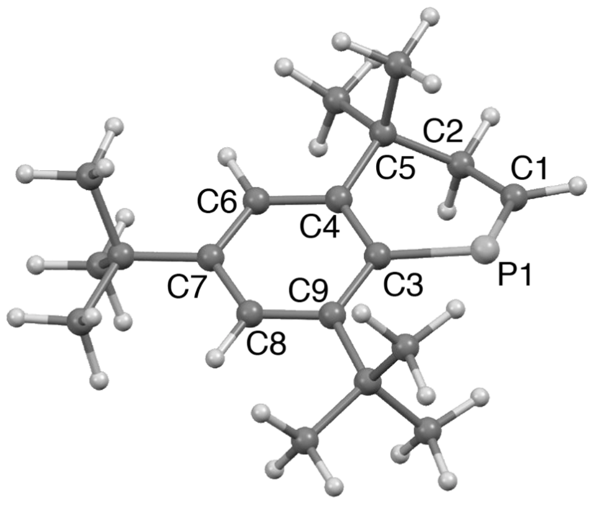


**Figure 4:** Optimized structure of **2** [MP2(full)/6-31G(d)]. Bond distances (Å): P1–C1 1.678, C1–C2 1.491, P1–C3 1.840, C2–C5 1.534, C3–C4 1.424, C4–C5 1.530, C4–C6 1.396, C6–C7 1.394 C7–C8 1.393, C8–C9 1.403, C3–C9 1.427. Bond angle and dihedral angles (°): C3–P1–C1 101.7, C1–P1–C3–C4 22.9, C1–P1–C3–C9 160.1.

ring [τ(C1–P1–C3–C4] = 22.9°, τ(C1–P1–C3–C9) = 160.1°]. Steric encumbrance causes elongation of the C–C bonds of C3–C4 and C8–C9.

Except for such as phosphinines (or phosphabenzenes), **2** would be one of key compounds that are available for understanding the conjugation effect between the heavier π-system and the aromatic moiety. The P=C skeleton of **2** would interact with the nearly coplanar benzene ring, and indeed, the UV absorption spectra exhibited a large absorption coefficient in comparison with the Mes*-substituted phosphaalkene. The HOMO and LUMO orbitals of **2** indicate remarkable contribution of the benzene ring for conjugation with the P=C π-system (Figure 5). The TD-SCF calculation of **2** using CAM-B3LYP/DGDZVP conditions characterized the HOMO–LUMO transition at 289 nm with a relatively large absorption coefficient (*f* = 0.162). On the other hand, the absorption maximum of **2** was slightly blue-shifted in comparison with that of the Mes*-substituted phosphaalkenes, which corresponded the TD-SCF calculation of Mes*P=CH$_2$ determining absorption at 292 nm. In the case of Mes*P=CH$_2$, the HOMO orbital is composed of the lone pair of the phosphorus, which corresponds to the weak absorption (*f* = 0.0139) [15] (see also Supporting Information File 1).

## Conclusion

In conclusion, the chemistry of the intramolecular C–H insertion of phosphanylidenecarbene **1** affording **2** was studied by ab initio and DFT calculations. The intramolecular cyclization

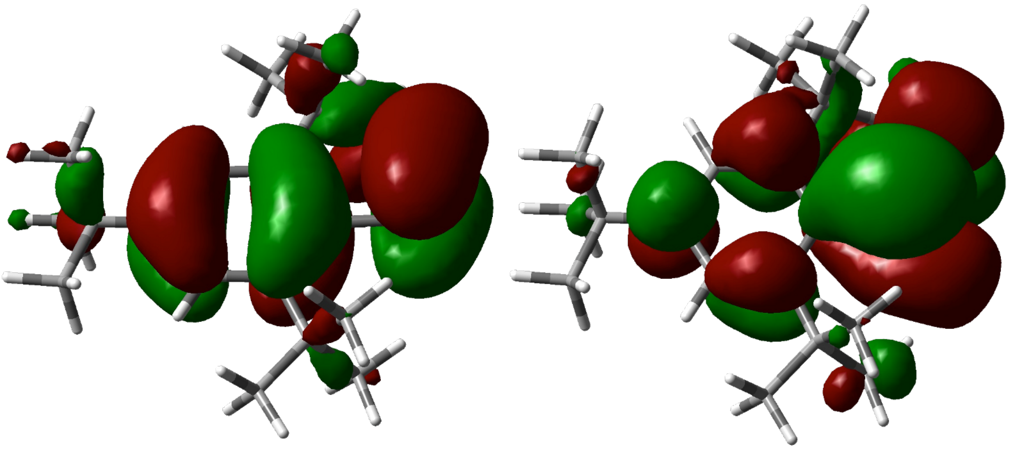


**Figure 5:** HOMO (left) and LUMO (right) of **2**.

requires an activation energy, whereas the phosphorus version of the FBW rearrangement proceeded without an energetic barrier. The optimized structure of **2** indicates the possible conjugation between the P=C π-system and aromatic substituent, which induces remarkably different physicochemical properties for the Mes*-substituted phosphaalkenes, where the P=C moiety is almost perpendicular to the aromatic plane.

## Supporting Information

### Supporting Information File 1

UV Spectra for **2** and Mes*P=C(H)Me and MO for **2** and Mes*P=$CH_2$.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-103-S1.pdf]

### Supporting Information File 2

Calculation data for **1**, **TS**, **2**, Mes*P=$CH_2$ and [MeP=C:].
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-103-S2.pdf]

## Acknowledgements

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# Preparation of phosphines through C–P bond formation

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Review

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## Abstract

Phosphines are an important class of ligands in the field of metal-catalysis. This has spurred the development of new routes toward functionalized phosphines. Some of the most important C–P bond formation strategies were reviewed and organized according to the hybridization of carbon in the newly formed C–P bond.

## Introduction

Phosphines are an important class of organophosphorus compounds. They are often used as ligands in metal complex catalysis and they have become a popular reagent for organocatalysis [1]. The methods most widely used for the synthesis of phosphines include the reaction of organometallic compounds with halophosphines, the reaction of metal phosphides with alkyl halides, the reduction of other phosphorus compounds and the hydrophosphination [2]. Research in the past years has focused on the catalytic synthesis of phosphines [3,4]. The asymmetric catalytic synthesis of chiral phosphines has only recently emerged and is under full development. Chiral phosphines are interesting ligands for the preparation of transition metal complex catalysts for asymmetric synthesis [5,6]. Only a minor part of the chiral phosphines are chiral at the phosphorus atom (*P*-stereogenic) [7-9].

A major drawback of phosphines is their highly oxidizable nature. They are easily converted to the corresponding phosphine oxide which makes the isolation difficult. To prevent losses during purification, the phosphines are sometimes deliberately transformed into the corresponding oxides (or sulfides). However, this requires an additional reduction step afterwards to get the phosphine back [10-15]. Therefore phosphines are sometimes protected by generation of the corresponding phosphine–borane complex [16,17]. The phosphine–borane complex is a stable intermediate toward the free phosphine. If necessary the boranato group can be removed by treatment with an excess of amine [18]. However, not all phosphines are prone to oxidation and show good air-stability [19].

This review will provide a general overview on phosphine synthesis over the last 10 to 15 years. Only reactions establishing a C–P bond will be discussed. The synthesis of phosphine-based polymers was not included [20]. Reactions involving pentavalent phosphorus derivatives (phosphine oxides, phosphonates, phosphinates and phosphate derivatives, etc.) are out of the scope of this review.

# Review

## Preparation of alkylphosphines via formation of a C(sp$^3$)–P bond

### Reaction of organometallic reagents with halophosphines

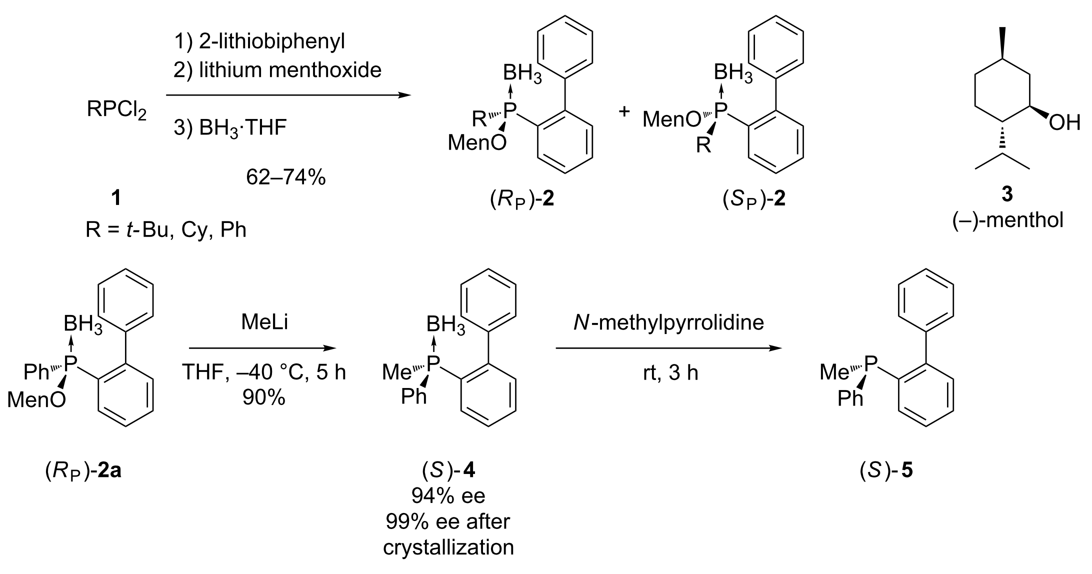
One of the main approaches to synthesize a carbon–phosphorus bond involves the displacement of a halogen atom from phosphorus by an organometallic reagent. This method has proven its usefulness for many years. A variety of organometallic compounds have been described. Most frequently used are the Grignard [21,22] and lithium species. But also organozinc [23,24], organolead [25], organomercury [26] or aluminum-based [27] reagents have been used. However, nowadays it is recommended to avoid the use of certain reagents such as organomercury or organolead compounds as they pose a serious toxicological hazard [28,29].

Despite the fact that the methodology is historically useful it also has major drawbacks. The presence of an anionic carbon reagent in the reaction restricts the scope of the methodology. The aspired phosphines cannot contain certain functional groups that are able to react with the organometallic compound. Further, stoichiometric amounts of reagents are required. Also, attention should be paid to the handling of halophosphines as some of the simple alkyldichlorophosphines are extremely corrosive and flammable in air.

Asymmetric phosphines are difficult to access via a nucleophilic substitution at a halophosphine due to the limited availability of unsymmetrical halophosphines and their weak configurational stability. *P*-stereogenic chlorophosphines racemize easily even at room temperature [30].

Enantiopure *P*-stereogenic compounds can be synthesized via a diastereoselective nucleophilic substitution at phosphorus utilizing chiral auxiliaries. Diastereomeric intermediates are formed that are separable by chromatography or recrystallization. The protocol has proven to be effective and has become the preferred approach for the synthesis of chiral phosphines. Commonly used chiral auxiliaries are chiral secondary alcohols (for example (−)-menthol (**3**), *endo*-borneol, etc.) or thiols that are reacted with halophosphines [31-34].

The diastereoisomers of menthylphosphinite boranes are popular synthetic intermediates for this approach (Scheme 1) [35]. The diastereomeric phosphinites **2**, that were prepared from an alkyldichlorophosphine **1**, were separated by preparative HPLC or recrystallization. Nucleophilic substitution of pure diastereomer ($R_P$)-**2a** with methyllithium afforded the phosphine–borane (*S*)-**4** with 94% enantiomeric excess. The substi-

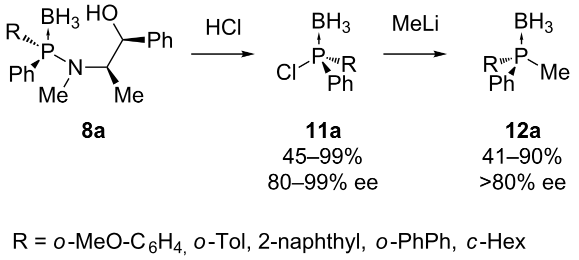


**Scheme 1:** Synthesis of *P*-stereogenic phosphines **5** using menthylphosphinite borane diastereomers **2**.

tution resulted in inversion of the configuration at the phosphorus center. Deboranation of the air stable borane adduct (*S*)-**4** to obtain **5**, was achieved by treatment with *N*-methylpyrrolidine.

An alternative method is based on ephedrine as a chiral auxiliary and was developed by Genêt and Jugé [36,37]. The key synthetic intermediates in this approach are 1,3,2-oxazaphospholidine boranes **7**. These compounds are the result of the reaction between bis(diethylamino)alkylphosphine **6** and ephedrine, followed by protection with borane. The subsequent stereoselective ring opening of compound **7** with an organolithium reagent gives way to acyclic products **8** with retention of configuration at the phosphorus center. These phosphamide boranes **8** undergo methanolysis with inversion of configuration to produce intermediate phosphinite boranes **9** that are subsequently substituted with a second nucleophile. A following deprotection of the boranato group gives the chiral phosphines **10**. Both enantiomers can be obtained by preparation of different starting oxazaphospholidine borane complexes **7** from (−)-ephedrine or (+)-ephedrine [38] or by starting from the same oxazaphospholidine borane adduct **7** and then changing the order of addition of the organolithium reagents (Scheme 2).

Acidolysis with HCl of compounds **8a** results in the stereoselective synthesis of chiral chlorophosphine boranes **11a** [39]. The borane complex has a good configurational stability with borane as a protecting group, in contrast to chlorophosphines that can undergo inversion at the phosphorus center [30]. They allow the synthesis of a variety of *P*-chiral tertiary phosphine boranes **12a** via substitution of the chlorine atom with organometallic nucleophiles. This substitution causes an inversion of configuration at the phosphorus center (Scheme 3). Schuman et al. have prepared several dialkenylphosphines using this methodology [40].



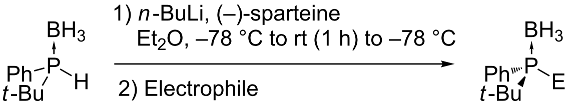
**Scheme 3:** Chlorophosphine boranes **11a** as *P*-chirogenic electrophilic building blocks.

## Nucleophilic substitution with metallated organophosphines

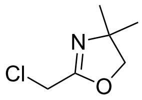
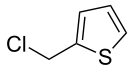
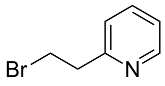
Another classical method for the preparation of phosphines is the nucleophilic substitution of alkyl halides with phosphide anions derived from secondary phosphines or phosphine–borane complexes [41]. This approach requires stoichiometric amounts of base. Numerous examples of this approach are available [22,42-48].

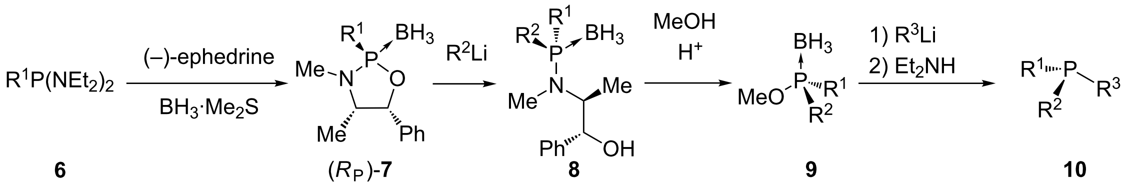
In recent years methodologies were developed for the asymmetric alkylation. Livinghouse and Wolfe have reported an enantioselective method for the preparation of chiral tertiary phosphine–boranes starting from a racemic secondary phosphine borane precursor such as **13a** (Table 1) [49]. A nucleophilic phosphide reagent was prepared by deprotonation of **13a**

**Table 1:** Alkylations of dynamically resolved *tert*-butylphenylphosphine borane **13a**.



**13a** **14a**

| Entry | Electrophile | Yields of **14a** (%) | ee of **14a** (%) |
|---|---|---|---|
| 1 |  | 90 | >82 |
| 2 |  | 85 | 95 |
| 3 |  | 90 | 92 |



**Scheme 2:** Enantioselective synthesis of chiral phosphines **10** with ephedrine as a chiral auxiliary.

in the presence of (−)-sparteine. The subsequent alkylation of the lithium phosphide with an electrophile proceeded with good enantiocontrol via dynamic resolution. One enantiomer is thermodynamically favored by the spartein auxiliary. The enantioselectivity was found to be time and temperature dependent. Simple stirring of the intermediate (−)-sparteine–lithium complex of **13a** for 1 h at 25 °C prior to alkylation resulted in an increase in enantiomeric excess of **14a**.

The organocatalyst **16** has also been used to carry out an asymmetric alkylation reaction (Scheme 4). The monoalkylation of phosphine–borane complex **15** was performed in the presence of the *Cinchona* alkaloid ammonium salt **16** [50]. However, the enantioselectivity of the reaction was low.

Imamoto et al. prepared a new tetraphosphine ligand **19** by deprotonation of enantiopure secondary diphosphine borane **17** at low temperature (Scheme 5) [51]. The configuration was retained during the nucleophilic attack at **18**. This approach provides a very straightforward access to *P*-stereogenic tertiary phosphines but requires the availability of *P*-chiral substrates.

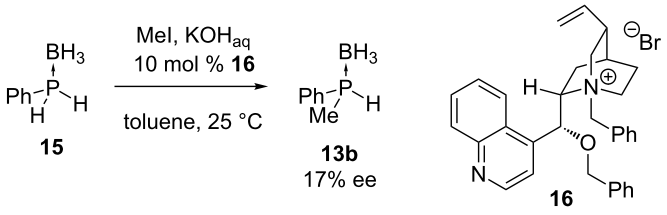
Jugé and co-workers synthesized chiral tertiary phosphine–borane complexes **12b** starting from *P*-stereogenic chlorophosphine–borane complexes **11b** (Scheme 6) [52]. These complexes are accessible with the ephedrine methodology (vide supra). Treatment of **11b** with *t*-butyllithium leads to metal–halogen exchange. After reaction of the phosphide anion **20** with an electrophile, the chiral tertiary phosphine boranes **12b** are formed with retention of configuration at the phosphorus atom.

## Catalytic C($sp^3$)–P bond formation

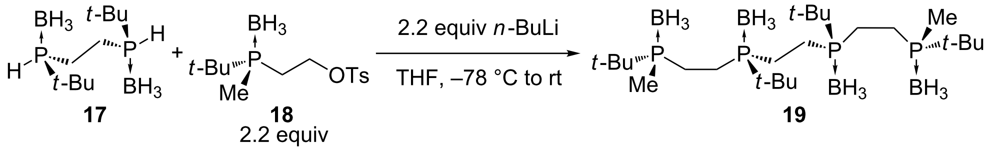
Only a few examples of a metal catalyzed C($sp^3$)–P cross-coupling exist and they are mostly restricted to benzylic and allylic coupling partners.

Ager and Laneman have synthesized tertiary phosphine oxide **23** through the nickel-catalyzed coupling of benzyl bromide (**21a**) with diphenylphosphine chloride (**22a**) (Scheme 7) [53]. However oxidation occurred during work-up.

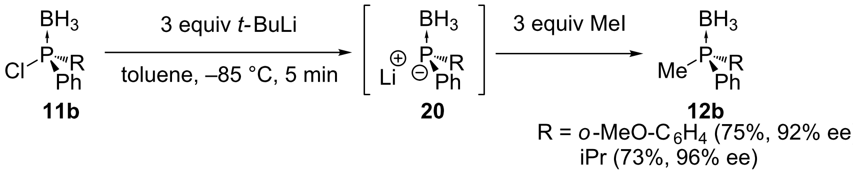
The group of Togni has investigated a palladium-catalyzed enantioselective coupling reaction between allylic substrates **24** and several secondary phosphines **25a** as nucleophiles [54]. The scope of the reaction was limited to 1,3-diphenylallyl acetate **24**. The reaction produced not only **26**, but gave several side products **27**–**29** (Table 2).



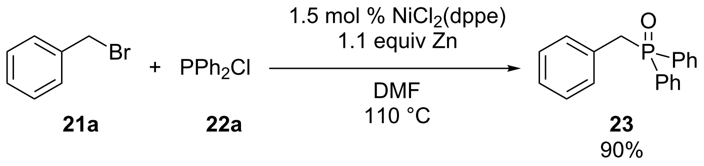
**Scheme 4:** Monoalkylation of phenylphosphine borane **15** with methyl iodide in the presence of *Cinchona* alkaloid-derived catalyst **16**.



**Scheme 5:** Preparation of tetraphosphine borane **19**.

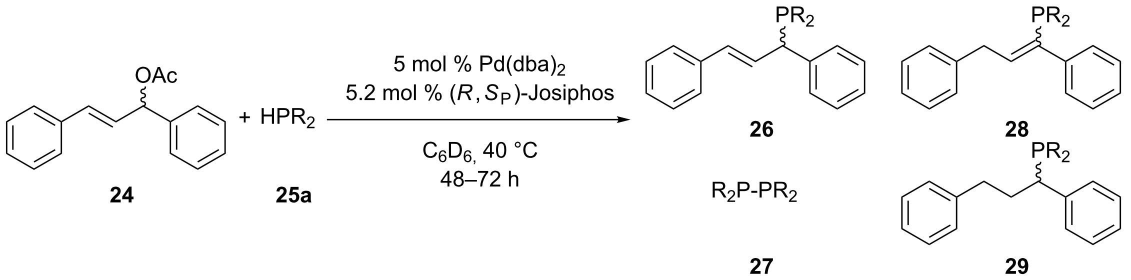


**Scheme 6:** Using chiral chlorophosphine-boranes **11b** as phosphide borane **20** precursors.



**Scheme 7:** Nickel-catalyzed cross-coupling (dppe = 1,2-bis(diphenylphosphino)ethane).

**Table 2:** Palladium-catalyzed asymmetric allylic phosphination (dba = dibenzylideneacetone).

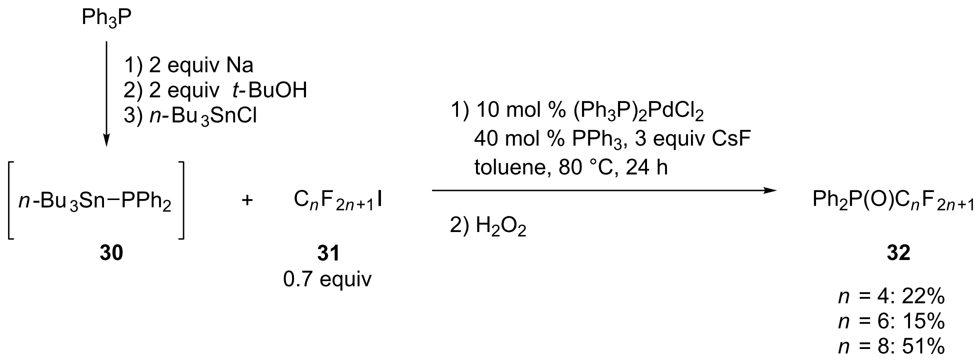


| Entry | R | **26**:**27**:**28**:**29** (%) | Yield of **26** (%) | ee of **26**(%) |
|---|---|---|---|---|
| 1 | Ph | 89:11:0:0 | 79 | 96 |
| 2 | Cy | 65:28:6:1 | 44 | 45 |
| 3 | 2-naphthyl | 91:6:1:2 | 85 | 83 |
| 4 | *o*-Tol | 88:8:2:2 | 82 | 42 |

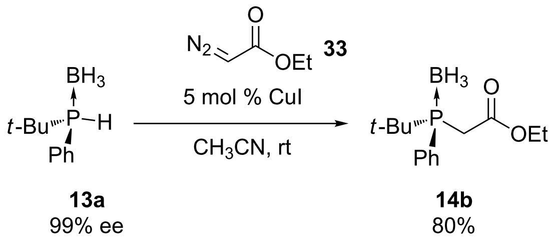
Another example of a C($sp^3$)–P cross-coupling was reported by Lanteri et al. [55]. A palladium catalyst effectuated the coupling of $n$-$Bu_3SnPPh_2$ (**30**) with several perfluoroalkyl iodides **31** (Scheme 8). The stannane **30** was in situ generated by the reaction of the diphenylphosphide anion with $n$-$Bu_3SnCl$. After oxidation, the perfluoroalkyl-substituted phosphine oxides **32** were obtained in low to moderate yields (15–51%) although full conversion was observed. The byproduct formed was reduced perfluoroalkane $HC_nF_{2n+1}$.

Ethyl diazoacetate (**33**) was reacted with the secondary phosphine borane **13a** in the presence of a copper catalyst [56]. The product **14b** was obtained in good yield with retention of configuration at the phosphorus center (Scheme 9). Other chiral phosphine boranes **13** were reacted similarly. This protocol is limited to the availability of these chiral substrates.

Protocols for the enantioselective cross-coupling of benzyl or alkyl halides with racemic secondary phosphines have been

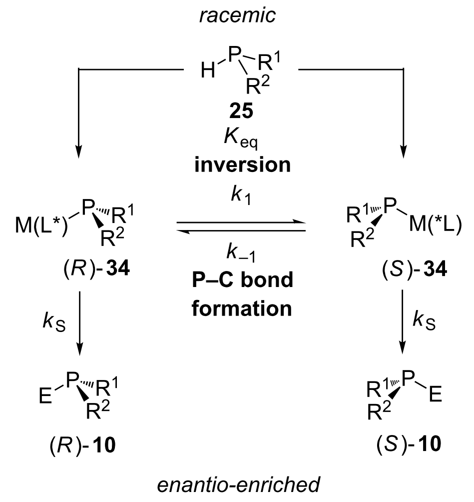


**Scheme 8:** Pd-catalyzed cross-coupling reaction with organophosphorus stannanes **30**.



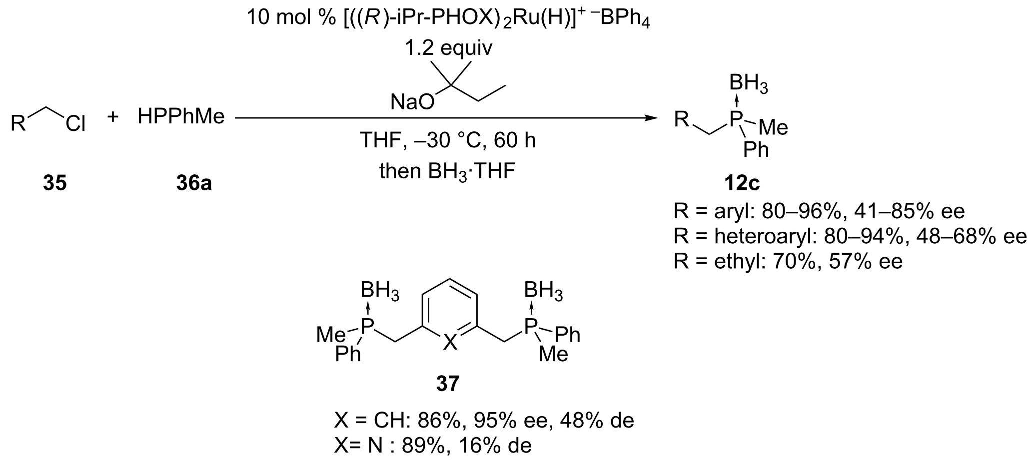
**Scheme 9:** Copper iodide catalyzed carbon–phosphorus bond formation.

developed. These reactions were catalyzed by chiral platinum or ruthenium complexes. The enantioselectivity is based on a dynamic kinetic resolution. Upon reaction with the catalyst precursor containing a chiral ligand (L*), a diastereomeric metal–phosphido complex **34** is formed. Rapid pyramidal inversion of this key catalytic intermediate **34** occurs. This complex performs a nucleophilic attack on the electrophile resulting in tertiary phosphines **10**, in which the substituent ‘E’ comes from the electrophile. If the inversion of the diastereomers **34** is much faster than their reactions with an electrophile, *P*-stereogenic phosphines **10** are formed enantioselectively. The ratio of phosphine end products **10** is determined by the equilibrium ($K_{eq}$) between the complexes **34** and the rate of nucleophilic attack ($k_S$ and $k_R$) on the electrophile. The enantioselectivity of the end products **10** is related to the ratio of the diastereomeric phosphido complexes **34**. The major phosphine product is derived from the major diastereomeric phosphido complex. The dynamic kinetic resolution approach has been reviewed in more detail by Glueck [57,58]. Scheme 10 relates to reactions of secondary phosphines with several electrophiles, including alkyl halides (alkylation), alkenes (hydrophosphination) and aryl iodides (arylation).



**Scheme 10:** Thermodynamic kinetic resolution as the origin of enantioselectivity in metal-catalyzed asymmetric synthesis of *P*-stereogenic phosphines.

Chan et al. synthesized *P*-stereogenic phosphine boranes using a ruthenium catalyst. The secondary phosphine **36a** underwent an enantioselective alkylation to **12c** (Scheme 11). The mechanism of the reaction is based on the formation of an electron-rich ruthenium–phosphido complex that enhances the nucleophilicity at the phosphorus atom. This permitted the reaction to proceed with the less electrophilic benzylic chlorides **35** instead of bromides. The metal-catalyzed reaction was faster than the achiral base-mediated alkylation of **36a**. Bisphosphines **37** were also reported with high enantiomeric excesses. The procedure is mainly restricted to benzylic halides but also allowed for the asymmetric alkylation with ethyl bromide. All the phosphines were isolated as their air-stable phosphine–borane complexes **12c**, **37** [59,60].



R = aryl: 80–96%, 41–85% ee
R = heteroaryl: 80–94%, 48–68% ee
R = ethyl: 70%, 57% ee

X = CH: 86%, 95% ee, 48% de
X= N : 89%, 16% de

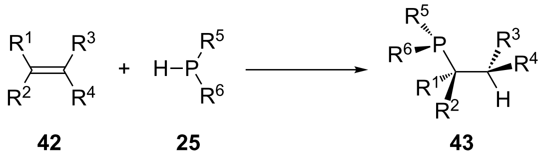
**Scheme 11:** Ru-catalyzed asymmetric phosphination of benzyl and alkyl chlorides **35** with HPPhMe (**36a**, PHOX = phosphinooxazoline).

The group of Glueck has reported a method for the asymmetric alkylation of racemic secondary phosphines **36b** by means of a chiral platinum-based catalyst **39** (Scheme 12) [61]. The enhanced nucleophilicity at phosphorus of the platinum–phosphido intermediate was beneficial for the alkylation. The scope of the reaction was investigated using diverse benzylic bromides **22b** and secondary phosphines **36b**. Bidentate ligands **40** and **41** were also synthesized [61,62]. This procedure was also restricted to benzylic halides. High enantiomeric excesses were reported. As expected, a mechanistic study suggested that the major enantiomer of product was formed from the major diastereomer of the platinum–phosphido intermediate [63]. Glueck and co-workers also developed an analogous method for the tandem alkylation/arylation of primary phosphines on the basis of a platinum catalyst resulting in several enantio-enriched phosphaacenaphtalenes [64].

## Hydrophosphination

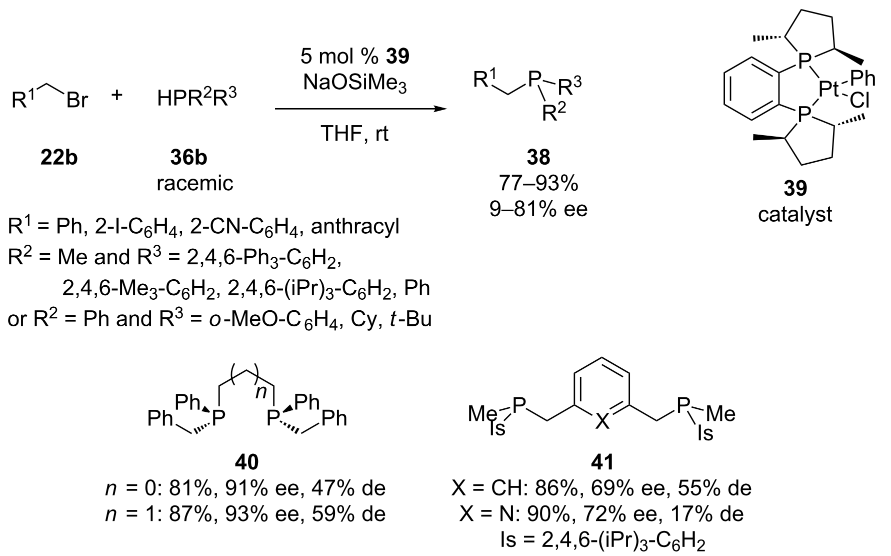
Hydrophosphination involves the addition of P–H to an unsaturated C–C bond. In this reaction phosphines, silylphosphines [65,66] or phosphine–borane complexes are used as phosphinating agents to react with unactivated or activated alkenes, dienes and alkynes. Hydrophosphination has gained much interest as an alternative to the classical phosphine syntheses involving a substitution that is incompatible with certain functional groups. Moreover the addition of P–H to an unsaturated C–C bond is more efficient than substitution reactions when considering atom efficiency, what makes it not only greener but also more economical. Other phosphination reactions of unsaturated bonds, such as diphosphination, thiophosphination or selenophosphination, were not included [67].

Depending on the regioselectivity of the reaction, the addition of P–H to the unsaturated bond results in the formation of different products **43** (Scheme 13). The product that results from the Markovnikov addition of P–H corresponds to the α-adduct and the anti-Markovnikov addition is referred to as the β-adduct. The stereoselectivity of the method determines the conformation at the newly formed chiral centers.



**Scheme 13:** Different adducts **43** can result from hydrophosphination.

The hydrophosphination typically proceeds via thermal [68,69], radical, acidic [70-72] or basic [73,74] initiation. Radical addition of secondary phosphines to alkenes can be accomplished by thermal activation [75,76], through the use of radical initiators (AIBN) [77-82] or photochemically by irradiation with UV or visible light [22,83-85]. Most of these reactions give anti-Markovnikov products. The hydrophosphination of activated alkenes (e.g., Michael acceptors) has also been shown to take place at room temperature in the absence of a catalyst [86,87] and even under solvent-free conditions [88]. More recently also metal complex-assisted or organocatalyzed hydrophosphinations have been reported. Several reviews focusing on hydrophosphination have been pusblished [89-91].



$R^1$ = Ph, 2-I-$C_6H_4$, 2-CN-$C_6H_4$, anthracyl
$R^2$ = Me and $R^3$ = 2,4,6-$Ph_3$-$C_6H_2$,
2,4,6-$Me_3$-$C_6H_2$, 2,4,6-$(iPr)_3$-$C_6H_2$, Ph
or $R^2$ = Ph and $R^3$ = *o*-MeO-$C_6H_4$, Cy, *t*-Bu

*n* = 0: 81%, 91% ee, 47% de
*n* = 1: 87%, 93% ee, 59% de

X = CH: 86%, 69% ee, 55% de
X = N: 90%, 72% ee, 17% de
Is = 2,4,6-$(iPr)_3$-$C_6H_2$

**Scheme 12:** Pt-catalyzed asymmetric alkylation of secondary phosphines **36b**.

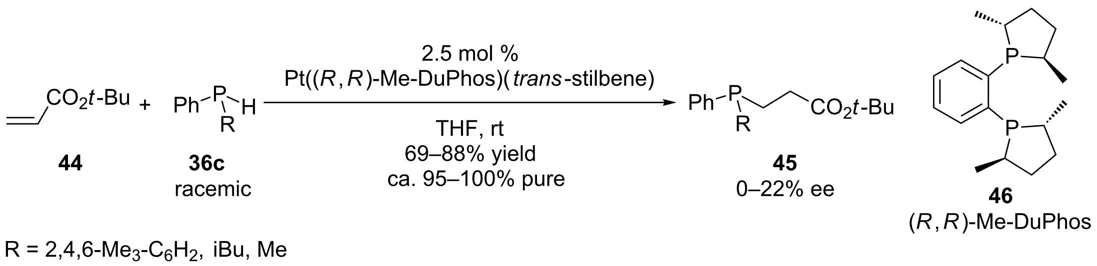
In recent years a lot of progress has been made in the metal complex-catalyzed hydrophosphination. It was shown that several metals can function as catalysts for the inter- and intramolecular addition of $PH_3$ and $R_2PH$ to alkenes. Most research has focused on the use of platinum [92-96], palladium [97-99] or nickel [100-104] complexes. Other catalysts that have been less investigated are iron [105-107], rhodium [108-110], lanthanides [111-114], copper [115] and alkaline-earth metals [114,116]. The catalyst activates either the P-nucleophile or the C-electrophile.

Chiral phosphines have attracted more and more interest since they are employed as ligands in transition metal complexes to perform asymmetric catalysis [117]. Enantiopure phosphines have mostly been prepared by starting from enantiopure products or by resolution. The methodologies for catalytic asymmetric hydrophosphination of olefins are limited. Chiral metal complexes have been used to promote and control the asymmetric P–H addition reaction. Recent reviews covering the asymmetric hydrophosphination reaction catalyzed by metal catalysts have been published by Glueck [118,119] and Pullarkat and Leung [120]. Some recent developments in the asymmetric catalytic hydrophosphination will be discussed.

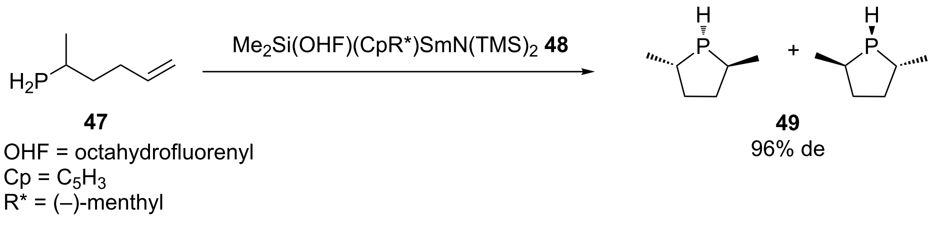
The group of Glueck reported on an approach to chiral phosphines by the addition of secondary phosphines **36c** to Michael acceptor alkenes (acrylonitrile or derivatives and acrylate esters **44**) in the presence of Pt((*R*,*R*)-Me-DuPhos) complexes (Scheme 14). However, the products **45** suffered from low enantioselectivities [121]. The mode of action is based on the activation of the P-nucleophile. The proposed mechanism includes the P–H oxidative addition to platinum giving a platinum–phosphido complex. Subsequent nucleophilic attack on a Michael acceptor alkene was suggested to lead to a zwitterion intermediate. Addition of a protic additive was beneficial for the selectivity and reaction rate [95].

Several chiral cyclic phosphines were acquired via the lanthanide catalyzed intramolecular hydrophosphination of phosphinoalkenes. Scheme 15 shows the diastereoselective synthesis of 2,5-dimethylphospholanes **49** from **47** with a lanthanide catalyst **48** [122]. The common mechanism when using lanthanide [113] or alkaline earth metal [123] catalysts is based on the formation of a phosphido–metal complex that undergoes insertion of the olefin. Protonolysis of the metal–alkyl complex via σ-bond metathesis with the phosphine reagent completes the catalytic cycle giving the product and regenerating the phosphido intermediate.

The group of Togni has developed an enantioenriched hydrophosphination of vinyl nitriles catalyzed by a dicationic nickel complex (Table 3). The method is based on the activation of the electrophile. It was suggested that complexation of the nitrile **50** to the chiral nickel Lewis acid activates the double bond towards 1,4-addition of the phosphine **25b**. A final proton transfer yields the phosphine product **51** [124,125].

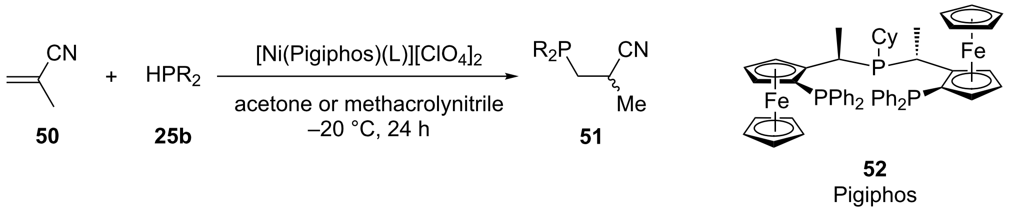


**Scheme 14:** Pt-catalyzed asymmetric hydrophosphination.



**Scheme 15:** Intramolecular hydrophosphination of phosphinoalkene **47**.

**Table 3:** Ni-catalyzed asymmetric hydrophosphination of methacrylonitrile **50**.

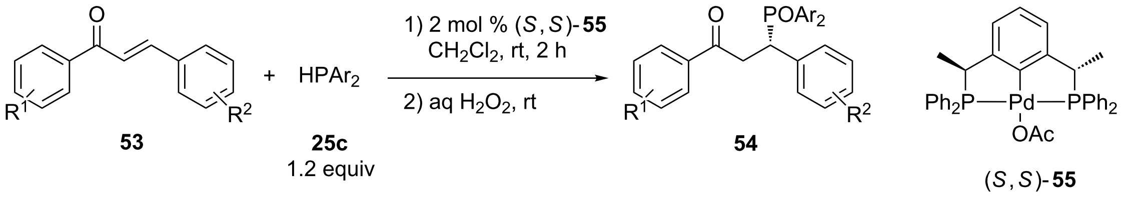


| Entry | R | Yield of **51** (%) | ee of **51** (%) |
|---|---|---|---|
| 1 | Ph | 10 | 32 |
| 2 | Cy | 71 | 70 |
| 3 | iPr | not isolated | 78 |
| 4 | Ad | 95 | 94 |
| 5 | *t*-Bu | 97 | 89 |
| 6 | EtMe$_2$C- | 86 | 90 |

A chiral Pincer-palladium complex **55** has been used for the addition of diarylphosphines **25c** to enones **53** (Table 4) [126]. Several enones **53**, having electron-donating or -withdrawing groups on the aromatic ring, reacted with a variety of electron-rich and -poor diarylphosphines **25c**. The chiral phosphine oxides **54** were obtained in high yield with excellent stereoselectivities. In the proposed mechanism the catalyst **55** acts as a base toward the diarylphosphine **25c**. Some other examples of palladium-catalyzed asymmetric hydrophosphination are the addition of diphenylphosphine to α,β-unsaturated ketones [127,128], esters [129], sulfonic esters [130] or to dienones [131]. The proposed mechanism is ubiquitous in metal-catalyzed hydrophosphination involving a P–H oxidative addition, insertion of the olefin into the Pd–H bond and reductive elimination.

In 2007 several papers appeared reporting on organocatalyzed asymmetric hydrophosphinations. The organocatalytic process

**Table 4:** Palladium-catalyzed asymmetric addition of diarylphosphines **25c** to enones **53**.



| Entry | R$^1$ | R$^2$ | Ar | Yield of **54** (%) | ee of **54** (%) |
|---|---|---|---|---|---|
| 1 | H | H | Ph | 93 | 99 |
| 2 | *p*-Br- | H | Ph | 89 | 99 |
| 3 | *p*-MeO- | H | Ph | 75 | 98 |
| 4 | *m*-Br- | H | Ph | 93 | 97 |
| 5 | *p*-NO$_2$- | H | Ph | 78 | 95 |
| 6 | H | *p*-Br- | Ph | 90 | 98 |
| 7 | H | *p*-NO$_2$- | Ph | 88 | 99 |
| 8 | H | *m*-Br- | Ph | 90 | 99 |
| 9 | H | *o*-MeO- | Ph | 69 | 90 |
| 10 | H | *p*-Me- | Ph | 63 | 90 |
| 11 | H | H | *p*-MeO-C$_6$H$_4$ | 86 | 94 |
| 12 | H | H | *p*-Cl-C$_6$H$_4$ | 92 | 96 |

has the advantage that in contrast to a metal-catalyzed method, it cannot undergo product inhibition as a result of the coordination ability of phosphorus to a metal catalyst.

The addition of diphenylphosphine to a range of nitroalkenes **56** has been described using a bifuntional *Cinchona* alkoid/thiourea catalyst **58** [132]. The catalyst **58** is able to simultaneously activate both the electrophilic and nucleophilic reagents. On one hand the thiourea presumably binds the nitro group while on the other hand the tertiary amine enables proton transfer from phosphorus to carbon (Table 5).

The organocatalyzed hydrophosphination of α,β-unsaturated aldehydes has been described by Carlone et al. [133] and Ibrahem et al. [134]. The method is based on activation of the aldehyde **59** via iminium-ion formation by reaction with chiral pyrrolidine **62** derivatives and acid (Scheme 16). Subsequent treatment with sodium borohydride forms the air-stable phosphine–borane product and also reduces the aldehyde. The method gives compounds **61** in high yields and enantioselectivities (ee up to 99%) for α,β-unsaturated aldehydes containing either aliphatic or aromatic groups.

## Preparation of alkenylphosphines via formation of a C($sp^2$)–P bond

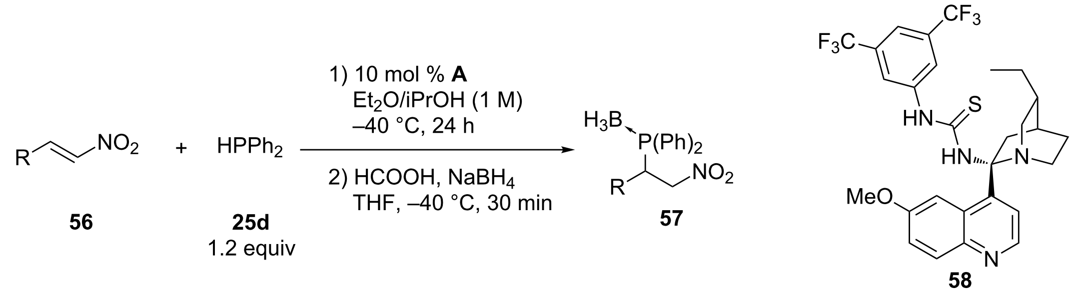
The C($sp^2$)–P bond formation is reviewed for arylic and vinylic phosphines. The group of Gaumont has provided a recent review (2010) on the main synthetic methods to obtain alkenylphosphines [135].

### Reaction of organometallic reagents with halophosphines

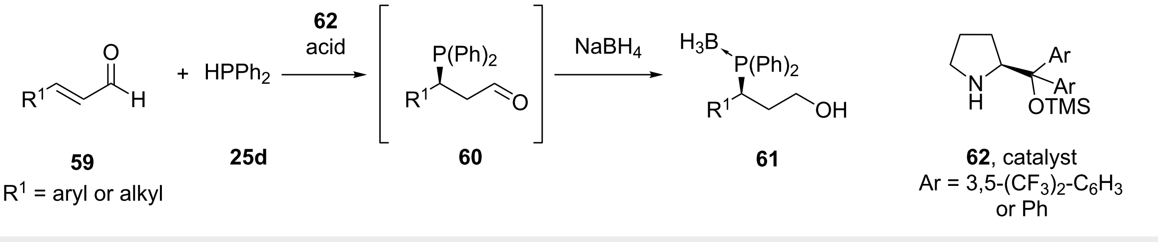
The reaction of an organometallic reagent with the P-atom of halophosphines is a classical method used for the synthesis of both alkenyl- and arylphosphines. The organometallic reagents are mostly Grignard reagents [136-138] or organolithium [139-142] derivatives. Other organometallic reagents such as aluminum [143] or organomercury [26,144] reagents have been used less frequently.

Grignard or organolithium compounds are highly reactive nucleophiles and do not tolerate the presence of various functional groups. As a consequence, new approaches were developed including zinc, zirconium and copper reagents.

**Table 5:** Organocatalytic asymmetric hydrophosphination of nitroalkenes **56**.



| Entry | R | Yield of **57** (%) | ee of **57** (%) | After crystallizaton<br>Yield of **57** (%) | After crystallizaton<br>ee of **57** (%) |
|---|---|---|---|---|---|
| 1 | Ph- | 86 | 67 | 36 | 99 |
| 2 | *p*-Me-$C_6H_4$- | 67 | 52 | | |
| 3 | *o*-F-$C_6H_4$- | 83 | 45 | 24 | 99 |
| 4 | *o*-BnO-$C_6H_4$- | 90 | 60 | 37 | 99 |



**Scheme 16:** Organocatalytic asymmetric hydrophosphination of α,β-unsaturated aldehydes **59**.

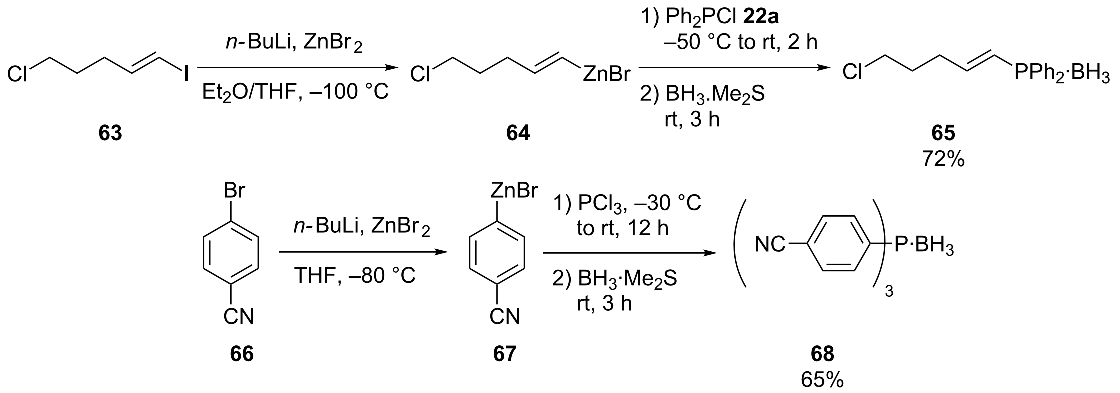
Polyfunctional alkenylphosphine **65** was accessible via the reaction of organozinc derivative **64** with chlorophosphine **22a**. The organozinc bromide **64** was prepared from the corresponding alkenyl iodide **63**. To prevent oxidation, the phosphines were protected as the corresponding borane adducts **65**. The methodology is also applicable for aryl bromide **66** (Scheme 17) [23,24].

Alkenylphosphines were also synthesized by reacting alkenylzirconocenes **69** with a chlorophosphine **22b**. Alkenylzirconocene compounds **69** displaying different substitution patterns were used, giving access to a variety of alkenylphosphines **71a** via this method. If a more sterically hindered substrate ((α-substituted alkenyl)zirconocene) or reagent ($iPr_2PCl$) is used, a transmetallation of Zr(IV) to Cu(I) is necessary for the reaction in order to proceed (Scheme 18). An intermediate phosphorus-copper complex **70** is formed. The phosphines **71a** were liberated by treatment with $Na_2$(dtc) or $Na_4$(edta) [145].

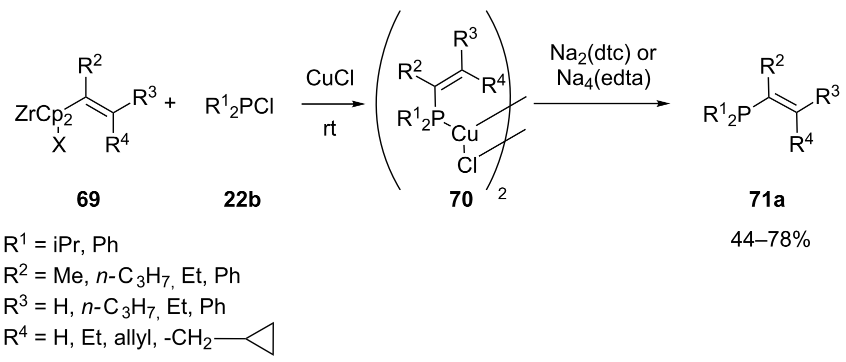
## Nucleophilic substitution with metallated organophosphines

The method is based on the reaction of phosphorus nucleophiles, derived from secondary phosphines or phosphine–borane complexes, and carbon electrophiles. Nucleophilic substitution with metallated organophosphines is less frequently used for the synthesis of vinylphosphines [42,146] due to possible isomerization to phospha-alkenes under basic conditions [147]. The method is mainly applied for the synthesis of arylphosphines. However, the nucleophilic reagents are incompatible with functional groups susceptible to nucleophilic attack. These sensitive groups have to be protected first to avoid undesired reactions. Despite these limitations this approach is still generally used for the synthesis of simple phosphines [137,138,148,149].

The group of Imamoto reported the $S_NAr$ reaction of *P*-chiral secondary phosphine boranes **13c** with halobenzenechromium complexes **72** in the presence of *sec*-butyllithium [150]. The



**Scheme 17:** Preparation of phosphines using zinc organometallics.



**Scheme 18:** Preparation of alkenylphosphines **71a** from alkenylzirconocenes **69** (dtc = *N*,*N*-diethyldithiocarbamate, edta = ethylenediaminetetraacetate).

stereochemistry at the phosphorus atom was retained during the substitution when it was performed in THF at low temperature (Scheme 19). When fluorobenzenechromium complex **72** was used as a substrate, the yields of **73** were high (81–93%), in contrast to the reaction with chloro- and bromobenzenechromium complexes. The former reacted in low yield (7%), the latter did not react. The highly electronegative fluorine atom is needed for the $S_NAr$ reaction to take place, even though the arenechromium complexes are already very electron-deficient aromatic compounds.

The same group also developed a *P*-chiral ligand, QuinoxP **74**, via deprotonation of chiral secondary phosphine borane **13d** with *n*-butyllithium and subsequent nucleophilic substitution with 2,3-dichloroquinoxaline at low temperature (Scheme 20) [151]. After removal of the boranato group, the ligand was obtained in a good yield (80%).

## Catalytic C(sp$^2$)–P bond formation

The transition metal typically used for catalytic C–P bond formation is palladium [152] and, in some cases, nickel or copper. The phosphinating agents may comprise primary and secondary phosphines, silylphosphines [153] or phosphine–borane complexes.

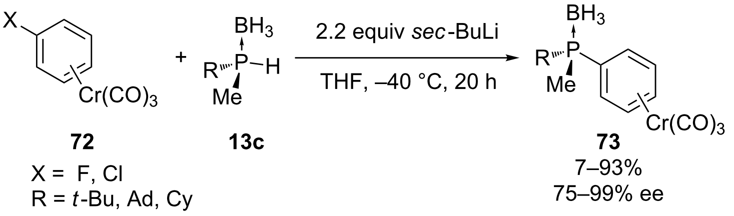
The vinylic coupling partner mostly consists of alkenylhalides or alkenyltriflates. Vinyl triflates are used more since they can easily be derived from the corresponding ketone and they are more reactive then the vinyl chloride or bromide during the oxidative addition. More recently also vinyl tosylates and enol phosphates have proven to be suitable reagents.

The catalytic arylic C–P cross-coupling reaction can be a greener approach towards the widely used arylphosphines that are inaccessible by hydrophosphination. Recent advances in this area concern the synthesis of *P*-stereogenic phosphines through a dynamic kinetic resolution of racemic secondary phosphines in a metal-catalyzed P–H/aryl halide coupling.

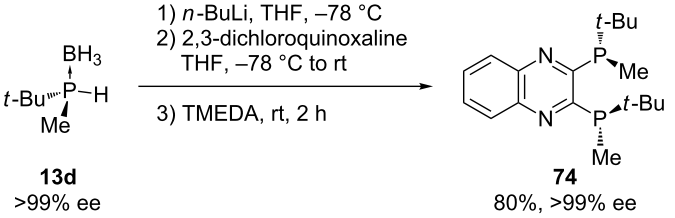
## C(sp$^2$)–P bond formation of vinylphosphines

**Palladium:** Beletskaya and co-workers have described the synthesis of secondary and tertiary vinylphosphines by means of palladium catalyzed cross-coupling of vinylhalides and (silyl)phosphines [154-156]. Table 6 shows the protocols (A or B) generally used [157]. The vinylhalide substrates **75a** were cross-coupled with diphenylphosphine or diphenyltrimethylsilylphosphine. When diphenylphosphine was used, triethylamine was added for the basic activation of the phosphinating agent. All the tested substrates **75a** contained an alkoxy or amino group and depending on their position relative to the halogen, it was necessary to adjust the reaction temperature. The substrates bearing the halogen in the α-position to the alkoxy or amino group proved to be more reactive. With the halogen in β-position the substrate was less activated and the temperature had to be raised. Method B gave lower yields and longer reaction times were required to compensate for the use of the less reactive diphenyltrimethylsilylphosphine.

Lipshutz et al. used a Pd(0) catalyst to synthesize triarylphosphine boranes by coupling secondary diphenylphosphine borane **13e** with aryl nonaflates or triflates [158]. The article included one example with vinyl triflate **76** as a substrate (Scheme 21). The vinyl electrophile **76** was activated by the presence of the

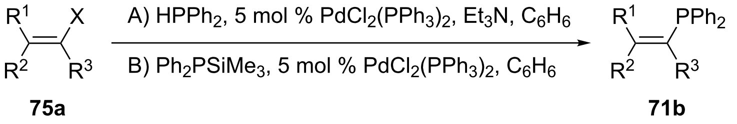


**Scheme 19:** $S_NAr$ with *P*-chiral alkylmethylphosphine boranes **13c**.



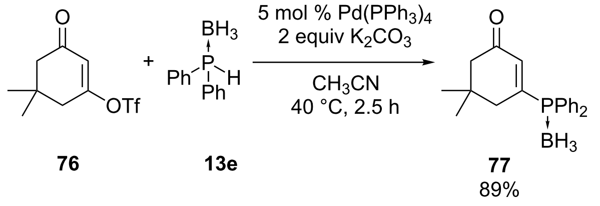
**Scheme 20:** Synthesis of QuinoxP **74** (TMEDA = tetramethylethylenediamine).

**Table 6:** Pd-catalyzed cross-coupling reactions of diphenylphosphine with alkenylhalides **75a**.



| Entry | $R^1$ | $R^2$ | $R^3$ | X | Method | Temp (°C) | Time (h) | Yield of **71b** (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | H | H | OEt | Br | A<br>B | 20<br>20 | 1<br>1.5 | 97<br>92 |
| 2 | Me | Me | $NEt_2$ | Cl | A<br>B | 20<br>20 | 6<br>12 | 84<br>80 |
| 3 | H | OBu | Br | Br | A<br>B | 120<br>120 | 36<br>40 | 94<br>90 |
| 4 | Ph | *N*-morpholine | H | Br | A<br>B | 70<br>70 | 24<br>50 | 92<br>60 |
| 5 | Ph | *N*-piperidine | H | Br | A<br>B | 70<br>70 | 24<br>45 | 90<br>55 |

carbonyl group so the reaction also took place without a palladium catalyst albeit in lower yield (60%) and with formation of byproducts.

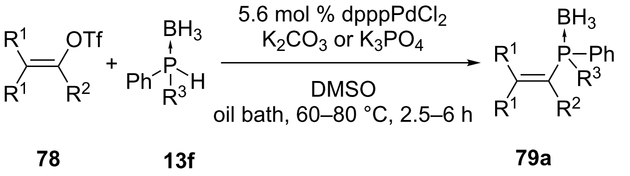


**Scheme 21:** Pd-Mediated couplings of a vinyl triflate **76** with diphenylphosphine borane **13e**.

Julienne et al. have reported the coupling of secondary phosphine boranes with unactivated vinyl triflates (Table 7 and Table 8) [159]. Cyclic and acyclic vinyl triflates (**78** and **80a**) were reacted with diaryl-, dialkyl- and alkylarylphosphine–borane complexes, **13f** and **13g** respectively. The reactions were performed with a palladium catalyst in the presence of a weak base. Sometimes microwave irradiation was used to shorten the reaction time.

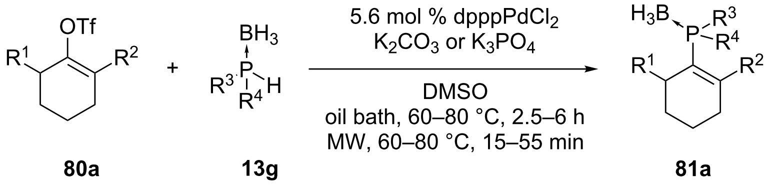
Gilbertson et al. have converted a series of vinyl triflates **80b** into the corresponding vinyl phosphine boranes **81b** through palladium catalysis with $HPPh_2$ (Table 9) [160]. The reaction proceeded under mild conditions (40 °C). These vinyltriflates **80b** were obtained from the corresponding ketone **82** opening access to a range of other structures. The chiral phosphines **83** and **84** were prepared from the natural products menthone and camphor in the same manner (Figure 1). All products were converted to the corresponding borane complex to facilitate further handling. However, when the same conditions were applied with diphenylphosphine borane and cyclohexenyltriflate no reaction was observed. A similar methodology has been applied for the synthesis of several ligands [161-163].

**Table 7:** Palladium-catalyzed C–P coupling between acyclic vinyl triflates and phosphine boranes (dppp = 1,3-bis(diphenylphosphino)propane).



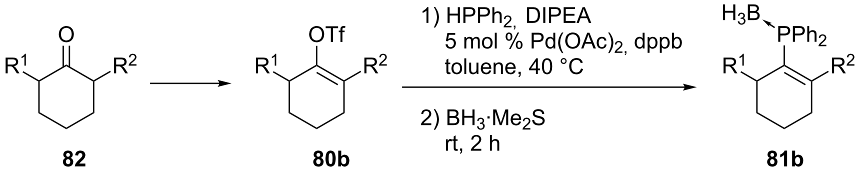
| Entry | $R^1$ | $R^2$ | $R^3$ | Yield of **79a** (%) |
|---|---|---|---|---|
| 1 | H | *t*-Bu | Ph | 71 |
| 2 | H | *t*-Bu | Me | 72 |
| 3 | Ph | Me | Ph | 82 |
| 4 | Ph | Me | Me | 87 |

**Table 8:** Palladium-catalyzed C–P coupling between cyclic vinyl triflates and phosphine boranes (dppp = 1,3-bis(diphenylphosphino)propane).

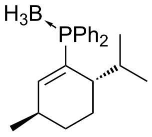


| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Heating | Yield of **81a** (%) |
|---|---|---|---|---|---|---|
| 1 | H | H | Ph | Ph | Oil bath | 68 |
| 2 | H | H | Ph | Ph | MWI | 71 |
| 3 | H | H | Me | Ph | Oil bath | 71 |
| 4 | H | H | *t*-Bu | Ph | Oil bath | 70 |
| 5 | H | H | *t*-Bu | Ph | MWI | 77 |
| 6 | H | H | Et | Et | Oil bath | 50 |
| 7 | H | H | Cy | Cy | MWI | 67 |
| 8 | Me | H | Ph | Ph | Oil bath | 70 |
| 9 | H | Me | Ph | Ph | Oil bath | 65 |

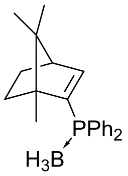
**Table 9:** Palladium-catalyzed synthesis of vinylphosphines **81b** from ketones **82** (dppb = 1,4-bis(diphenylphosphino)butane).



| Entry | $R^1$ | $R^2$ | Yield of **81b** (%) |
|---|---|---|---|
| 1 | H | H | 96 |
| 2 | Me | H | 89 |
| 3 | H | Me | 89 |
| 4 | *t*-Bu | H | 88 |



**83**
74%

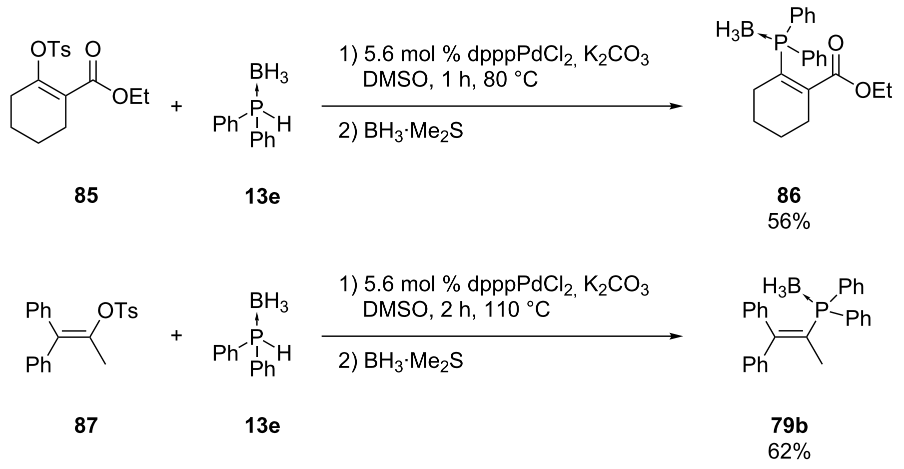


**84**
84%

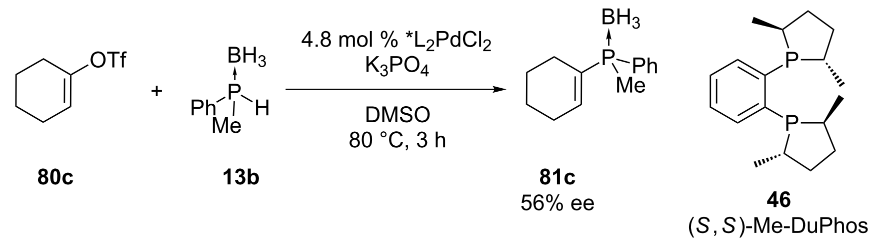
**Figure 1:** Menthone (**83**) and camphor (**84**) derived chiral phosphines.

Julienne et al. succeeded in coupling vinyl tosylates **85** and **87** with diphenylphosphine borane **13e** despite the fact that alkenyl tosylates are poor reagents for cross-coupling [164]. The products **86** and **79b** were formed in the presence of a palladium catalyst. The reaction proceeded at lower temperature when the vinyl tosylate was substituted with an electron-withdrawing group like in **85** (Scheme 22).

The group of Gaumont has also reported their preliminary results for the enantioselective palladium-catalyzed C–P cross-coupling reaction between an achiral vinyl triflate **80c** and a racemic secondary phosphine–borane complex **13b** (Scheme 23) [165]. Chiral phosphines with a *C*-stereogenic center have been studied but this was the first attempt for the asymmetric synthesis of a *P*-stereogenic compound. After evaluating several conditions the best catalyst was (*S*,*S*)-Me-DuPhos (**46**). An enantioenriched alkenylphosphine **81c** was formed. The highest enantiomeric excess measured by chiral HPLC was 56%. No reaction was observed without the palladium catalyst [165].

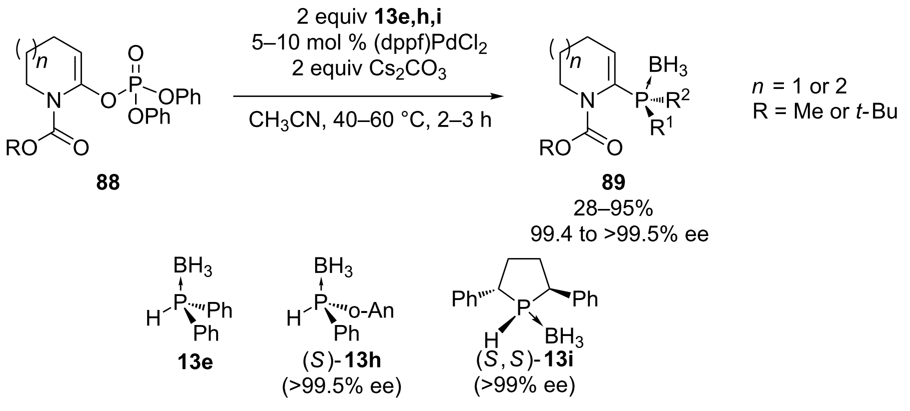


**Scheme 22:** Palladium-catalyzed cross-coupling reaction of vinyl tosylates **85** and **87** with diphenylphosphine borane **13e** (dppp = 1,3-bis(diphenylphosphino)propane).



**Scheme 23:** Attempt for the enantioselective palladium-catalyzed C–P cross-coupling reaction between an alkenyltriflate **80c** and a phosphine borane **13b**.

Gillaizeau and co-workers have demonstrated the use of α-amido enol phosphates **88** as vinylic coupling partners in the palladium-catalyzed C–P cross-coupling reaction (Scheme 24) [166]. The enol phosphates **88** were prepared from the corresponding amides. The phosphane function was introduced in the α-position of the nitrogen. Several chiral and achiral secondary phosphine borane complexes **13** were used. The coupling was achieved under mild conditions. Most reactions gave **89** in low to good yields but in some cases the product could not be isolated, probably due to instability of the product. During the



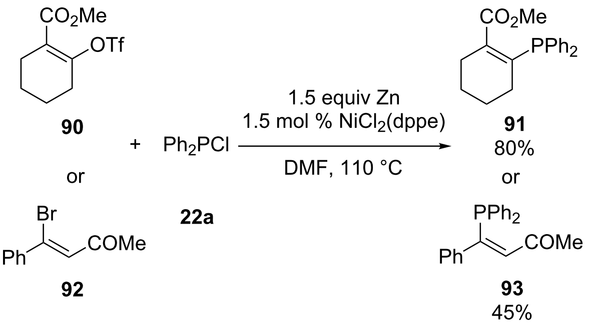
**Scheme 24:** Enol phosphates **88** as vinylic coupling partners in the palladium-catalyzed C–P cross-coupling reaction (dppf = 1,1'-bis(diphenylphosphino)ferrocene).

coupling reaction with **13h** partial inversion of the phosphorus atom occurred, resulting in racemization.

**Nickel:** Most research has focused on the use of a palladium catalyst to perform the C–P cross-coupling between secondary phosphines and vinylic electrophiles. A few reports are available concerning the nickel-catalyzed cross-coupling. Ager and Laneman have prepared phosphines **91** and **93** from vinyl triflate **90** and vinyl bromide **92**, respectively, under similar conditions (Scheme 25) [53]. The reaction was catalyzed by $NiCl_2$(dppe) in the presence of zinc. The role of zinc was to reduce Ni(II) to Ni(0) and to form $Ph_2PZnCl$ for the transmetallation step.

Kazankova and co-workers have explored the catalysts $(Ph_3P)_2NiCl_2$ and $Ni(acac)_2$ for the coupling of several vinyl bromides **75b** and chlorides with **25d** (Table 10). These reactions proceeded without the addition of zinc [167].

**Copper:** The group of Buchwald has reported one example of a copper catalyst to accomplish the phosphination of the vinyl halide **94** (Scheme 26) [168]. The protocol uses CuI as catalyst in combination with *N,N'*-dimethylethylenediamine (**96**) as ligand and a weak base $Cs_2CO_3$.The desired phosphine **95** is isolated in good yield.



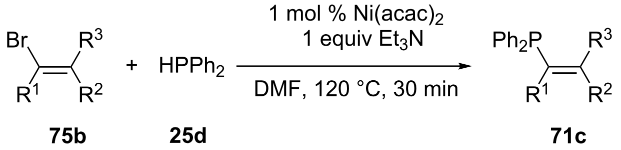
**Scheme 25:** Nickel-catalyzed cross-coupling in the presence of zinc (dppe = 1,2-bis(diphenylphosphino)ethane).

## C(sp$^2$)–P bond formation of arylphosphines

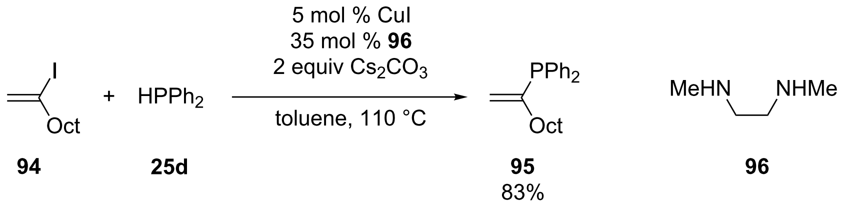
The C–P bond formation of aryl phosphines is typically catalyzed by palladium, nickel and less frequently copper. The phosphorus coupling partners used are primary, secondary and tertiary phosphines, secondary phosphine–borane complexes, silyl- and stannylphosphines and phosphine chlorides. These phosphinating agents are coupled with aryl halides and triflates. Several general protocols are available.

**Palladium:** In 1987, Tunney and Stille reported on the palladium-catalyzed synthesis of several aryldiphenylphosphines by

**Table 10:** Alternative nickel-catalysed cross-coupling without zinc (acac = acetylacetone).



| Entry | $R^1$ | $R^2$ | $R^3$ | Yield of **71c** (%) |
|---|---|---|---|---|
| 1 | H | OEt | H | 90 |
| 2 | Me | H | Me | 90 |
| 3 | TMS | H | H | 93 |
| 4 | TES | H | H | 96 |
| 5 | H | Ph | H | 90 |



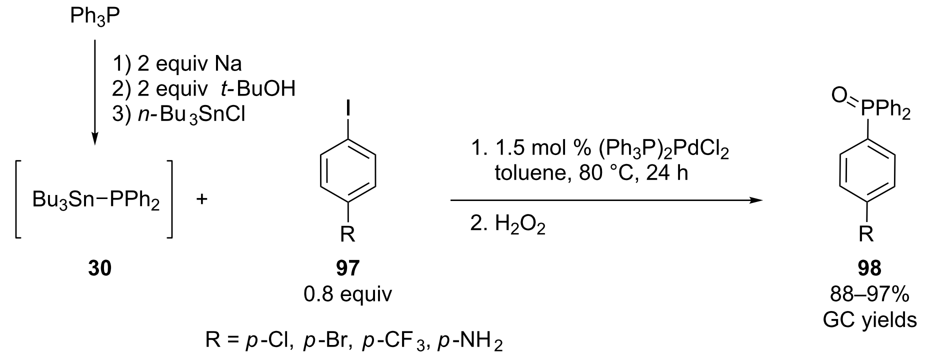
**Scheme 26:** Copper-catalyzed coupling of secondary phosphines with vinyl halide **94**.

cross-coupling aryl halides with (trimethylsilyl)diphenylphosphine or (trimethylstannyl)diphenylphosphine [169]. No base is required for this method. Trimethylsilyl compounds are preferred over tristannyl derivatives since they are less toxic. However, in recent years the group of Rossi has reported a one-pot procedure for the palladium-catalyzed coupling of aryl iodides **97** with in situ generated $Ph_2SnBu_3$ (**30**, Scheme 27) [170]. When naphthyl triflate was used as a substrate, CuI was added as a co-catalyst [171].

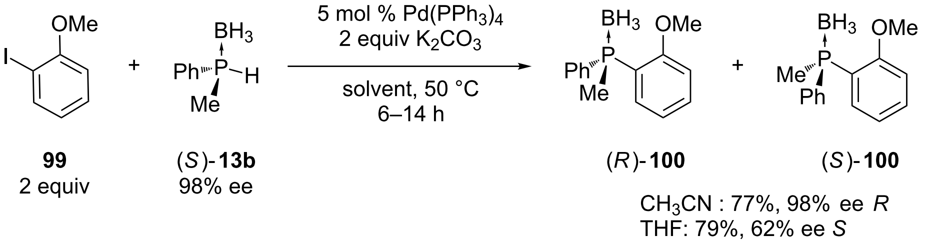
Imamoto et al. have developed a method for the palladium-catalyzed C–P bond formation using secondary phosphine boranes [41]. The authors also discovered how the choice of the solvent influences the stereochemistry of **100**. When the coupling between aryl iodide **99** and asymmetric secondary phosphine borane **13b** was performed in acetonitrile or DMF, the stereochemistry at the phosphorus atom was almost completely retained while the reaction performed in THF or toluene resulted mainly in inversion (Scheme 28) [172,173]. The stereochemistry also depended on the base used. The presence of $K_2CO_3$ or KOAc favored a good stereoselectivity in contrast to $K_3PO_4$ or DBU. Sodium hydride or $Ag_2CO_3$ promoted retention of configuration. The mechanism of the reaction was studied by Gaumont et al. through isolation of the reactive intermediate [174]. Lipshutz et al. reported the palladium-catalyzed phosphination of aryl triflates and nonaflates instead of aryl iodides with phosphine boranes [158]. The first examination towards an enantioselective C–P cross-coupling starting from racemic secondary phosphine boranes was performed by Gaumont and Pican [175]. The highest enantiomeric excess obtained was 45%. The same group has shown that imidazolium based ionic liquids can be used as a medium to perform the C–P cross-coupling reactions. This method allows an easy separation of the product from the catalyst and the recycling of the palladium catalyst [176].

Stelzer and co-workers have developed a general method for the coupling of primary or secondary phosphines instead of their silyl derivatives or borane complexes with functional aryl-iodides **101** [177-179]. It should be noted, however, that the reactions were again limited to (di)phenylphosphine (Scheme 29). The protocols use palladium as a catalyst in the presence of tertiary amines as base. A variety of hydrophilic phosphines (**102**, **103**) was synthesized. Since no protective groups were introduced, the method proves to be compatible with several functionalities. This methodology or in a slightly modified form has been used by several authors for the phosphination of a large variety of compounds [180-188]. Microwave-assisted procedures have also been developed [189-191].

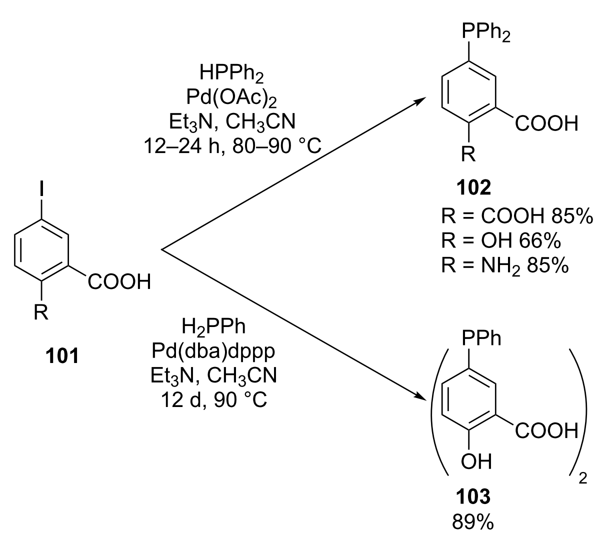
Kwong et al. implemented a palladium-catalyzed phosphination of aryl bromides and triflates **104** with triarylphosphines



**Scheme 27:** Palladium-catalyzed cross-coupling of aryl iodides **97** with organoheteroatom stannanes **30**.



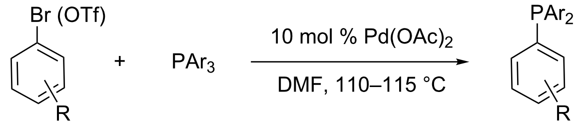
**Scheme 28:** Synthesis of optically active phosphine boranes **100** by cross-coupling with a chiral phosphine borane **13b**.



**Scheme 29:** Palladium-catalyzed P–C cross-coupling reactions between primary or secondary phosphines and functional aryliodides **101** (dba = dibenzylideneacetone, dppp = 1,3-bis(diphenylphosphino)propane).

**105a** as phosphinating agents. This aryl–aryl exchange reaction was compatible with several functional groups such as ketones, aldehydes, esters, nitriles, ethers (Table 11) [192-195]. Products **106a** were isolated in only moderate yields. Several *P*,*N*-biaryl ligands were prepared from the corresponding triflate under similar conditions [196,197]. The reaction also proceeded under solvent-free conditions with slightly higher yields [198]. A heterogeneous Pd/C catalyst has been applied as well [199,200].

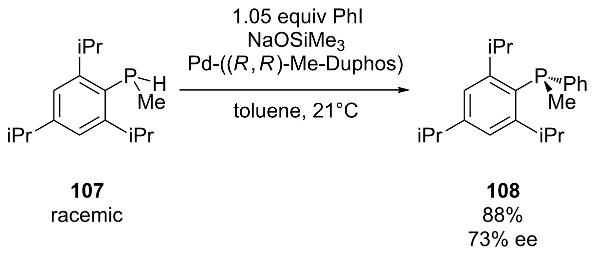
**Table 11:** The phosphination of aryl bromides **104** with tertiary arylphosphines **105a**.



**104** **105a** 2.3–2.5 equiv **106a**

| Entry | R | Ar | Yield of **106a** (%) |
|---|---|---|---|
| 1 | -CHO | Ph | 32 |
| 2 | -C(O)Me | Ph | 40 |
| 3 | -CO$_2$Me | Ph | 30 |
| 4 | -CN | Ph | 36 |
| 5 | -OMe | Ph | 27 |
| 6 | -C(O)Me | *p*-Tol | 39 |
| 7 | -C(O)Me | 3,5-Me$_2$-C$_6$H$_3$ | 34 |
| 8 | -C(O)Me | *p*-MeO-C$_6$H$_4$ | 33 |

The group of Glueck has reported the first asymmetric palladium-catalyzed C–P bond formation for the synthesis of *P*-stereogenic phosphines by adding a catalytic amount of a chiral auxiliary. The enantioenriched phosphine **108** was obtained through coupling of racemic bulky secondary phosphine **107** with PhI in the presence of the base NaOSiMe$_3$ and the Pd-catalyst (Scheme 30) [201]. In the following years, the scope and mechanism were elaborated [202-204]. In accordance with the mechanism given in Scheme 10, it was concluded that the major enantiomer of the product **108** was derived from the major diastereomer of the Pd-phosphido intermediate. Korff and Helmchen have prepared several triarylphosphines with this methodology. However, a modified catalyst system [Pd(Et-FerroTANE)] containing a ferrocene-based ligand was used [205]. This catalyst had the advantage that it was easily prepared in situ while the unstable catalyst used by Glueck et al., required storage at −25 °C in the dark.

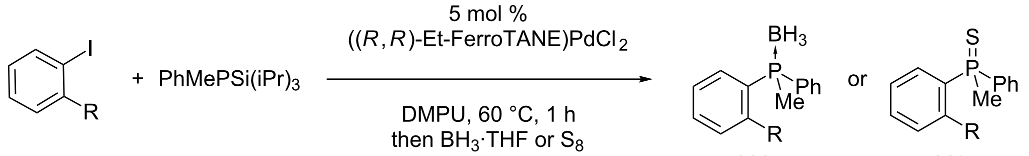


**Scheme 30:** Enantioselective synthesis of a *P*-chirogenic phosphine **108**.

The protocol of Tunney and Stille starting from silylphosphines has been modified by Chan, Bergman and Toste to be enantioselective by using a [Pd(Et-FerroTANE)] catalyst. *P*-stereogenic phosphine boranes **111** and **112** were synthesized by arylation of racemic silylphosphines **110** under dynamic kinetic control (Scheme 31). The best enantiomeric excess was obtained when an *ortho*-amide substituent was present in the substrate **109** [206].

**Nickel:** Cristau et al. were the first which achieved the nickel-catalyzed arylation of diphenylphosphine [207]. Upon reaction of bromobenzene (**113**) with **25d** in the presence of NiBr$_2$ a mixture of triphenylphosphine **105b** and tetraphenylphosphonium bromide salt **114** was obtained (Scheme 32).

The first conversion of an aryltriflate to an arylphosphine using diphenylphosphine was reported by Cai et al. (Scheme 33) [208,209]. The method was developed for the synthesis of chiral (*R*)-BINAP **116**; a successful chiral ligand. Nickel was chosen as catalyst instead of palladium to minimize catalyst poisoning by binding of the metal with the phosphines present.

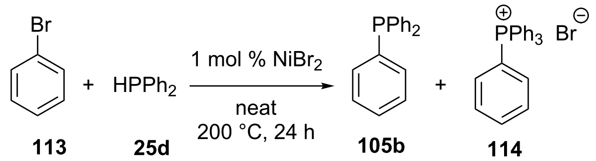


**109** **110** **111** **112**

R = OMe, SMe, NMe$_2$, CH$_2$C(O)N(iPr)$_2$,
R = CO$_2$R' with R' = *t*-Bu, 2,6-Me$_2$-Ph, 2,6-(iPr)$_2$-Ph or
R = C(O)NR''$_2$ and R'' = Me(OMe), Me, iPr

**111** or **112**
53–83%
32–98% ee

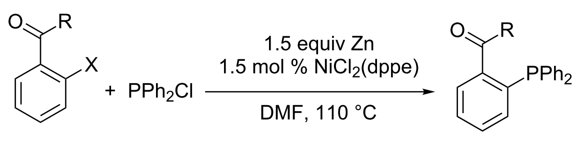
**Scheme 31:** Enantioselective arylation of silylphosphine **110** ((*R,R*)-Et-FerroTANE = 1,1'-bis((*2R*,*4R*)-2,4-diethylphosphotano)ferrocene).



**113** **25d** **105b** 51% **114** 19%

**Scheme 32:** Nickel-catalyzed arylation of diphenylphosphine **25d**.

**Table 12:** Preparation of tertiary phosphines **118** via nickel-catalyzed cross-coupling (dppe = 1,2-bis(diphenylphosphino)ethane).



**117** **22a** **118**

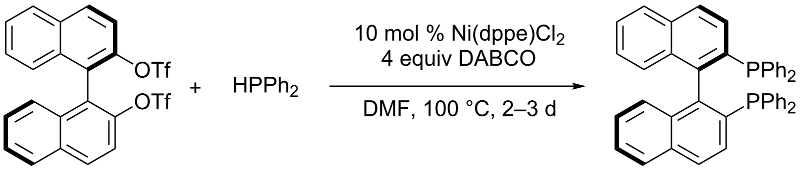
| Entry | R | X | Yield of **118** (%) |
|---|---|---|---|
| 1 | OMe | OTf | 84 |
| 2 | OMe | Br | 46 |
| 3 | NHBn | OTf | 67 |
| 4 | (*S*)-NHCHMePh | Br | 46 |

After optimization, the desired chiral BINAP **116** was obtained in 77% yield. This protocol has been adopted by other research groups for the synthesis of a range of phosphines [138,210-216]. Analogous palladium-catalyzed reactions coupling aryl triflates with diphenylphosphine have been reported [217,218].

Laneman et al. later developed a modified version of Cai's method and synthesized several tertiary phosphines **118** via the cross-coupling of aryl triflates and halides **117** with chlorodiphenylphosphine (**22a**) instead of diphenylphosphine (Table 12) [53]. The reaction was catalyzed by NiCl$_2$(dppe) in the presence of zinc. A hydrodehalogenation side reaction resulted in lower yields of aryl halide substrates compared to aryl triflates.

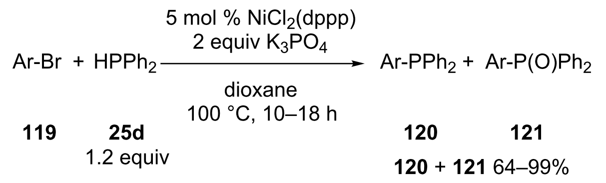
Zhao and co-workers disclosed a method for the cross coupling of various aryl bromides **119** with diphenylphosphine (**25d**) in the absence of external reductants and supporting ligands [219]. The reaction gave mixtures of phosphines **120** and phosphine oxides **121** (Scheme 34). Several functional groups (ester, ether, ketone and cyano groups) remained intact under the conditions. The reaction was also performed with diphenylphosphine–borane complex but this resulted in only small amounts of products due to decomposition of the phosphinating reagent at 100 °C.

**Copper:** Copper was first used as a co-catalyst in palladium-catalyzed phosphorylation reactions, Livinghouse et al. demonstrated that the aromatic phosphorylation proceeded even at low temperatures of ≤0 °C when copper was added [220]. The method also allows for the stereocontrolled Pd(0)−Cu(I)



**115** **25d** 2.2 equiv **116** 77% 99% ee

**Scheme 33:** Nickel-catalyzed synthesis of (*R*)-BINAP **116** (dppe = 1,2-bis(diphenylphosphino)ethane, DABCO = 1,4-diazabicyclo[2.2.2]octane).



**Scheme 34:** Nickel-catalyzed cross-coupling between aryl bromides **119** and diphenylphosphine (**25d**) (dppp = 1,3-bis(diphenylphosphino)propane).

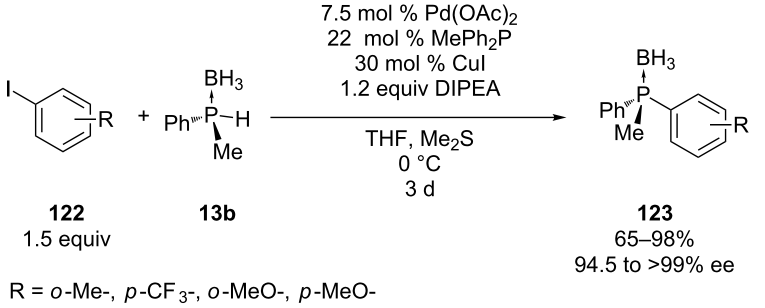
co-catalyzed coupling of enantiopure secondary phosphine borane **13b** with aryl iodides **122** (Scheme 35) [221].

In 2003, copper-catalyzed palladium free phosphorylation methods were developed by Venkataraman and Van Allen [222] and Buchwald et al. [168]. Both methodologies use catalytic amounts of copper(I) salts in the presence of $K_2CO_3$ or $Cs_2CO_3$ as a base. Buchwald et al. also added *N,N'*-dimethylethylenediamine **96** as a ligand to enhance the efficiency of the coupling. A secondary phosphine **25e** was coupled with a variety of aryl halides **124** with electron-withdrawing or -donating substituents. The method tolerated the presence of functional groups such as esters or amines (Table 13). This approach was also used for the synthesis of phosphinoxazolines [223].

## Hydrophosphination of alkynes

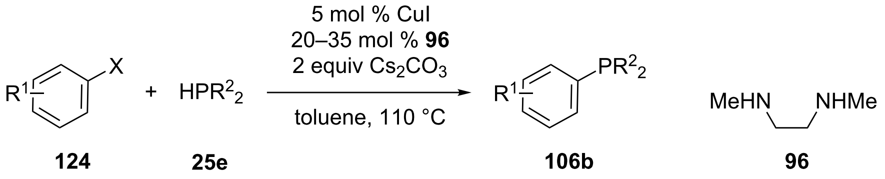
The addition of P–H to a triple bond is a highly desirable method when taking atom economy principles into account. Activated [224,225] or unactivated alkynes were investigated as substrates. Phosphines as well as silylphosphines [65,66,226,227] or phosphine–borane complexes can be used as phosphinating agents. The addition reaction has been initiated in several ways including base [228-233], radical (thermal radical [234] or AIBN radical [77,78,83,235,236]) or transition metal activation.

Depending on the regioselectivity of the procedure, the addition of P–H to the triple bond results in the formation of two regioisomers (Scheme 36). The product that results from the Markovnikov addition of P–H corresponds to the α-adduct **126**

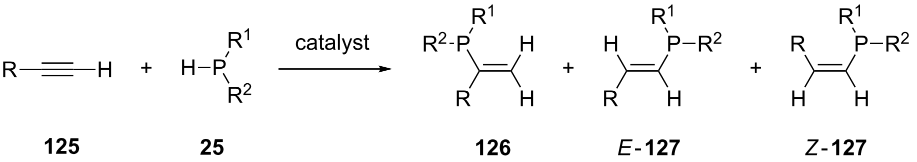


**Scheme 35:** Stereocontrolled Pd(0)−Cu(I) cocatalyzed aromatic phosphorylation.

**Table 13:** Copper-catalyzed synthesis of triarylphosphines **106b**.



| Entry | $R^1$ | X | $R^2$ | Yield of **106b** (%) |
|---|---|---|---|---|
| 1 | 2-MeO | I | Ph | 91 |
| 2 | 2-$NH_2$ | I | Ph | 86 |
| 3 | 4-$CO_2Me$ | Br | Ph | 70 |
| 4 | 2-Ph | I | tol | 79 |
| 5 | 4-$NH_2$ | I | Cy | 72 |
| 6 | 4-$CO_2Et$ | I | Cy | 85 |
| 7 | 4-CN | I | iBu | 65 |



**Scheme 36:** Preparation of alkenylphosphines by hydrophosphination of alkynes.

and the anti-Markovnikov addition results in the β-adduct **127**. The stereoselectivity of the reaction determines the formation of *E*- or *Z*-**127**.

Despite the great appeal of this method for the preparation of vinylphosphines it does not allow the syntheses of the widely used arylphosphines or alkenes bearing no hydrogen on the double bond. Additionally, due to the absence of small rings containing a triple bond, no cyclic alkenylphosphines are accessible. Until now, the protocols lack sufficient control over selectivity and mostly give mixtures. Most addition products (radical, base, metal) are anti-Markovnikov **127**, only a few palladium catalyzed reactions give the Markovnikov products **126**.

Several reviews on hydrophosphination of alkynes have been published [90,91,237]. Some recent developments will be discussed. In recent years research has mainly focused on metal-catalyzed hydrophosphinations.

## Metal complex-catalyzed hydrophosphinations

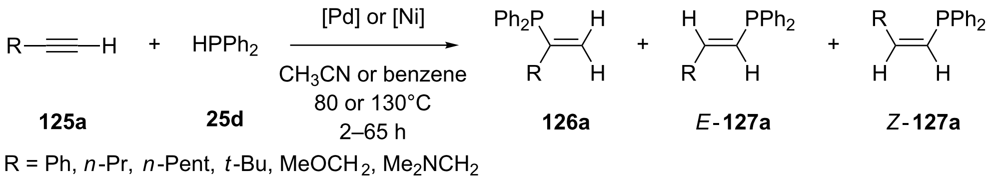
Hydrophosphination catalysts are mainly based on transition metals. However, it has been shown that lanthanides and alkaline earth metals can offer a valid alternative.

Palladium and nickel complexes were used to catalyze the addition of the P–H bond to alkynes **125a** (Scheme 37). The regioselectivity was strongly dependent on the catalytic precursor. In the presence of palladium(0) and nickel(0) complexes the β-adduct **127a** was formed as the major product. By contrast palladium(II) and nickel(II) complexes mainly gave rise to the α-adduct **126a** [98,238]. The nickel based catalyst was more effective than the palladium so the reaction proceeded at lower temperature.

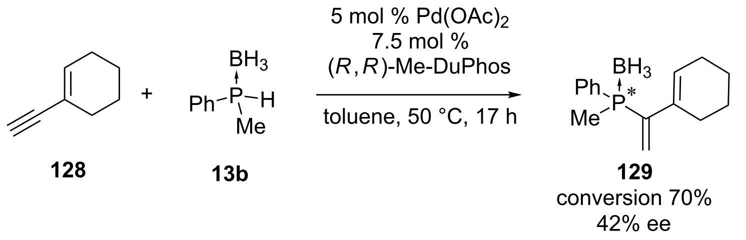
Join et al. had the objective to enantioselectively create *P*-stereogenic vinylphosphine boranes [239]. To achieve this goal some asymmetric hydrophosphination reactions were performed using a palladium catalyst in combination with a chiral ligand. After optimizing the conditions, the addition of methylphenylphosphine borane (**13b**) to 1-ethynylcyclohexene (**128**) with the Pd-catalyst afforded tertiary phosphine borane **129** with a conversion of 70% and only 42% ee (Scheme 38).

Nagata et al. performed the palladium-catalyzed hydrophosphination of alkynes by using tetraphenyldiphospine (**130**) (Table 14) [240]. Since there is no P–H bond in this phosphinating agent, a bisphosphination was expected but a hydrophosphination took place. However, an excess (3–5 equiv) of alkyne was used. The reaction proceeded regioselectively and the α-adducts **126b** of several terminal alkynes **125b** were formed. Air-oxidation during work-up resulted in the formation of the corresponding phosphine oxides **131**. The products **131** were isolated in moderate yields with respect to the diphosphine **130** as limiting reagent. It was suggested that the alkynyl hydrogen acts as the hydrogen source for the hydrophosphination. This can also explain why the method was not applicable to internal alkynes. Silanes have also been added as the source for hydrogen [241].

Ruthenium complexes are the first catalysts reported for the direct hydrophosphination of propargyl alcohols [242]. Several catalytic systems were tested and the reaction with 5 mol % RuCl(cod)($C_5Me_5$) in the presence of $Na_2CO_3$ provided the best

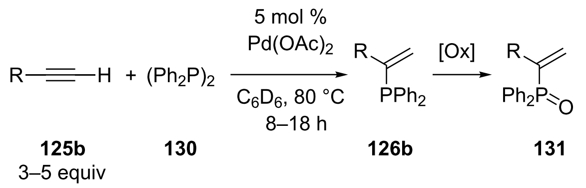


**Scheme 37:** Palladium and nickel-catalyzed addition of P–H to alkynes **125a**.



**Scheme 38:** Palladium-catalyzed asymmetric hydrophosphination of an alkyne **128**.

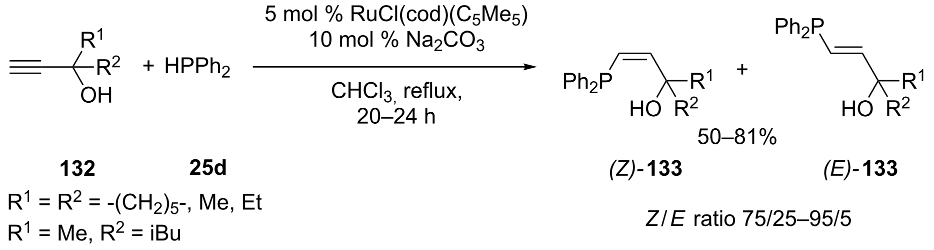
**Table 14:** Pd-catalyzed hydrophosphination of alkynes **125b** using diphosphine **130**.



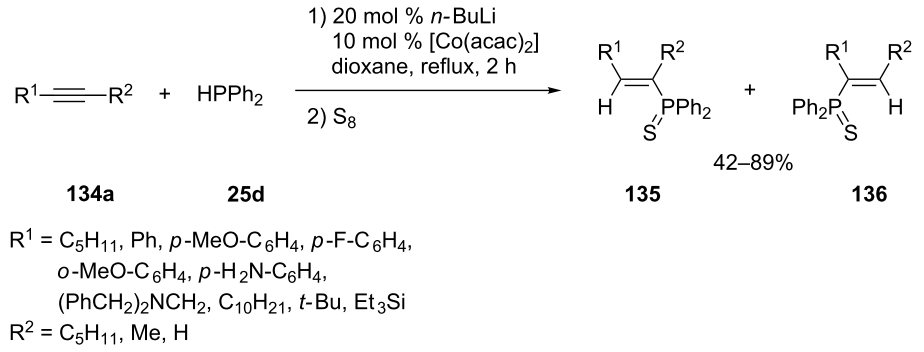
| Entry | R | Yield of **131** (%) |
|---|---|---|
| 1 | *n*-Hex | 58 |
| 2 | Ph | 66 |
| 3 | $-(CH_2)_3CN$ | 50 |
| 4 | $-(CH_2)_3Cl$ | 75 |

results (Scheme 39). The reaction gave two stereoisomeric adducts (*Z*)-**133** and (*E*)-**133**. The hydrophosphination of **132** proceeded with excellent regioselectivity and good stereoselectivity as the *Z*-isomers, (*Z*)-**133**, were preferentially formed with *Z*/*E* ratios around 80/20. This method could not be performed on alkynes with an internal triple bond, only terminal alkynes were accessible.

A catalytic amount of $Co(acac)_2$ in combination with butyllithium can mediate the hydrophosphination of internal alkynes [243]. Various alkynes **134a** were subjected to these conditions to provide the corresponding *syn*-adducts exclusively (Scheme 40). The regioselectivity is mostly influenced by steric hindrance. To avoid loss of product by oxidation, the adducts were isolated as their thiophosphine analogues **135** and **136**.



**Scheme 39:** Ruthenium catalyzed hydrophosphination of propargyl alcohols **132** (cod = 1,5-cyclooctadiene).

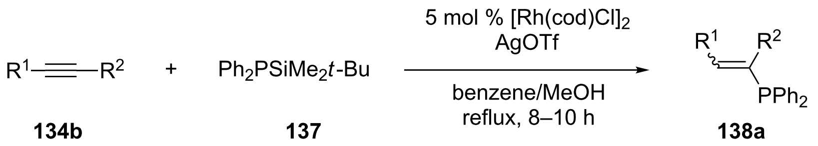


**Scheme 40:** Cobalt-catalyzed hydrophosphination of alkynes **134a** (acac = acetylacetone).

Hayashi and co-workers have reported a rhodium-catalyzed phosphination of alkynes **134b** using silylphosphines **137** as phosphinating agents (Table 15) [108]. The cationic rhodium catalyst was generated in situ by adding silver triflate to a chlororhodium complex. The silylgroup was not incorporated in the vinylphosphine product **138a** and methanol was added as a proton source for completing the reaction. The adducts **138a** were formed with good to high *syn*-selectivity.

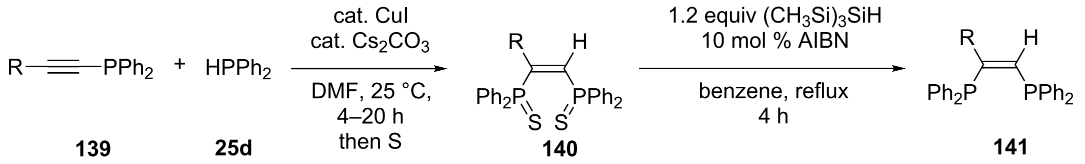
Kondoh et al. demonstrated the P–H addition to 1-alkynylphosphines under copper catalysis (Table 16) [244]. Besides copper(I) iodide several other copper salts effectuated the reaction albeit in lower yields as did silver(I) iodide, palladium(II) chloride and platinum(II) chloride. Other transition metal catalysts such as gold(I) chloride, nickel(II) chloride and cobalt(II) chloride gave no reaction. In the presence of copper(I) iodide and cesium carbonate diphenylphospine (**25d**) added to the triple bond in an *anti*-fashion. A diverse set of alkynylphosphines **139** was subjected to the protocol proving the compatibility of the method with certain functional groups. The *Z*-adducts were formed exclusively and isolated as the phosphine sulfides **140** to prevent lower yields by oxidation to the

**Table 15:** Rhodium-catalyzed hydrophosphination of alkynes **134b** with a silylphosphine **137** (cod = 1,5-cyclooctadiene).



| Entry | $R^1$ | $R^2$ | Yield of **138a** (%) | *E*/*Z* |
|---|---|---|---|---|
| 1 | Ph | H | 89 | 96/4 |
| 2 | MeO-$C_6H_4$ | H | 53 | 92/8 |
| 3 | *n*-$C_5H_{11}$ | H | 78 | 95/5 |
| 4 | $HOCH_2$ | H | 66 | 80/20 |
| 5 | Ph | Me | 68 | 92/8 |
| 6 | Ph | *n*-Bu | 72 | 95/5 |
| 7 | *n*-$C_5H_{11}$ | *n*-$C_5H_{11}$ | 67 | >99/1 |
| 8 | $EtO_2C$ | *n*-Bu | 81 | >99/1 |
| 9 | $EtO_2C$ | Ph | 76 | 80/20 |

**Table 16:** Copper-catalyzed hydrophosphination of 1-alkynylphosphines **139**.



| Entry | R | Yield of **140** (%) | Yield of **141** (%) |
|---|---|---|---|
| 1 | *n*-Hex | 88 | 87 |
| 2 | iPr | 84 | |
| 3 | *t*-Bu | 84 | 89 |
| 4 | Ph | 72 | 78 |
| 5 | 4-Ac-$C_6H_4$ | 87 | 63 |
| 6 | 3-pyridyl | 62 | 44 |
| 7 | $EtOC(O)(CH_2)_3$ | 79 | |
| 8 | $AcS(CH_2)_9$ | 75 | |
| 9 | PhCH(OH) | 84 | |

corresponding oxides. The phosphines **141** were obtained by radical reduction of **140** with tris(trimethylsilyl)silane (TTMSS).

However, when Kumaraswamy et al. explored the copper-catalyzed hydrophosphination on substituted phenylacetylenes **125c** further oxidation of the double bond led to the corresponding phenacyl tertiary phosphine boranes **142** in moderate to good yields (Scheme 41). The products **142** were obtained when the reactions were performed under inert atmosphere and in open air. Since the latter gave slightly better yields, it was argued that the dissolved air contributed to the product formation. A Cu(II)–TMEDA catalyzed tandem phosphorus–carbon bond formation–oxyfunctionalization was developed [245]. When methyl propiolate was subjected to the same reaction conditions only the β-adducts were isolated.

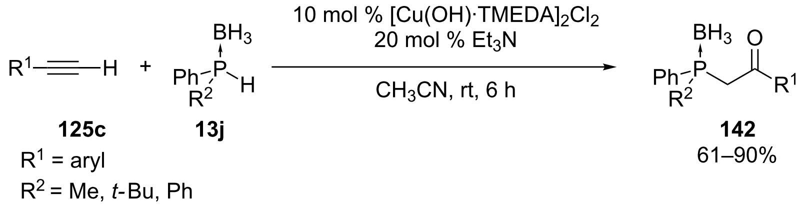
The intramolecular hydrophosphination and cyclization of primary alkynyl phosphines **143** has been accomplished using organolanthanide precatalysts of the type $Cp'_2LnCH(SiMe_3)_2$ ($Cp' = \eta^5\text{-}C_5Me_5$) and $Me_2Si(Me_4C_5)(t\text{-}BuN)SmN(SiMe_3)_2$ [111,112]. The reaction succeeded also using homoleptic lanthanocenes of the form $Ln[CH(SiMe_3)_2]_3$ (Ln = La, Nd, Sm, Y, Lu) or $Ln[N(SiMe_3)_2]_3$ (Ln = La, Nd, Sm, Y) [246]. The reaction was performed in NMR tubes until full conversion to the phospholane **144** (*n* = 1) or phosphorinane **144** (*n* = 2) was obtained (Scheme 42). The reaction is regioselective as only one adduct was obtained. Several butadiene derivatives were synthesized by hydrophosphination of the triple bond in enynes in the presence of yttriumcomplexes [247].

An ytterbium–imine complex **145** $[Yb(\eta^2\text{-}Ph_2CNPh)(hmpa)_3]$ has also been applied for the synthesis of alkenylphosphines [245,248-251]. The products were isolated as their corresponding phosphine oxides (**146** and **147**) after oxidative work-up (Scheme 43). The reaction proceeded under mild conditions (rt, 5 min to 4 h), except for the less reactive aliphatic internal alkynes (80 °C, 6 h). The regio- and stereoselectivity was mainly affected by the nature of the substrate and not so much by the reaction conditions. An active ytterbium phosphide species is generated in situ and therefore the imine complex could be categorized as a basic catalyst.

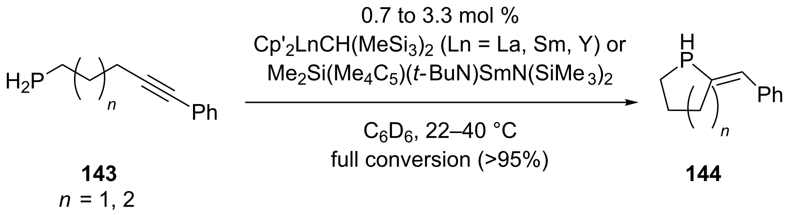
The only catalysts based on heavy alkaline earth metals for the hydrophosphination of alkynes are derived from calcium [123,252,253]. A similar behavior of calcium(II) and ytterbium(II) compounds seems possible as the oxidation state of Yb(II) does not change during the ytterbium(II)-catalyzed hydrophosphination of alkynes. The reaction of alkyne **134d** in the presence of the calcium catalyst resulted in diphenylvinylphosphine **138b** in good yield (Scheme 44). A set of butadiynes was reacted in a similar way [254]. Mixtures of butadienyldiphosphine isomers were obtained depending on the bulkiness of the end groups at the butadiyne moieties.

## Other hydrophosphinations

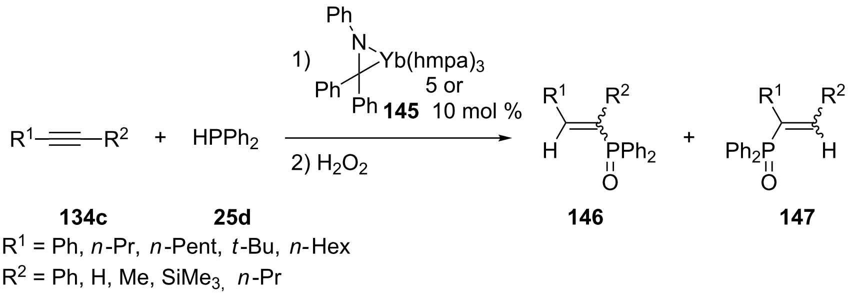
A relatively recent example for the thermal activated hydrophosphination was from Mimeau and Gaumont and described the use of a microwave reactor [254]. This reaction is performed with secondary phosphine–borane complexes **13j** and terminal alkynes **125d**. Mimeau and Gaumont demon-



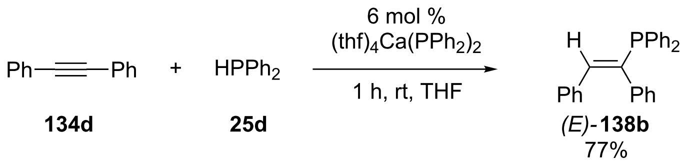
**Scheme 41:** Tandem phosphorus–carbon bond formation–oxyfunctionalization of substituted phenylacetylenes **125c** (TMEDA = tetramethylethylenediamine).



**Scheme 42:** Organolanthanide-catalyzed intramolecular hydrophosphination/cyclization of phosphinoalkynes **143**.



**Scheme 43:** Hydrophosphination of alkynes **134c** catalyzed by ytterbium-imine complexes **145** (hmpa = hexamethylphosphoramide).



**Scheme 44:** Calcium-mediated hydrophosphanylation of alkyne **134d**.

strated that the regioselectivity of the hydrophosphination reaction can be controlled by adjusting the activation method. Thermal activation with the microwave reactor gave the β-adducts **148** (anti-Markovnikov addition) (Table 17). In the same article the α-adducts **149** (Markovnikov addition) were formed by using a palladium catalyst (Table 18). In both cases the regioselectivity was excellent, the stereochemistry in the case of the β-adduct **148** favoured the *Z*-product. The conditions are compatible with aliphatic and oxygen-functionalized alkynes.

Busacca et al. have described the hydrophosphination of internal alkynes with phosphine–borane complexes under basic conditions [255,256]. Several diaryl- and alkylarylalkynes **134e** were reacted with a variety of phosphine boranes **25f**, some examples are shown in Table 19. Mixtures of *E* and *Z*-isomers of **150** were formed, with the *E*-isomer as the major product.

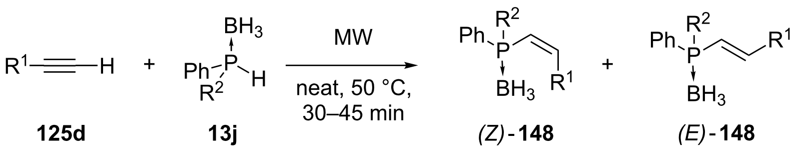
## Preparation of alkynylphosphines via formation of a C(sp)–P bond

An extensive review concerning the stoichiometric and catalytic synthesis of alkynylphosphines and their borane complexes has been published in 2012 by Gaumont et al. [257].

### Reaction of organometallic reagents with halophosphines

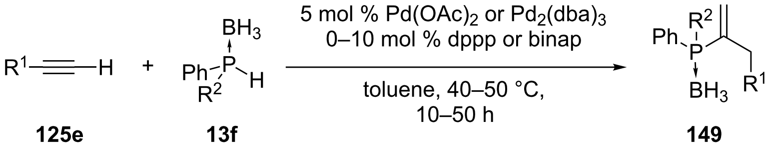
Alkynylphosphines are commonly synthesized by the nucleophilic displacement of the halogen at the phosphorus atom of a

**Table 17:** Hydrophosphination reactions of terminal alkynes **125d** with phosphine boranes **13j** under microwave conditions.



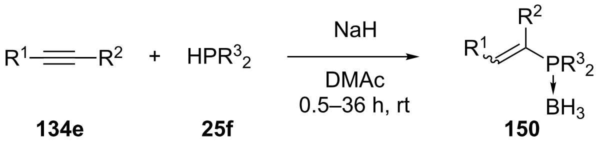
| Entry | $R^1$ | $R^2$ | Yield of **148** (%) | *Z*/*E* ratio |
|---|---|---|---|---|
| 1 | *n*-Hex | Ph | 76 | >95/5 |
| 2 | Ph | Ph | 0 | |
| 3 | $(CH_2)_2OH$ | Ph | 49 | >95/5 |
| 4 | $CH_2OCH_3$ | Ph | 33 | >95/5 |
| 5 | *n*-Hex | Me | 82 | 80/20 |
| 6 | *n*-Hex | *t*-Bu | 49 | 70/30 |

**Table 18:** Hydrophosphination reactions of terminal alkynes **125e** with phosphine boranes **13f** using a Pd catalyst (dba = dibenzylideneacetone, dppp = 1,3-bis(diphenylphosphino)propane).



| Entry | $R^1$ | $R^2$ | Yield of **149** (%) |
|---|---|---|---|
| 1 | *n*-Hex | Ph | 84 |
| 2 | Ph | Ph | 49 |
| 3 | -$(CH_2)_2OH$ | Ph | 71 |
| 4 | -$CH_2OCH_3$ | Ph | 73 |
| 5 | Cy | Ph | 60 |
| 6 | *n*-Hex | Me | 85 |
| 7 | Ph | Me | 53 |

**Table 19:** Hydrophosphination of alkynes **134e** with phosphine–borane complexes **25f** (DMAc = dimethylacetamide).



| Entry | $R^1$ | $R^2$ | $R^3$ | Yield of **150** (%) | *E/Z* ratio |
|---|---|---|---|---|---|
| 1 | Ph | Me | Cy | 85 | >20/1 |
| 2 | Ph | Ph | *t*-Bu | 88 | >20/1 |
| 3 | Ph | Me | *p*-(iPrO)-$C_6H_4$ | 78 | >20/1 |
| 4 | Ph | Ph | iBu | 79 | 4/1 |
| 5 | *p*-$CF_3$-$C_6H_4$ | *p*-$CF_3$-$C_6H_4$ | Ph | 98 | >20/1 |
| 6 | *o*-Tol | *o*-Tol | Cy | 99 | >20/1 |

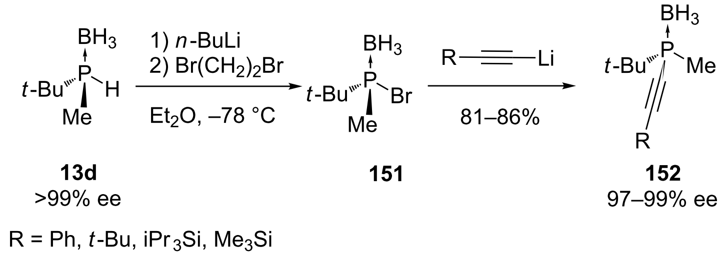
halophosphine with a metal acetylide. Grignard [258,259] and organolithium [244,260-262] reagents have frequently been used since many years. The main disadvantage is the incompatability of lithium and magnesium reagents with alkynylphosphines having labile functional groups susceptible to nucleophilic attack.

This approach is mainly used for the synthesis of tertiary phosphines. It is difficult to synthesize secondary alkynylphosphines since they easily convert into their phosphaallene tautomer. They can only be obtained when they have sterically hindering substituents [263,264].

The asymmetric synthesis of alkynylphosphines also suffers from limited availability of unsymmetrical halophosphines and their weak configurational stability. Stereospecific substitution at chiral phosphorus atoms by alkynyl nucleophiles has been reported by Imamoto et al. (Scheme 45) [265]. Firstly, a bromo(*tert*-butyl)methylphosphanyl borane **151** was formed in situ by treating the enantiomerically pure (*S*)-(*tert*-butyl)methylphosphine borane **13d** with *n*-BuLi and 1,2-dibromoethane. An alkynyl lithium reagent was directly added to intermediate **151**. The expected substitution products **152** were obtained in high yield and almost exclusively with inversion of configuration, resulting in excellent stereospecificities.

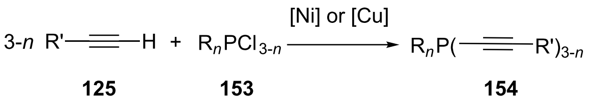
## Catalytic C(sp)–P bond formation

This type of carbon–phosphorus bond formation relies on the cross-coupling reaction in the presence of a catalyst. The cross-coupling reaction is in general performed between a terminal alkyne **125** and an electrophilic phosphorus reagent in the form of a halophoshine **153**, mostly chlorophosphine, in the presence of a catalyst such as nickel ($Ni(acac)_2$) [244,266,267] or copper (CuI) [268-270] (Scheme 46). The nickel based catalyst was not



**Scheme 45:** Formation and substitution of bromophosphine borane **151**.

suitable for the cross-coupling of alkynes containing a sensitive alkoxy or amino functional group. Therefore, another catalytic method was developed using copper(I) salts.



**Scheme 46:** General scheme for a nickel or copper catalyzed cross-coupling reaction.

Alkynylphosphines were synthesized through the use of a copper-catalyzed reaction between a secondary phosphine borane **13k** and various 1-bromoalkynes **155** in the presence of 1,10-phenanthroline as a ligand and $K_2CO_3$ or $K_3PO_4$ as a base (Scheme 47). This was the first method involving a nucleophilic phosphorus reagent in the synthesis of alkynylphosphines and was presented by the group of Gaumont [271,272]. The method was applicable for dialkyl, diaryl or alkylaryl phosphine boranes **13k** and required only mild conditions.

## Conclusion

The developments over the past years in the field were reviewed. The use of phosphines as ligands in metal complex catalysis has been a major driving force for the synthesis of functionalized phosphines. In recent years many catalytic procedures have emerged. In general these catalytic protocols proceed under milder conditions that tolerate the presence of functional groups. Gradually a broader variety of phosphines is accessible. Due to the growing importance of asymmetric catalysis, a lot of attention has been paid to the asymmetric synthesis of chiral phosphines. The challenge to find a general protocol that permits simple access to chiral phosphines, is still ongoing and further developments are required.

## Acknowledgements

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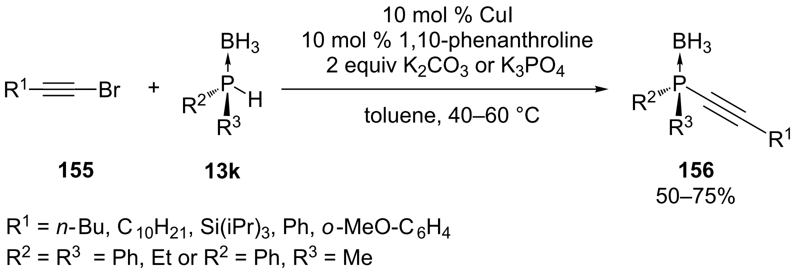

**Scheme 47:** Copper-catalyzed synthesis of alkynylphosphines **156**.

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# Atherton–Todd reaction: mechanism, scope and applications

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Review

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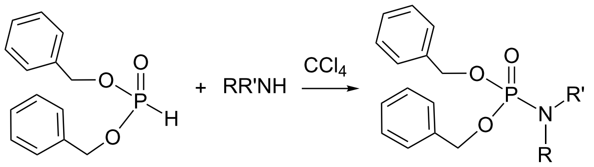
## Abstract

Initially, the Atherton–Todd (AT) reaction was applied for the synthesis of phosphoramidates by reacting dialkyl phosphite with a primary amine in the presence of carbon tetrachloride. These reaction conditions were subsequently modified with the aim to optimize them and the reaction was extended to different nucleophiles. The mechanism of this reaction led to controversial reports over the past years and is adequately discussed. We also present the scope of the AT reaction. Finally, we investigate the AT reaction by means of exemplary applications, which mainly concern three topics. First, we discuss the activation of a phenol group as a phosphate which allows for subsequent transformations such as cross coupling and reduction. Next, we examine the AT reaction applied to produce fire retardant compounds. In the last section, we investigate the use of the AT reaction for the production of compounds employed for biological applications. The selected examples to illustrate the applications of the Atherton–Todd reaction mainly cover the past 15 years.

## Review

### 1. Introduction

The reaction of dialkylphosphite with primary or secondary amines in the presence of a base in carbon tetrachloride produces phosphoramidates. This reaction, initially studied by F. R. Atherton, H. T. Openshawand, and A. R. Todd [1] in 1945 (Scheme 1) and now identified as the Atherton–Todd (AT) reaction, was actually discovered by chance. Indeed, these authors attempted to purify a solution of dibenzyl phosphite in carbon tetrachloride by its treatment with an aqueous ammonia solution. They observed the formation of a precipitate that was identified as *O*,*O*-dibenzyl phosphoramidate. However, no reaction occurred when dibenzyl phosphite was mixed alone with carbon tetrachloride, whereas an exothermal reaction occurred if gaseous ammonia was passed through this solution or if this solution was shaken with an aqueous ammonia solution, with chloroform and ammonium chloride as byproducts. The replacement of ammonia with primary and secondary amines yielded N-substituted phosphoramidates (Scheme 1). It is noteworthy, that less nucleophilic amines like aniline can also be engaged in the AT reaction, but the expected phosphoramidates are only produced in modest yields if a tertiary amine is added to the reaction media. These findings were published in the initial works of Atherton and Todd and completed in 1947 [2].



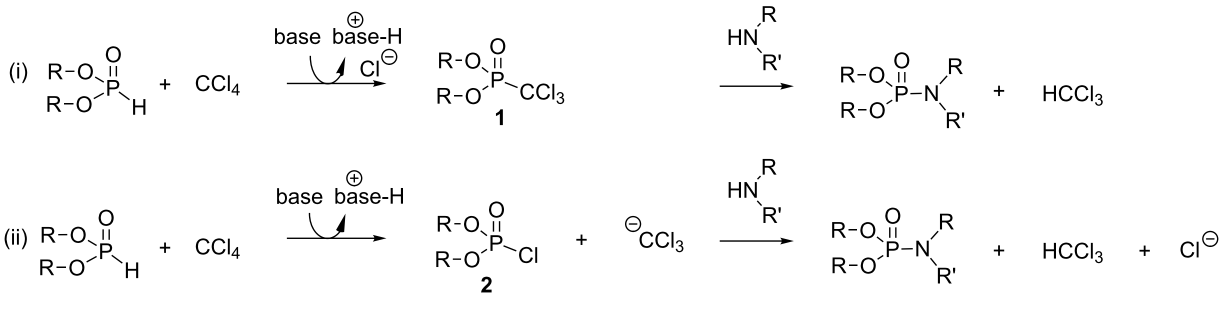
**Scheme 1:** Pioneer works of Atherton, Openshaw and Todd reporting on the synthesis of phosphoramidate starting from dibenzylphosphite (adapted from [1]).

To the best of our knowledge, we herein report the first compilation of the works which studied or used this reaction. First the question of the mechanism of the Atherton–Todd reaction, which has been widely discussed in literature, is addressed. Then, the scope of this reaction is presented. Finally selected applications of this reaction are discussed. This selection mainly covers the applications of the past 15 years. A special focus is put on the synthesis of flame-retardant materials and the design of phosphorus-based amphiphilic compounds.

## 2. Mechanism of the Atherton–Todd reaction

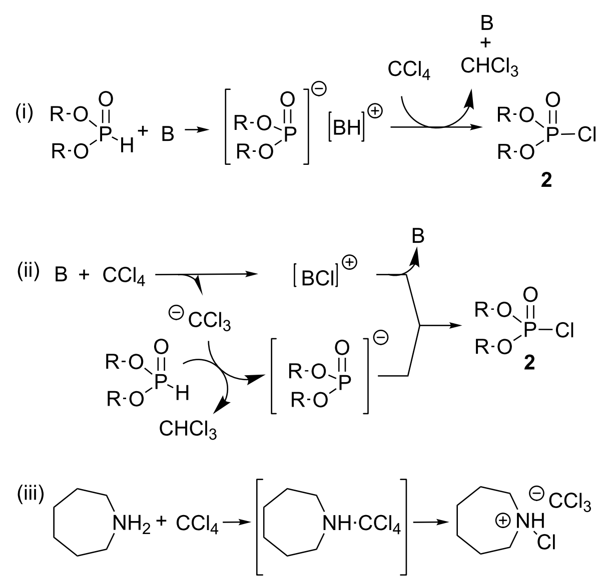
In their initial publication, Atherton and Todd have suggested two possible mechanisms to explain the formation of phosphoramidate [1]. The first one (Scheme 2-i) was based on a two-step sequence with the formation of dialkyl trichloromethylphosphonate **1** as the intermediate species. The second mechanism, which was not preferred at that time by these authors (Scheme 2-ii), was based on the formation of dialkyl chlorophosphate **2** as a possible intermediate species. The preference for mechanism 1 was justified by the existence of some similitude with the reactivity of carbon tetrachloride reported in literature (e.g., the synthesis of arylcarboxylate according to a Reimer–Tiemann reaction [3,4]) and because the second step (i.e., the nucleophilic substitution on the electrophilic phosphorus) shares some characteristics with the reactivity of trichloroacetophenone (haloform reaction [5]). Moreover, the absence of the reactivity of alcohol when mixed with dialkyl phosphite and carbon tetrachloride in the presence of trialkylamine convinced the authors to prefer this first mechanism 1 (i). Nevertheless the same authors [2] revised their preference two years later and mentioned that the reaction may probably occur following mechanism 2 (Scheme 2-ii). This assumption was based on the observation that the replacement of carbon tetrachloride by bromotrichloromethane enhanced the reaction rate. They explained this increase of reactivity by the easier nucleophilic attack of the dialkylphosphite salt on the bromine atom of $CBrCl_3$ when compared to the reaction with $CCl_4$. It is also noteworthy, that the use of bromotrichloromethane allowed the phosphorylation of ethanol. The formation of tetrabenzyl pyrophosphate, observed by Atherton and Todd during the reaction that engaged benzyl phosphite, potassium hydroxide and carbon tetrachloride (or bromotrichloromethane), is also more easily explained by mechanism 2. Moreover, the impossibility to isolate the intermediate species in this reaction incited Atherton and Todd to prefer mechanism 2 (ii) because diethyl chlorophosphate **2** is a more reactive intermediate.

After these pioneering works, the first investigation of the mechanism of the Atherton–Todd's reaction was reported by Steinberg in 1950 [6]. In this work, the synthesis of dialkyl chlorophosphate **2** is reported by reacting dialkyl phosphite with carbon tetrachloride in the presence of 10 to 15 mol percent of trialkylamine acting as a catalyst. These authors proposed a more detailed mechanism for the formation of dialkyl chlorophosphate **2** with the suggestion of two distinct pathways (Scheme 3). One possibility included the nucleophilic attack of



**Scheme 2:** Mechanisms 1 (i) and 2 (ii) suggested by Atherton and Todd in 1945; adapted from [1].

the deprotonated dialkyl phosphite on one chlorine atom of carbon tetrachloride (Scheme 3-i), whereas the second synthetic pathway (Scheme 3-ii) involved the nucleophilic attack of the base on carbon tetrachloride as a preliminary step. The kinetic data reported by Steinberg did not allow for discrimination between these two possibilities. Beside the kinetic study, Steinberg accumulated further interesting information relative to the mechanism of the Atherton–Todd reaction. First, Steinberg indicated that no reaction occurred when dialkyl trichloromethylphosphonate, prepared unambiguously by another method, was mixed with ammonia. This claim is in contradiction with one previous publication by Kamai [7,8], stipulating that phosphoramidate was produced by the reaction of dialkyl trichloromethylphosphonate and a selected amine. Steinberg has also shown that the structure of the amine has an influence on the rate of the reaction. Indeed, triethylamine is a much more efficient catalyst (1000 fold) than pyridine. Interestingly, tributylamine or tripentylamine catalyzed this reaction with the same rate than triethylamine. This last observation by Steinberg is in favor of the first mechanism (Scheme 3-i), since differences of the reaction rate should be expected for the nucleophilic addition of trialkylamine on carbon tetrachloride (Scheme 3-ii) depending on the structure of the alkyl chains. The works of Steinberg eliminated the possibility of a mechanism proceeding by radical processes. Indeed, the use of UV irradiation or radical initiators in the absence of trialkylamine was found to be unsuccessful to produce phosphoramidates. Recently, Krutikov et al. [9] have reported that hexahydroazepine (a secondary amine with a p$K_a$ of 11.1 (Scheme 3-iii), used as a base in the AT reaction) probably reacted first with carbontetrachloride to produce a charge-transfer complex (this type of interaction was confirmed by refractometric titration). However, in this reaction the trichloromethylphosphonate, which would result from the reaction of the anion $CCl_3^-$ with chlorophosphate, was never observed because $CCl_3^-$ probably reacted as a base in the presence of dialkylphosphite (Scheme 3-ii). This experiment indicates that the basicity/nucleophilicity of the amine has an impact on the first step of the mechanism (a charge-transfer complex was not observed with a less basic amine like 2-aminopyridine) while the chlorophosphate **2** was assumed to be one common intermediate independent from the nature of the initial step.



**Scheme 3:** Two reaction pathways (i and ii) to produce chlorophosphate **2**. Charge-transfer complex observed when hexahydroazepine was used as a base (iii); adapted from [6] and [9].

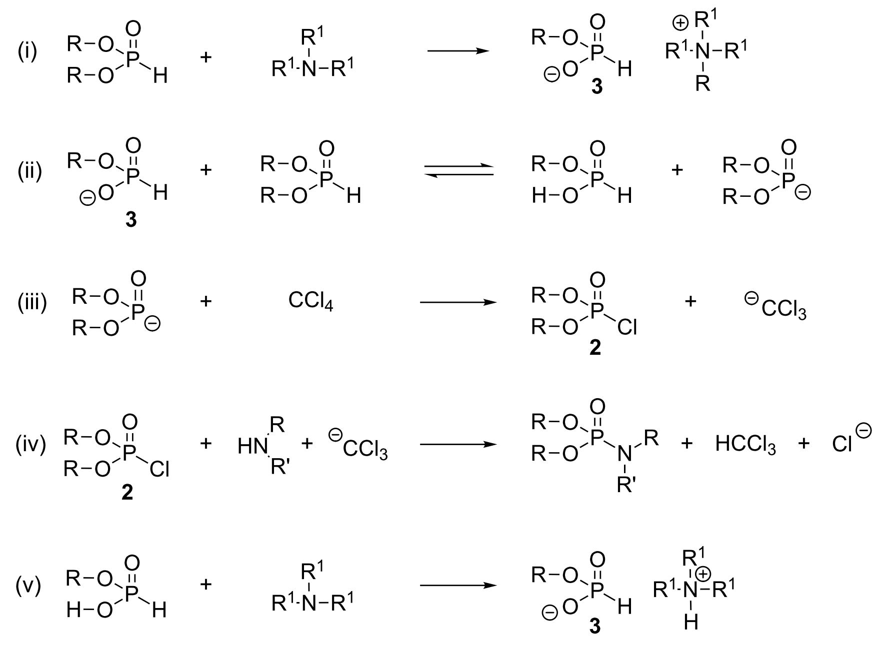
Almost 35 years after the work of Steinberg, Engel et al. [10] have re-investigated the mechanism of the Atherton–Todd reaction, more specifically the first step (reaction of dialkyl phosphite with carbon tetrachloride and a base) by using CPG as an analytical tool. Triethylamine or sodium hydride was used as base. With sodium hydride the deprotonation occurs in a preliminary step to produce sodium dialkyl phosphite. All these attempts were never able to identify trace amounts of diethyl trichloromethylphosphonate (mechanism i, Scheme 2), thereby favoring mechanism 2 (Scheme 2). Additional experiments with the aim of discarding the involvement of a carbene species as an intermediate were carried out. The reactions achieved in cyclohexene (a solvent with the capacity to trap any traces of carbene) produced the same conversion rate. One exception to this last observation was found when the experimental conditions combined both the use of strict aprotic conditions (use of sodium hydride for the deprotonation of phosphite) and dimethyl phosphite as a substrate. This result might be rationalized by the instability of trichloromethanide in aprotic media which in the presence of dimethyl phosphite or dimethyl chlorophosphate produced a significant amount of carbene. It must be mentioned that methyl esters of phosphate or phosphonate have a particular reactivity since the methyl group can be easily removed by trimethylamine as illustrated by the dealkylation of *O*,*O*-dimethyl phosphoramidate [11,12] or by the thermal sensitivity of dimethyl chlorophosphate as mentioned by Steinberg et al. [6]. However, no trace amount of carbene was detected when triethylamine was replaced with sodium hydride as a base, while all other parameters were identical. These results indicated that the carbene pathway is unlikely to occur under the classical conditions of the Atherton–Todd reaction (dialkyl phosphite, trialkylamine, alkyl- or dialkylamine and carbon tetrachloride or bromotrichloromethane).

The use of dimethyl phosphite as a substrate in the AT reaction was also studied by Roundhill and co-workers in a series of articles. They investigated the role of the salt **3** (Scheme 4-i), which can be produced by reacting trialkylamine with dialkyl phosphite [13]. Indeed, it was previously reported that this salt can catalyze (2 mol percent) an AT reaction [14,15]. However, there is no evidence that this mechanism could have a general scope. Roundhill et al. [16] have first studied the consequences of the replacement of carbon tetrachloride by a member of the chlorofluorocarbon class of compounds. In this study, they observed that the introduction of a fluorine atom in place of a chlorine atom reduced the reactivity leading to the following relative reactivity: $CCl_4$ > $CFCl_3$ > $CF_2Cl_2$ >> $CHCl_3$. In this study, dimethyl phosphite was primarily used as a substrate, and cyclohexylamine as a nucleophilic amine. The formation of the salt **3** was observed when cyclohexylamine was added to dimethyl phosphite, thus pointing out the influence of the order of addition of the reactants.

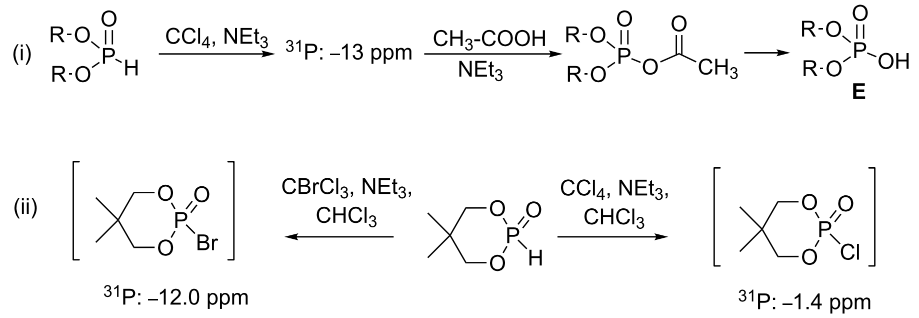
Roundhill et al. [17] used computational chemistry to further investigate the mechanism of the Atherton–Todd reaction (HF-6.31G* level of theory and Moller–Plesset (MP2) to correct correlation effects). They found that the calculation supported the mechanism shown in Scheme 4 that starts with the dealkylation of dimethyl phosphite by an amine (Scheme 4-i). Then, this salt acted as a base to deprotonate dimethyl phosphite (Scheme 4-ii), which subsequently reacted with $CCl_4$ to produce chlorophosphate **2** as an intermediate species. In the last step, the salt **3** is regenerated by deprotonation with trialkylamine (Scheme 4-v). Nevertheless, the scope of this theoretical study may be regarded as limited, since only dimethyl phosphite was considered in this study. It is indeed well-established that dimethyl phosphite has a singular reactivity when compared to others dialkyl phosphites [6,11]. Moreover, only unsubstituted amine (ammonia) and monosubstituted amine were considered in this theoretical study.

More recently, dialkyl trichloromethylphosphonate was again proposed as an intermediate species in a reaction producing dialkyl phosphate (Scheme 5-i) [18]. The authors postulated its formation on the basis of $^{31}P$ NMR analysis. The $^{31}P$ chemical shift reported for the intermediate in this study (−13 ppm) was not consistent with the chemical shift of dialkyl trichloromethylphosphonate reported in other studies (6.5 ppm [19,20]). A $^{31}P$ chemical shift at −13 ppm would be more likely attributed to a pyrophosphate (−12.6 ppm, R = Et) [1], whereas diethyl chlorophosphate is observed at 3.5 ppm [21]. The formation of pyrophosphate could be explained by the presence of trace amounts of water concomitantly with the absence of nucleophile species. Then, the addition of acetic acid produced a mixed anhydride as suggested by the authors (Scheme 5-i). In another recent study, chloro- and bromophosphate intermediates were characterized by $^{31}P$ NMR thus supporting the mechanism 2 (Scheme 2). In this study, Döring et al. reported that the shielding effect of bromine was also correlated to its higher reactivity (Scheme 5-ii) [22].

Feringa et al. developed a methodology for the determination of the enantiomeric excess of a chiral amine based on the use of phosphorinanes derivatives. Two synthetic pathways i) the AT



**Scheme 4:** Mechanism of the Atherton–Todd reaction with dimethylphosphite according to Roundhill et al. (adapted from [13] and [17]).

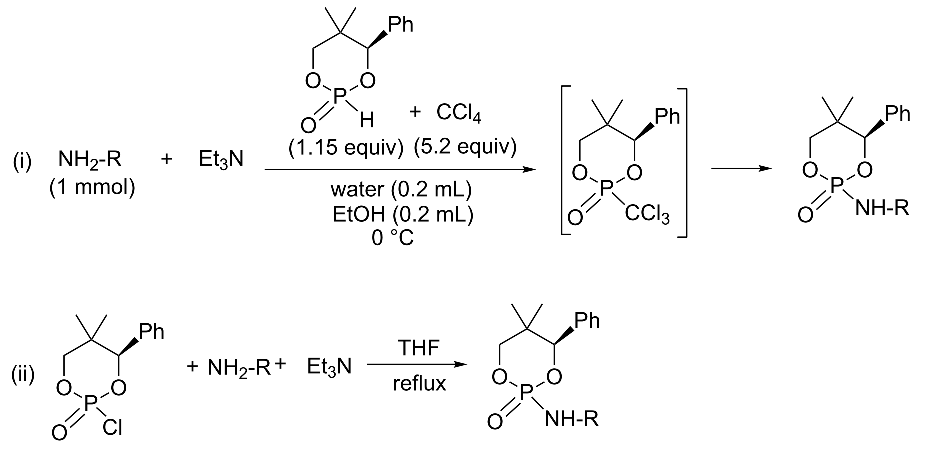


**Scheme 5:** Synthesis of dialkyl phosphate from dialkyl phosphite (i) and identification of chloro- and bromophosphate as reaction intermediate (ii) (adapted from [18] (i) and [22] (ii)).

reaction and ii) the direct use of chlorophosphate were evaluated for the derivatization of chiral amine (or alcohol) as reported in Scheme 6. For the AT reaction (i) [23] they used the conditions of Ji et al. [24], who have previously reported that the AT reaction can proceed in aqueous organic solvents (water/ethanol or water/DMF). Accordingly, a mixture of phosphorinane and $CCl_4$ was added dropwise on a cooled (0 °C) solution of amino derivative and triethylamine in a water/ethanol mixture. For this reaction, the volume of the solvent mixture must be limited as mentioned in a review published by Feringa et al. [25]. The use of aqueous organic condition for the AT reaction led the authors to postulate trichloromethylphosphonate as an intermediate species because it is less sensitive to water when compared to chlorophosphate (Scheme 6) [26,27].

It must be noted that the intermediates were not characterized by NMR spectroscopy. Furthermore, we can hypothesize that when aqueous organic conditions are used, competitive reactions could take place on the chlorodioxaphosphorinane as an intermediate that would involve the different nucleophilic species present, which are water, ethanol and amine. Different experimental parameters listed below are in favor of the existence of competitive reactions that could have crucial consequences on the issue of the reaction and on the nature of the intermediate species: i) the addition of the phosphorinane and trialkylamine was achieved at 0 °C (this should favor the formation of the kinetic product). ii) Phosphorinane and trialkylamine were added dropwise on the primary amine (this is the best condition to have an excess of the nucleophilic amine versus the chlorophosphorinate intermediate and consequently to favor its addition on the chlorophosphate), iii) the low quantities of solvent used (this is also in favor of the addition of the nucleophilic amine, which is in competition with water and ethanol).

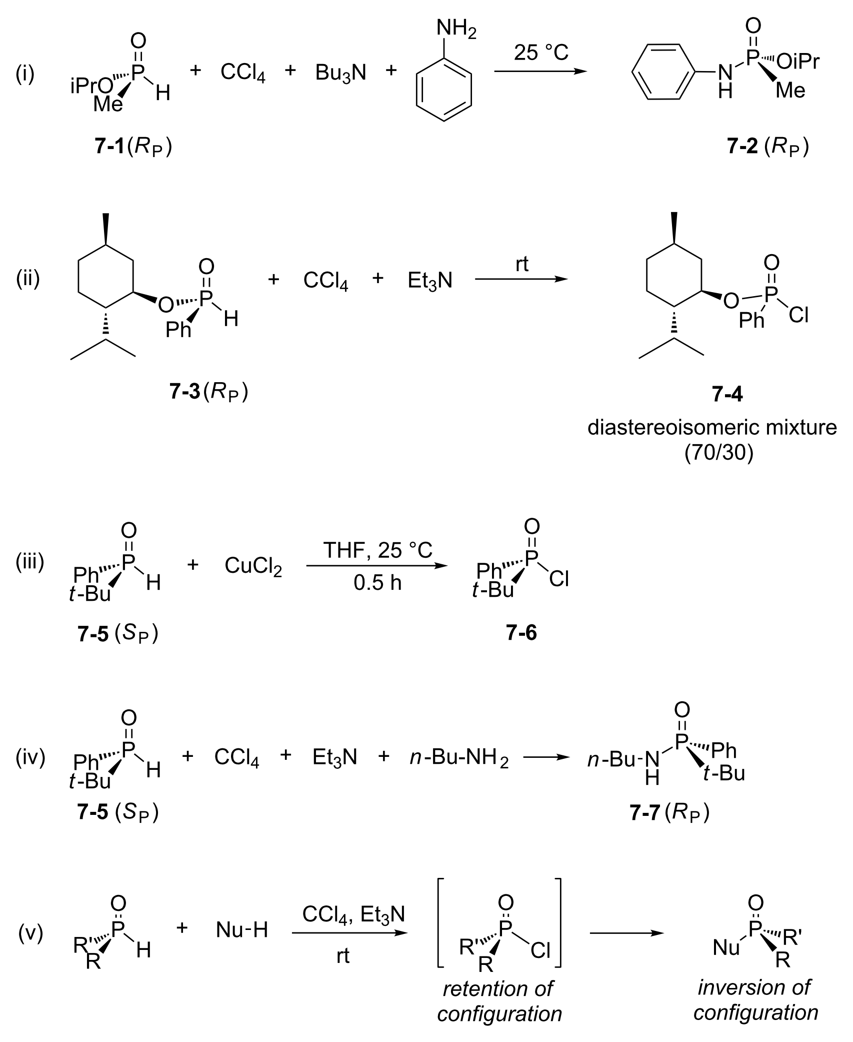
Moreover, these experimental details are also consistent with the reaction rate of chlorophosphate with nucleophiles reported by Corriu et al. [28]. Indeed, they have shown that the second-order rate constants for the solvolysis of diethyl chlorophosphate with different nucleophiles including water, ethanol,



**Scheme 6:** Synthesis of chiral phosphoramidate with trichloromethylphosphonate as the suggested intermediate (i) and directly from a chlorophosphate used as a substrate (ii) (adapted from [25-27]).

phenol and diethylamine were $0.35 \cdot 10^{-4}$, $0.12 \cdot 10^{-5}$, $0.38 \cdot 10^{-3}$ and $0.28 \cdot 10^{-1}$ L $mol^{-1}s^{-1}$, respectively. These data do not take into account the effect of an organic base present in the reaction media of an AT reaction. It reveals, however, that the secondary amine is much more reactive than phenol, water and ethanol in a reaction with chlorophosphate. Consequently, the existence of the trichloromethylphosphonate as an intermediate species in the experiments of Feringa et al. must be considered with caution because several experimental details are in favor of the existence of a competitive process that could, actually, be in favor of the addition of the nucleophilic amine on chlorophosphorinane as intermediate.

All the studies reported above shed some light on the mechanism of the AT reaction. None of these studies, however, focused on the chirality at the phosphorus atom. The first investigation of the stereochemistry of the AT reaction was reported by Reiff and Aaron [29]. They used enantiopure *O*-isopropyl methylphosphonite **7-1** (Scheme 7-i) as a substrate. This substrate was purified by distillation with no racemization. However, rapid racemization was observed when **7-1** was treated with sodium methoxide in methanol. The use of **7-1** in the AT reaction in the presence of $CCl_4$, tributylamine and aniline as a nucleophile produced **7-2** with full stereocontrol (note: due to the substitution of a hydrogen atom by an aniline moiety, the numbering used to determine the chirality at the phosphorus atom was changed; consequently, the (*R*) configuration is preserved in the course of this reaction). The authors also observed a racemization (Scheme 7-ii) when the same reaction was achieved without the addition of a nucleophile (aniline in the present case). The use of similar reaction conditions ($CCl_4$, $NEt_3$) led Mikolajczyk et al. [30] to observe the formation of a mixture of diastereoisomers due to a racemization at the phosphorus atom. However, this racemization was not always observed which points out the different stability of diastereoisomeric species (cyclic phosphite in the present case).



**Scheme 7:** Selection of results that address the question of the stereochemistry of the AT reaction (adapted from [29-32]).

Other conditions of chlorination such as the use of *N*-chlorosuccinimide or, as reported more recently, $CuCl_2$ produced, in the latter case, **7-6** with full stereocontrol (Scheme 7-iii) as unambiguously determined by X-ray diffraction analysis [31]. The addition of nucleophilic species (amine, alcohol, alkyllithium, etc.) on **7-6** or other chlorophosphonites was stereocontrolled with the inversion of the configuration at the phosphorus atom. In another publication it is reported on the AT reaction starting from enantiopure (*S*)-phenyl *tert*-butyl phosphinous acid **7-5** (Scheme 7 iv) [32]. In that case the final product **7-7** was isolated with full stereocontrol. This result indicates that both steps (i.e., the chlorination and subsequently the substitution of the chlorine atom with the nucleophile) were stereocontrolled. The detailed mechanism of each step, which may involve pentacoordinated phosphorus intermediates [28], is not well established. From a stereochemical point of view, these results can be summarized as shown in Scheme 7-v.

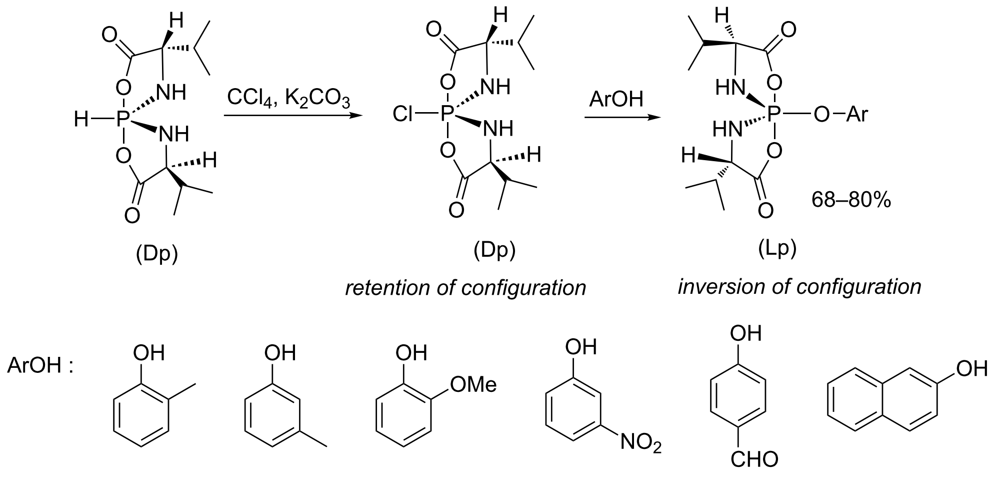
Other recent studies have reported stereocontrolled AT reactions. Han et al. [33] described the preparation of optically active organophosphorus acid derivatives from menthyl-based H-phosphinates (or secondary phosphine oxides) and a nucleophilic species (amines or alcohols) under AT reaction conditions. The reaction proceeded with a full stereoinversion at the phosphorus atom and led to the isolation of optically pure P–N coupling products with nearly quantitative yields (94%). The chemical structure and the stereochemistry of the products were unambiguously established by X-ray diffraction analysis. It is noteworthy that such coupling conditions have been extended to a wide variety of substrates including nitro-, methoxy-, trifluoromethylphenol or thiophenol with an almost similar reactivity. However, an exception was made when considering the reaction with aliphatic thiols (e.g., *n*-alkylthiols) [33]. In all studied cases, the authors concluded that the first step (i.e., the formation of a phosphoryl chloride intermediate) was achieved with retention of configuration (Scheme 7-v). Then, a subsequent attack of the nucleophilic substrate (amine, alcohol or thiophenol) occurred at the opposite side of the phosphorus–chlorine bond to afford the substitution product with high stereospecificity and an inversion of configuration.

Zhao et al. have also investigated the stereochemistry of the AT reaction by using chiral valine hydrospirophosphorane as a substrate and phenol derivatives as nucleophiles [34]. The mechanism described in their publication suggested the formation of a chlorinated spirophosphorane species as an intermediate, which retains the configuration at the phosphorus center. This hypothesis is strongly supported by X-ray diffraction analysis of a single crystal structure of the P–Cl intermediate species (Scheme 8). Thereafter, the reaction with phenol proceeds with an inversion of the configuration after a nucleophilic attack at the opposite side of the phosphorus–chlorine bond.

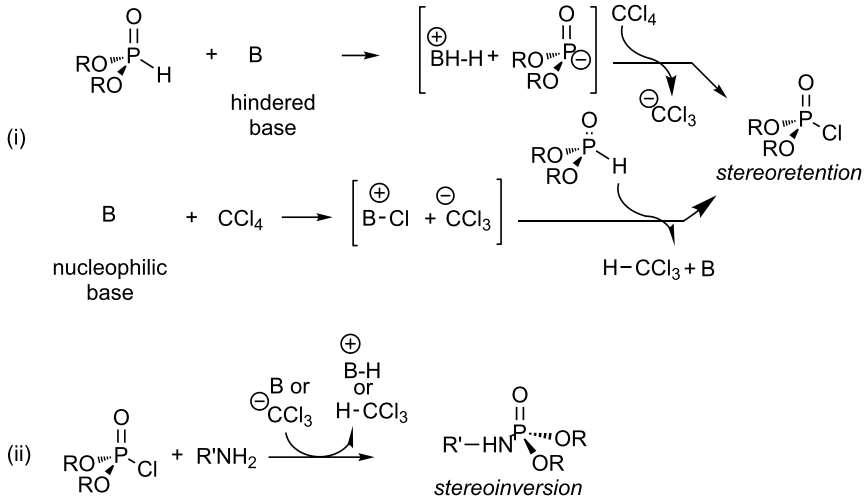
In conclusion, all studies which have investigated the mechanism of the Atherton–Todd reaction resulted in a summary of the likely reaction mechanism in Scheme 9. This mechanism seems to be general, but a different mechanism can take place when dimethyl phosphite is used due to its reaction with amine as shown in Scheme 4. On the basis of all these results, the hypothesis of the formation of dialkyl trichloromethylphosphonate as an intermediate of the Atherton–Todd reaction must be discarded.

## 3. Scope and synthetic conditions

$CCl_4$ was the first solvent used in AT reactions. It plays a double role since it also acts as a halogenating agent that reacts

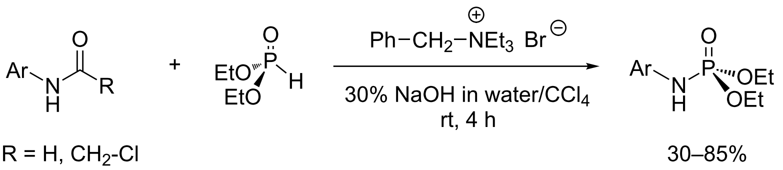


**Scheme 8:** Synthesis of phenoxy spirophosphorane by the AT reaction (adapted from [34]).



**Scheme 9:** Suggested mechanism of the Atherton–Todd reaction, (i) and (ii) formation of chlorophosphate with a hindered or nucleophilic base; (iii) nucleophilic substitution at the phosphorus center with stereoinversion.

with phosphite to produce chlorophosphate as an intermediate. However, many other solvents, including dichloromethane, chloroform, diethyl ether [35], THF [31], acetonitrile [34], DMF [36] and toluene [37] were also used. In that case a stoichiometric amount of the halogenating agent ($CCl_4$, $CBrCl_3$) is usually employed. Among these solvents, those that are not miscible with water are usually a good choice (e.g., $CH_2Cl_2$, $CHCl_3$). At several occasions, alcohol (methanol, ethanol) was also used as a solvent even though it may compete with the nucleophilic species. This choice was made when the reagents were poorly soluble in other solvents (e.g., reagents like ammonium chloride salts). When this type of solvent is employed, the addition order of reagents can influence the result. Indeed, it is better to add $CCl_4$ (or $CBrCl_3$) and the tertiary amine at the end to be sure that the nucleophile (e.g., an amine) will be present when the chloro- or bromophosphate derivatives will be formed in situ. The mixture of reagents is usually achieved at 0–5 °C. Then, an additional stirring period of a few minutes to a few hours at rt (20 °C) is applied. The use of an anhydrous solvent is usually preferred in order to avoid the hydrolysis of chlorophosphate to pyrophosphate or phosphate. It is also possible to add molecular sieves (4 Å) to the reaction medium to remove traces of water, which can be useful when a poor nucleophilic species is employed. However, there are also a few reports on AT reactions in water–organic solvent mixtures when reactive nucleophilic species were used (primary amine) and under biphasic conditions with a phase-transfer agent as shown in Scheme 10 [38]. In this study, water and $CCl_4$ were used to produce the biphasic system. NaOH is the base and benzyltriethylammonium bromide acted as a phase-transfer agent. This procedure was applied to the synthesis of *N*-arylphosphoramidate. It was observed that the classical AT reaction ($CCl_4$, base, anhydrous solvent) applied to ortho-substituted anilines was not successful. However, the use of formanilide (R = H) or chloroacetanilide (R = $CH_2Cl$) as a substrate (Scheme 10) produced the expected phosphoramidate by a mechanism which simultaneously involved deacetylation. The higher reactivity of formanilide and chloroacetanilide, when compared to aniline, was explained by the higher acidity of the remaining N–H bond. But the isolated yields were usually modest (50–70%) and only occasionally high (85%). With respect to the reactivity of chlorophosphate with water, Strawinski et al [21] reported that chlorophosphate can be placed in THF with 0.5 equiv of water without any trace of degradation but the addition of a base immediately gives rise to the formation of pyrophosphate ($^{31}$P NMR around −12 ppm alkyl pyrophosphate and −25 ppm tetraaryl pyrophosphate) and

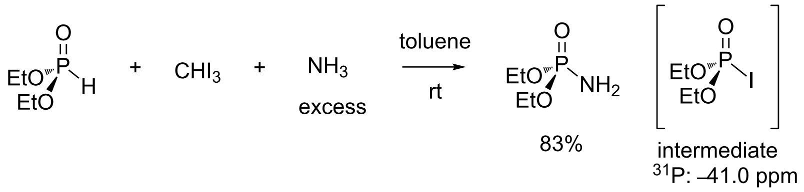


**Scheme 10:** AT reaction in biphasic conditions (adapted from [38]).

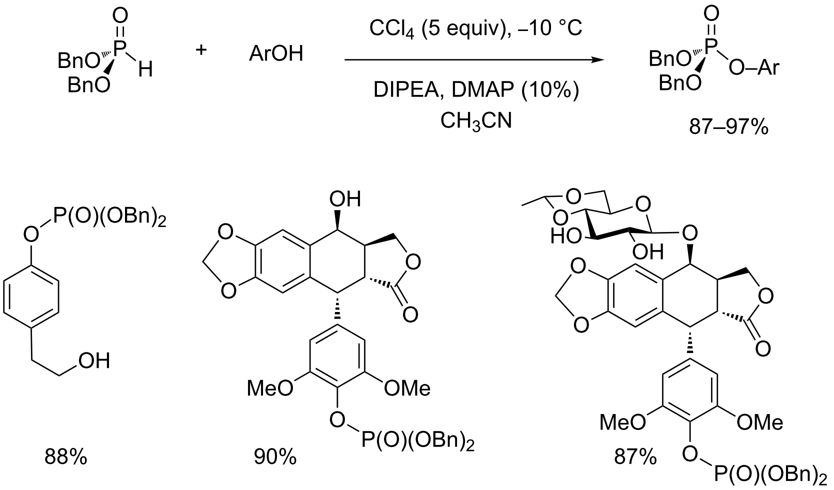
to phosphate in the presence of additional water ($^{31}$P NMR dialkyl phosphate 0.4 ppm and diaryl phosphate −9.6 ppm). With the use of a biphasic system it is likely that the reaction takes place in the $CCl_4$ phase because all the reagents, except the hydroxide anion, are soluble in $CCl_4$. The hydroxide anion is actually transferred to the organic phase thanks to the phase-transfer agent.

Different halogenating agents were used to produce in situ chlorophosphate from phosphite. $CCl_4$ was used systematically for a long period of time. However, Atherton and Todd [2] have shown that reaction rates were increased by using $CBrCl_3$. This last halogenating agent is likely the reagent of choice when a stoichiometric amount or a slight excess is employed. Other halogenating agents were studied for the AT reaction. $CBr_4$ [39] is also able to produce reactive bromophosphate as an intermediate species. However, it is more expensive compared to $CBrCl_3$ and, to the best of our knowledge, better results with the use of $CBr_4$ have not been published yet. The AT reaction was also reported with the use of trichloroacetonitrile as a halide source [35]. Accordingly, the chlorophosphate was formed in the presence of triethylamine. Iodoform ($CHI_3$) is another reagent that can be used as a halide source for the AT reaction [37]. As shown in Scheme 11, gaseous anhydrous ammonia was passed through a solution of diethyl phosphite and iodoform in toluene to produce the expected phosphoramidate in good yield (83%). In an independent experiment the authors have identified the iodophosphate ($^{31}$P at −41.0 ppm), a compound which decomposes when stored for a few hours at rt.

With respect to the base used for the AT reaction, it can be noticed that a trialkylamine is generally the best choice. This amine is frequently triethylamine or diisopropylethylamine (Hünig's base, DIPEA). It must be noted that the use of this hindered base (DIPEA) could favor the mechanism detailed in Scheme 3 instead of a mechanism that would involve a nucleophilic attack of the amine on the alkyl chain of the phosphite (Scheme 4). Some authors add catalytic quantities of dimethylaminopyridine (DMAP). For instance, this procedure was used to produce arylphosphate by reacting phenol with dibenzyl phosphite [40]. The presence of DMAP and limited excess of $CCl_4$ (5 equiv) produced the expected aryl phosphate in excellent yield even at a low temperature (−10 °C). Interestingly, this study illustrates that the AT reaction is chemoselective since only the phenol reacts even in the presence of primary or secondary alcohols (Scheme 12).



**Scheme 11:** AT reaction with iodoform as halide source (adapted from [37]).



**Scheme 12:** AT reaction with phenol at low temperature in the presence of DMAP (adapted from [40]).

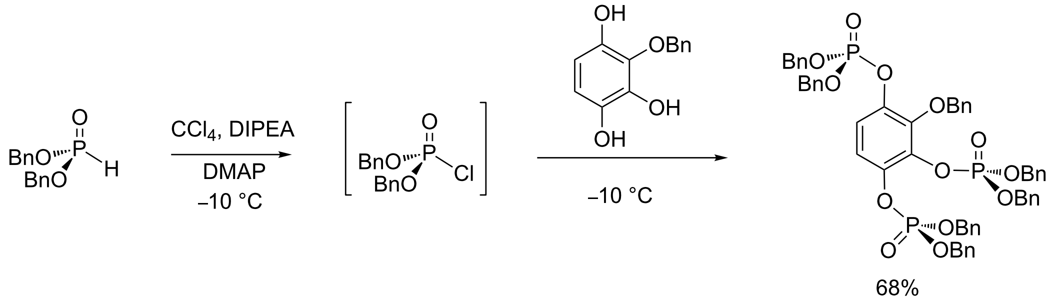
With the AT reaction, the order of addition of reagents can impact its efficacy. Usually, the phosphite or the halide source ($CBrCl_3$) is added dropwise to a mixture of the nucleophile (amine, phenol), trialkylamine (e.g., DIPEA) and a solvent cooled at −10 °C to 5 °C. According to this procedure, the chlorophosphate formed as an intermediate immediately reacts with the nucleophile already present in the reaction medium. It is noteworthy that another synthetic procedure consists to firstly prepare the chlorophosphate and then add the nucleophilic species (Scheme 13) [41]. Following this procedure, chlorophosphate was first prepared at a low temperature (−10 °C) by reacting dibenzyl phosphite with $CCl_4$ in the presence of DIPEA and a catalytic amount of DMAP. Then, the nucleophile (in that case a phenol) is added dropwise to the chlorophosphate solution at −10 °C to produce, after purification, the triphosphate in 68% yield. Generally, the first protocol is preferred to avoid any hydrolysis of chlorophosphate, which could be explained by the presence of trace amounts of water.

As indicated above, a tertiary amine is the preferred base for the AT reaction. However, primary or secondary amines can be also used when they simultaneously act as a nucleophile and a base. In that case, two equivalents of amine must be added (Scheme 11). The use of NaOH as a base was also reported (exemplified in Scheme 10) in a protocol involving phase-transfer catalysis.

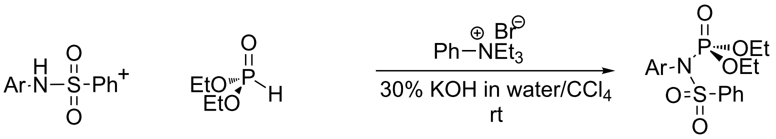
Initially, the nucleophile engaged in the AT reaction was a primary or secondary alkylamine. However, the use of other nucleophilic species was reported. First, as illustrated above, aniline can be used. However, ortho-substituted aniline reacts with more difficulties according to Lukanov et al. [38]. Indeed the aniline must be activated as a sulfonamide (or acetamide) to produce the expected phosphoramidate [42]. The authors, who used a phase-transfer agent, postulated that this activation resulted from the increase of the acidity of the N–H bond despite the evident reduction of the nucleophilic character (Scheme 14).

To further illustrate AT reactions with aniline, the work of Dumitrascu et al. [43] is worth mentioning. Recently, they have reported on the preparation of an aryl phosphoramidate with a styryl moiety from the corresponding aniline (Scheme 15). The phosphoramidate was isolated with an excellent yield (90%), and this product was subsequently used to prepare polymers.

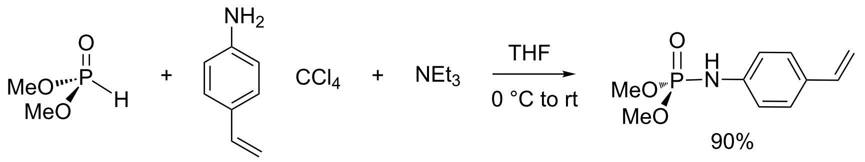
Other nitrogen-based nucleophiles were also engaged in AT reactions. Hydrazine is a substrate which produces phosphoramidate in high yield. The first example, reported by Prokof'eva et al. [44], used arylhydrazine as a substrate. The reaction proceeded in $CCl_4$ in the presence of triethylamine and produced phosphoramidates in 60–82% yield. Unsubstituted hydrazine can also be used as a nucleophile in the AT reaction [45-47]. The best synthetic conditions employed phase-transfer catalysis [48]. Accordingly, $CCl_4$ was used as a solvent or co-solvent, triethylbenzylammonium chloride acts as a phase-transfer agent, and $K_2CO_3$ was used as a base. Hydrazine hydrate was the source of hydrazine. The expected diethoxyphosphinylhydrazine was isolated in almost quantitative yield (99%) after a purification step by liquid/liquid extraction (Scheme 16). This procedure was also recently used by



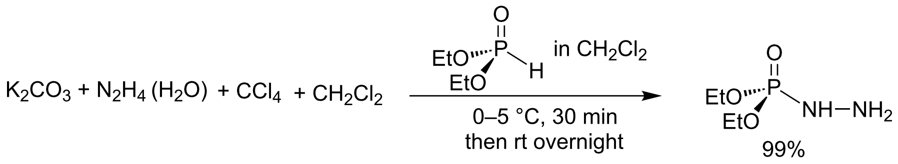
**Scheme 13:** Synthesis of a triphosphate by the AT reaction starting with the preparation of chlorophosphate (adapted from [41]).



**Scheme 14:** AT reaction with sulfonamide (adapted from [42]).



**Scheme 15:** Synthesis of a styrylphosphoramidate starting from the corresponding aniline (adapted from [43]).



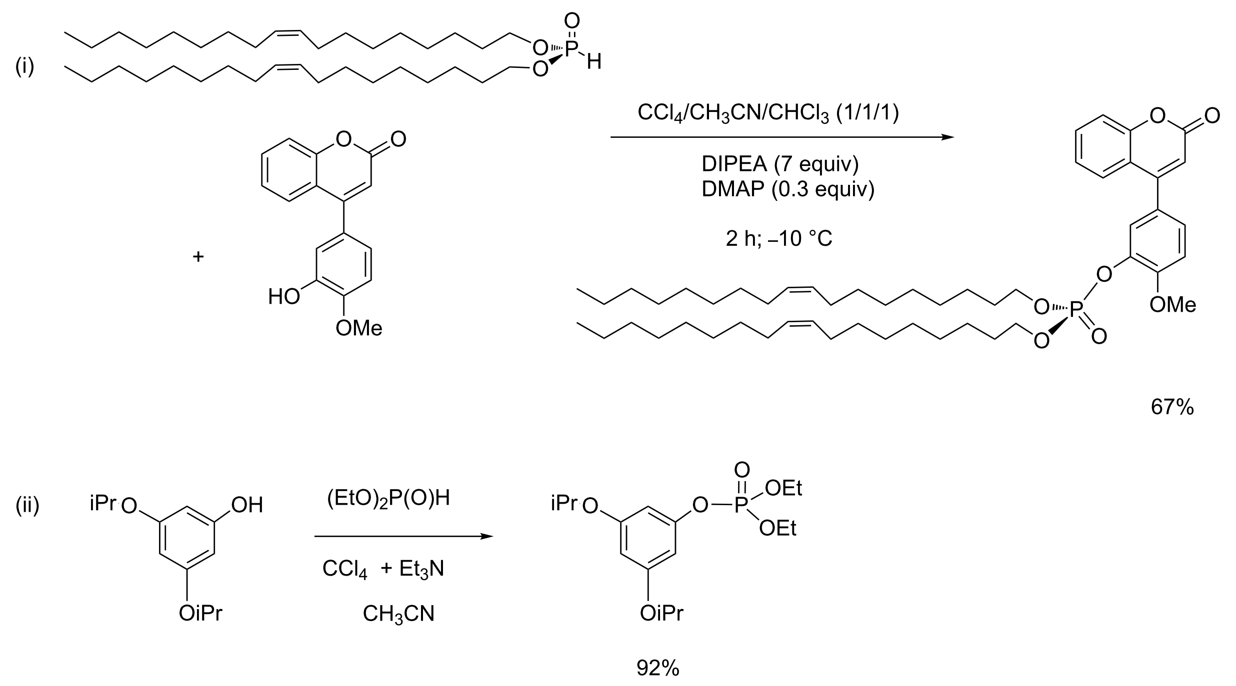
**Scheme 16:** Use of hydrazine as nucleophile in AT reactions (adapted from [48]).

Matthews et al. to produce the same compound (diethoxyphosphinylhydrazine) in a slightly lower yield (90%) [49]. *O*-Methoxyhydroxylamine is another nitrogen-based nucleophile engaged in AT reactions. The first example reported by Wadsworth et al. produced low yield [50]. The procedure was improved by the addition of a phase-transfer agent (triethylbenzylammonium chloride). Accordingly, a series of phosphorylated *O*-alkylhydroxylamine was produced in medium to good yield (45–97%) [51].

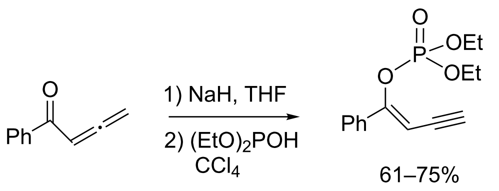
The use of alcohol as a nucleophile has been rarely reported indicating that its nucleophilicity is not good enough to produce the expected phosphate in good yield. This reaction was observed when $CBrCl_3$ or $CBr_4$ were used as a halide source according to the initial works of Atherton and Todd [1,2]. Nevertheless, this reaction is limited and successful only with an alcohol such as methanol or ethanol. In our group we have occasionally employed methanol as a solvent for selected reactions due to the low solubility of certain substrates (e.g., amino acid hydrochlorides). In that case, a noticeable amount of diethyl methyl phosphate was observed originating from the reaction of methanol on the chlorophosphate intermediate. Because the AT reaction is not efficient to produce alkylphosphate from alkylalcohol, an alternative is the usage of chlorophosphate in the presence of a Lewis acid catalyst. For this purpose, Ti(*t*-BuO)$_4$ was identified as an effective catalyst [52,53]. The use of phenol as a nucleophilic species resulted in better yields. Hence, the AT reaction applied to a substrate possessing both alcohol and phenol functional groups, produces the phosphate that engaged the phenol function as shown in Scheme 12. AT reactions with phenol are further illustrated by the work of Charette et al. who used this reaction in the first step of a multistep synthesis to produce chiral arylphospholane [54]. Another interesting example, reported by Selikhov et al., involved an AT reaction between a functionalized coumarine and dioleyl phosphite [55]. In this reaction the authors used a mixture of a solvent ($CH_3CN/CHCl_3$) and an excess of $CCl_4$. DIPEA and a catalytic amount of DMAP were also added in the reaction medium. The expected phosphate was isolated with 67% yield (Scheme 17-i). Better yields are usually obtained with phosphite possessing two shorter alkyl chains as exemplified by a reaction reported by Taylor et al (Scheme 17-ii) [56].

The phosphorylation of phenol by the AT reaction was also reported under biphasic conditions in the presence of a phase-transfer agent. Interestingly, the study of Ilia et al. [57], reports the use of both liquid/liquid and liquid/solid biphasic systems. They observed that the second reaction conditions (i.e., the ones without the addition of water) produced better results with yields between 72 and 86%. In this reaction NaOH or $K_2CO_3$ was used as a base, tetrabutylammonium bromide as a phase-transfer agent and $CCl_4$ as a reagent and solvent. Finally, enolate is another nucleophilic species that was engaged in the AT reaction as shown in Scheme 18. In this reaction, an allenylketone was mixed with NaH in THF at −10 °C. After deprotonation (30 min), diethyl phosphite in $CCl_4$ was added dropwise. Treatment with acetic acid and purification on silica gel finally afforded the β-alkynyl-enolphosphate in 61–75% yield [58].

Azide, nitrile and thiocyanate were three other nucleophilic species used to produce pseudohalogenated phosphorus species by the AT reaction. Among them, the commercially available diphenyl phosphorazidate (DPPA) and diethyl phosphorocyanidate (DEPC) are widely employed as peptide coupling reagents [59-62]. DPPA was also used in many organic reac-

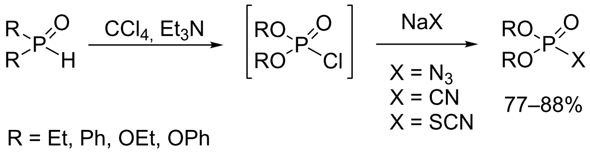


**Scheme 17:** AT reaction with phenol as a nucleophilic species; synthesis of dioleyl phosphate-substituted coumarine derivative (i) and synthesis of diethyl aryl phosphate (ii) (adapted from [55] and [56]).



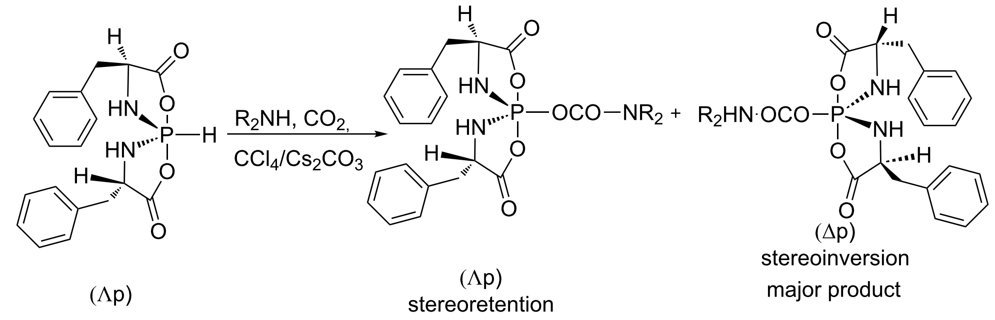
**Scheme 18:** Synthesis of β-alkynyl-enolphosphate from allenylketone with AT reaction (adapted from [58]).

tions such as the Curtius rearrangement [59], the thiol ester synthesis [63], the azidation of alcohol and phenol [64], and the synthesis of phosphoramidate [65]. The most common way to prepare pseudo-halogenated phosphorus species involves a nucleophilic substitution on chlorophosphate with sodium salts ($NaN_3$, NaCN or NaSCN) [66]. Due to the reactivity of chlorophosphate and its difficulty of storage, its production in situ by the AT reaction was studied by Shi et al. as depicted in Scheme 19 [67]. $(RO)_2P(O)Cl$ is generated from phosphite $(RO)_2P(O)H$, $CCl_4$ and a catalytic amount of $Et_3N$. This chlorophosphate is immediately engaged in a reaction with a sodium salt NaX (X = $N_3$, CN or NCS) to afford the pseudo-halide phosphorus species in satisfactory yields (77–88%). Interestingly, the same authors reported that pseudo-halide phosphate can also be obtained by using phase-transfer catalysis [68]. Accordingly, NaX (X = $N_3$, CN or NCS) reacts with dialkyl phosphate in water–organic solvent mixtures under phase-transfer catalysis. The catalyst was either TBAB (tetrabutylammonium bromide), TBAI (tetrabutylammonium iodide), TMAC (tetramethylammonium chloride) or 18-crown-6. The best result was obtained with TBAB and 18-crown-6 catalysts in a $CH_2Cl_2$/water or AcOEt/water mixture (yields included from 72 to 85%).



**Scheme 19:** Synthesis of pseudohalide phosphate by using AT reaction (adapted from [67]).

The carbamate anion is another nucleophilic species recently engaged in the AT reaction with hydrospirophosphorane as substrate [69]. This nucleophilic species was generated in situ by reacting a secondary amine and $CO_2$. Then, it reacted with chlorospirophosphorane produced in situ from hydrospirophosphorane, $CCl_4$ and $Cs_2CO_3$ (Scheme 20). This reaction can be viewed as an activation of $CO_2$ by an amine to produce the nucleophilic carbamoyl moiety. The major product of this reaction corresponds to an inversion of the configuration at the phosphorus with diastereoisomeric excess included from 6.8 to



**Scheme 20:** AT reaction with hydrospirophosphorane with insertion of $CO_2$ in the product (adapted from [69]).

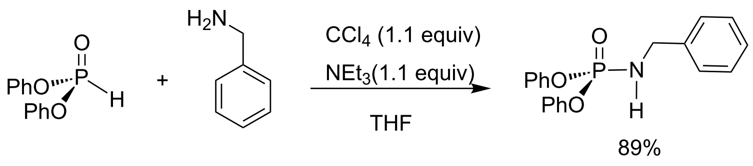
1. It is noteworthy that the usage of a primary amine as an educt in this reaction did not lead to the insertion of $CO_2$ , and the product resulted from the reaction of the amine on the chlorospirophosphorane. This result may be explained by the higher nucleophilicity of the primary amine in this reaction media.

The phosphorus species engaged in AT reactions mainly include dialkyl phosphites. It must be noted that the alkyl-chain length can be changed and extended to lipid chains as exemplified in Scheme 17 (oleyl chains). Diaryl phosphite can also be used for AT reactions as illustrated in a recent example published by Gaan et al. (Scheme 21) [70].

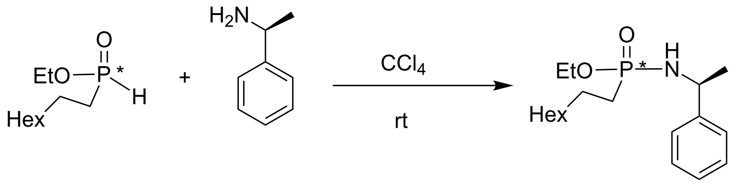
*O*-Alkyl phosphonite can also be engaged in AT reactions as recently illustrated by Montchamp et al. in a study dedicated to the hydrophosphinylation of terminal alkenes (Scheme 22) [71]. Shi et al. have also reported the reactivity of *O*-alkyl arylphosphonite in AT reactions with azide as the nucleophilic species [67].

Phosphinous acid ($R_2POH$) was less extensively studied as a phosphorus-based substrate in AT reactions. However, one full study was reported by Bondarenko et al. [72]. These authors reported three different methods to produce phosphinic amides by reacting primary or secondary amines with phosphinous acid in the presence of $CCl_4$ and aqueous NaOH. The first protocol was applied when methylamine or ammonia was used as a nucleophile (Scheme 23-i). In that case, a 50% aqueous solution of NaOH was slowly added to a biphasic solution composed of aqueous methylamine, $CCl_4$ and dichloromethane. The second protocol (Scheme 23-ii) is almost similar to the first one except that a hydrochloride salt (e.g., ethylamine hydrochloride) was used as a substrate without prior solubilization in water. Finally, for the third protocol (Scheme 23-iii), the phosphinous acid is added to a mixture of the other substrates placed in a biphasic solution (water/$CH_2Cl_2$). The yields were between 77 to 97%.

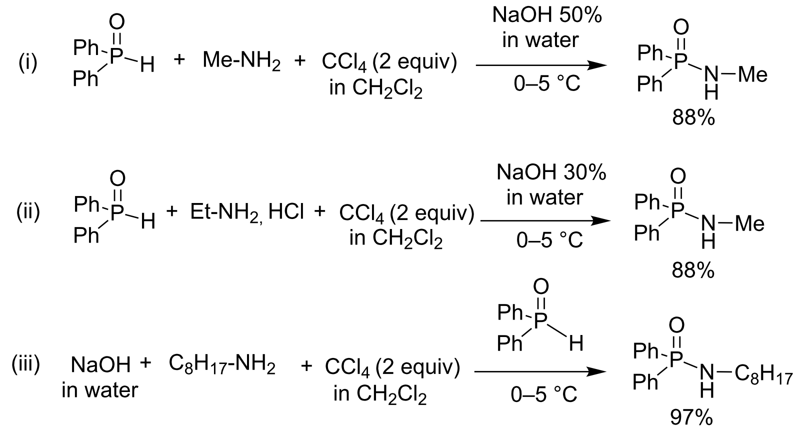
Thiophosphorus-based precursors can also be engaged in AT reactions. Recently, secondary phosphinethiooxide has been



**Scheme 21:** AT reaction with diaryl phosphite (adapted from [70]).



**Scheme 22:** AT reaction with O-alkyl phosphonite (adapted from [71]).

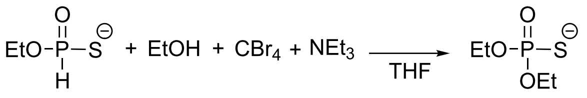


**Scheme 23:** Use of phosphinous acid in AT reactions (adapted from [72]).

engaged as a phosphorus-based precursor in the AT reaction [73]. The reaction proceeds in good yield (80%) with $CCl_4$ as a solvent, an amine as a nucleophile and triethylamine as a base. The use of secondary phosphineselenoxide was also reported by the same authors but the yields were lower (35–38%) [74]. The procedure was also applied to alcohol [75] or diphenol derivatives acting as a nucleophile as shown for hydroquinone in Scheme 24 [76]. *O,O*-dialkyl thiophosphite was also engaged in AT reactions to produce dinucleotide designed as an anti-HIV prodrug [77].

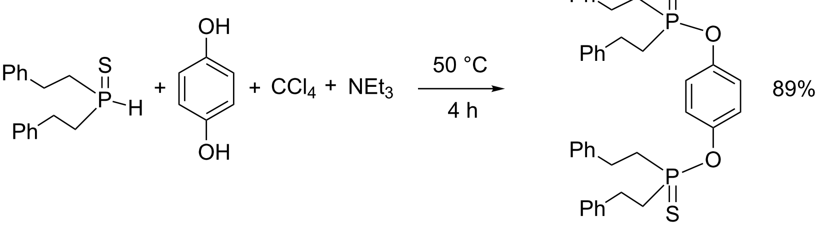
H-phosphonothioates are intermediates considered for the synthesis of nucleotide analogues. This functional group can be used as a nucleophilic species in a coupling reaction with a primary alcohol. This coupling reaction is usually achieved by $I_2$ acting as an oxidant, but Stawinski et al. also tested other halide sources including $CCl_4$ and $CBr_4$ [78]. Despite iodine is the reagent of choice in this reaction, $CBr_4$ is also efficient to produce the coupling product (Scheme 25), whereas $CCl_4$ was inefficient.

AT reactions usually proceed at 0–5 °C but lower temperatures (−10 °C [41]) and higher temperatures (50°C [76]) were also reported. The use of microwave (MW) activation was also reported by Beletskaya et al. [79]. This activation was applied to AT reactions which used α-aminophosphonate as a nucleophile in the presence of $CCl_4$ and triethylamine. The authors reported that no reaction occured at rt, whereas phosphoramidate was obtained in low yield (15–20%) when classical heating (24 h, 110 °C) was applied. However, phosphoramidates were isolated in 63–93% yields with MW heating. The reaction time was significantly shorter with MW since a full conversion was reached after only 30 to 40 minutes of heating.



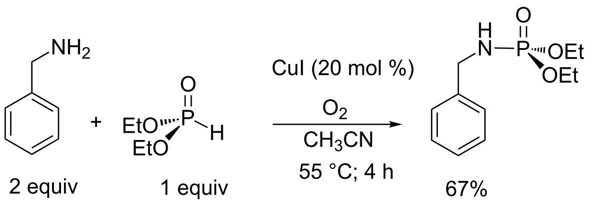
**Scheme 25:** Use of H-phosphonothioate in the AT reaction (adapted from [78]).

The recent works of Hayes et al. reported on the synthesis of phosphoramidates starting from dialkyl phosphite and primary amine without a halogen source [80]. Instead of using $CCl_4$ or $CBr_4$, the authors employed a catalytic amount of CuI as depicted in Scheme 26. These new synthetic conditions, that required $O_2$ for the reoxidation of copper, can be viewed as an



**Scheme 24:** AT reaction with secondary phosphinethiooxide (adapted from [76]).

extension of the AT reaction which facilitates the avoidance of a halide source. Even though the yield is usually lower compared to classical AT conditions, this result opens new perspectives for the development of green processes.



**Scheme 26:** AT-like reaction with CuI as catalyst and without halide source (adapted from [80]).

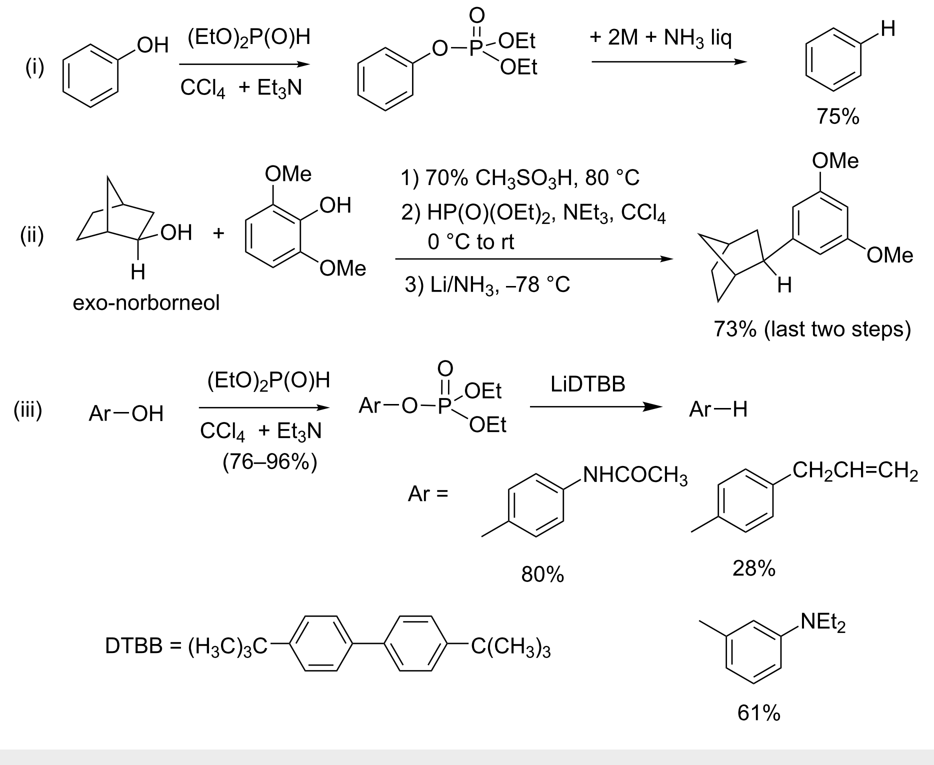
# 4. Applications

## 4.1 Synthetic utilities of AT reactions

In this section we will discuss the use of AT reactions to produce aryl phosphates or phosphoramidates which are important intermediates for a variety of subsequent transformations or can be used as organocatalysts.

Aryl dialkyl phosphates, prepared by the AT reaction from phenol derivatives, were employed to reduce phenol functional groups. It is noteworthy that phenol compounds and their related deoxygenated derivatives represent an important family of natural or synthetic compounds exhibiting, for example, antitumor or antiallergic activities. The reduction of a phenol group implies its activation as a good leaving group. Phosphate is one of the possible activating groups. Its use for the desoxygenation of phenol was first reported by Kenner et al. [81] who implemented the reaction with liquid ammonia as a solvent in the presence of metal as a reducing agent (e.g., Na) (Scheme 27-i). A similar methodology was used to produce 2-substituted bornane in a three-step sequence as shown in Scheme 27-ii [82]. Firstly, a Friedel–Crafts reaction produced the para-substituted phenol in 42% yield. Then, the phenol group was transformed in diethyl aryl phosphate with an AT reaction in 99% yield. Finally, the reduction of the phosphate was achieved in 74% yield. Similar synthetic schemes (AT reaction and reduction with Li/$NH_3$) were also reported in another publication [83]. This procedure was recently improved by Lusch et al. (Scheme 27-iii) by using a lithium di-*tert*-butylbiphenylide radical anion [84]. Accordingly, a wide panel of phenol derivatives was first transformed in diethyl aryl phosphate with the AT reaction (yields from 76 to 96%), and then these phosphates were reduced to the corresponding aromatic hydrocarbons with moderate to good yields (10 to 83%).

The phosphoramidate group can also be used to enhance the reactivity of an amine. This activation role of phosphoramidates



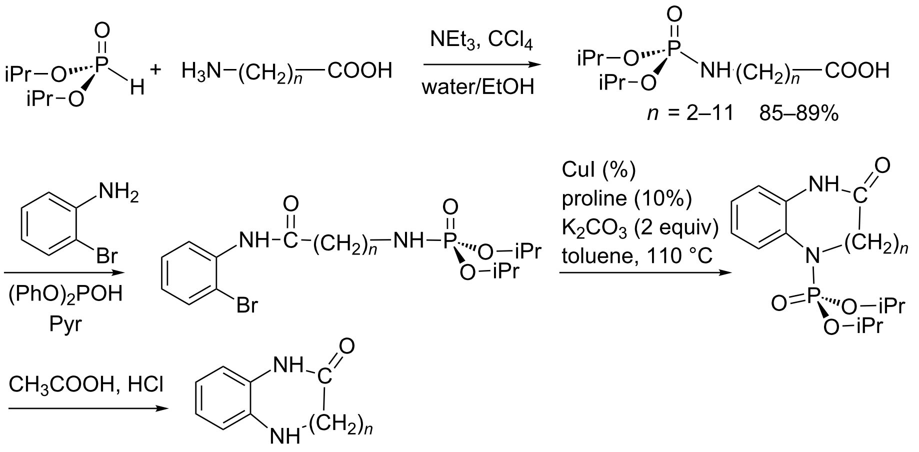
**Scheme 27:** Reduction of phenols after activation as phosphate derivatives (adapted from [81] i ; [82], ii; and [83], iii).

was illustrated for the synthesis of medium and large-sized cyclic diaza-compounds by Zhao et al. [85]. This sequence started with the AT reaction (Scheme 28) to produce ω-difunctionalized phosphoramidatecarboxylic acid. In the last step, the phosphoramidate group activates the amine which is cyclized by a copper-catalyzed N-arylation. In the last step, the phosphoramidate is cleaved by an acidic treatment. This sequence illustrates that the AT reaction is compatible with the presence of free carboxylic acid functional group.

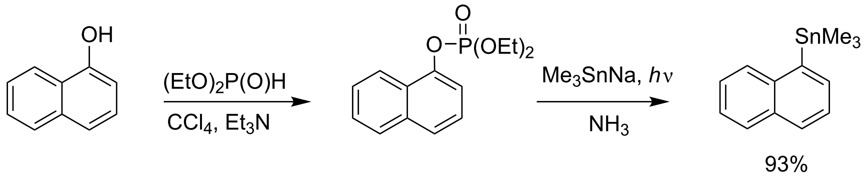
Aryl dialkyl phosphate, easily prepared starting from phenol in an AT reaction, can also be transformed into arylstannane derivatives by a $S_{RN}1$ reaction by the photostimulation of trialkyl [86] or triarylstannyl [87] ion in liquid ammonia as shown in Scheme 29. This example shows that the AT reaction was achieved with $CCl_4$ as a halogenating agent. Then, the stannylation reaction produced the arylstannane in 75 to 90% yield [88].

The Suzuki–Miyaura cross-coupling reaction is another type of reaction with the phosphate group acting as a leaving group. As exemplified in Scheme 30, the aryl dialkyl phosphate was produced in good yield by an AT reaction [89]. Then, this phosphate group reacted with aryl Grignard, as a Kumada–Tamao-Corriu cross-coupling, in the presence of a nickel catalyst [90].

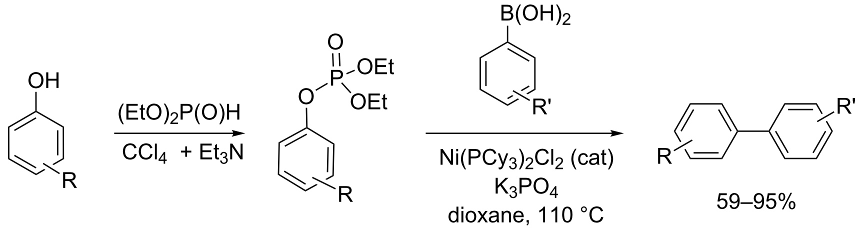
Aryl dialkyl phosphate, which was readily obtained by the AT reaction from phenol as shown in Scheme 31 [91], can be



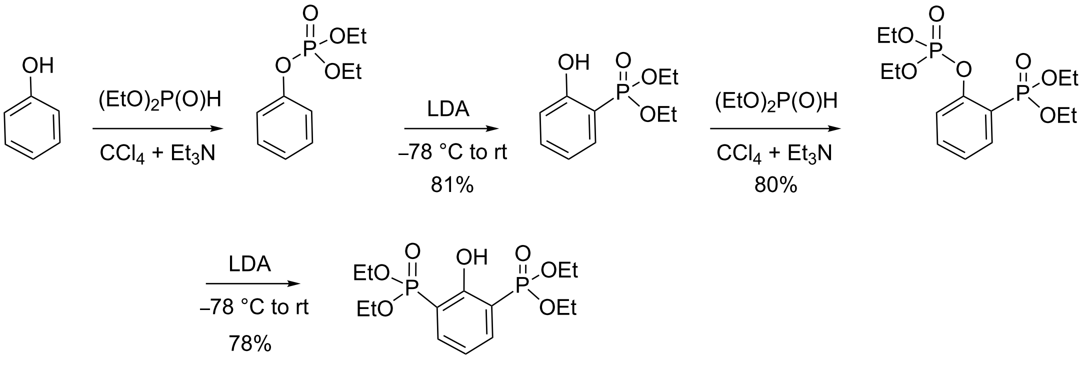
**Scheme 28:** Synthesis of medium and large-sized nitrogen-containing heterocycles (adapted from [85]).



**Scheme 29:** Synthesis of arylstannane from aryl phosphate prepared by an AT reaction (adapted from [86]).



**Scheme 30:** Synthesis and use of aryl dialkyl phosphate for the synthesis of biaryl derivatives (adapted from [89]).

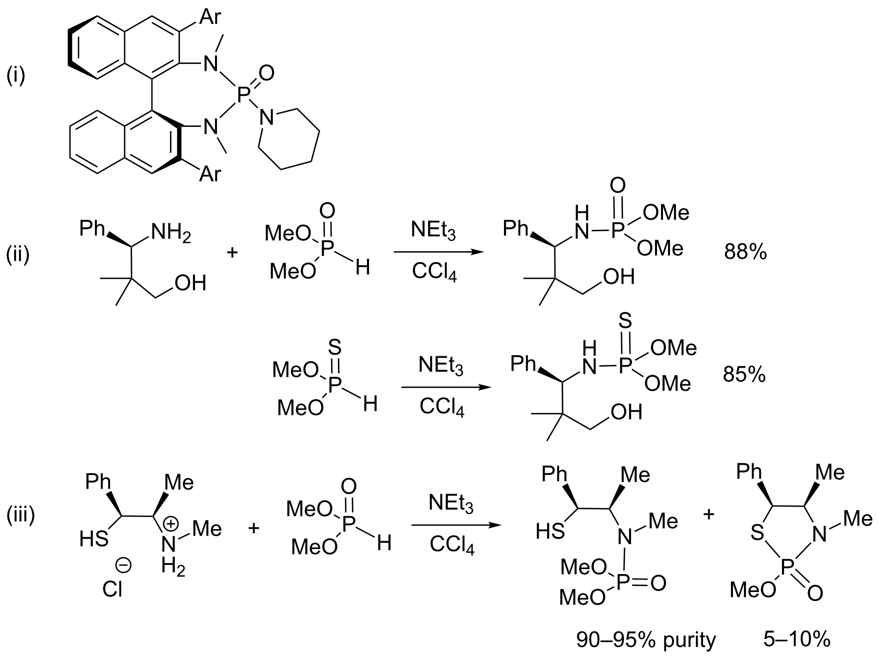


**Scheme 31:** Synthesis of aryl dialkyl phosphate by an AT reaction from phenol and subsequent rearrangement yielding arylphosphonate (adapted from [91]).

employed for the production of aryl phosphonate by applying a phospho-Fries rearrangement (a rearrangement initially reported by Melvin et al. [92]). This rearrangement proceeds by an ortho-metallation that can be characterized at a low temperature [93]. Then, the *o*-lithium species rearranges to produce 2-hydroxyarylphosphonate [94].

The recent publication of Yang et al. [95] reports the amination of either triaryl phosphate or dialkyl aryl phosphate catalyzed by nickel organometallic complexes. It is an additional illustration of the use of aryl phosphate, which can be readily obtained by AT reactions.

Beside the use of phosphorus species as a substrate in reactions as those reported above, phosphoramidates, prepared by AT reactions, can also act as an organocatalyst. Indeed, with the strongly polarized P–O bond on one hand, and the P–N or P–NH bond on the other hand phosphoramides are good Lewis bases [96-98]. Hexamethylphosphoric triamide (HMPA) (or analogues) was the first phosphoramide derivative that was extensively studied as an organocatalyst [98,99]. However, HMPA was classified as a human carcinogen [100]. One of the first examples of the use of chiral phosphoramide ligands (Scheme 32-i) in organocatalysis was described by Denmark et al. who studied the enantioselective crossed aldol reaction of



**Scheme 32:** Selected chiral phosphoramidates used as organocatalyst; i) chiral phosphoramidate used in the pioneer works of Denmark et al. [101]; ii, iii) synthesis of organocatalysts by using AT reaction (adapted from [107]).

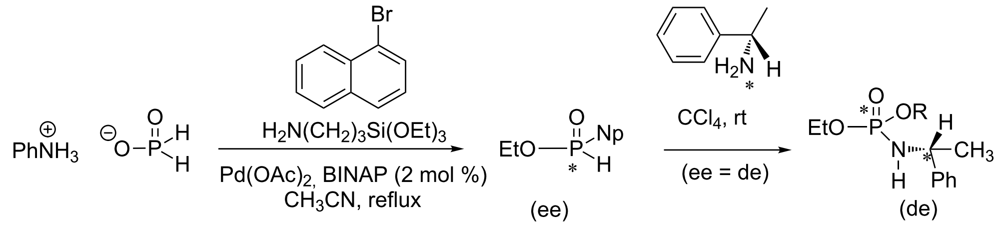
aldehydes with trichlorosilyl enol ethers. They obtained the aldol products in high yields with moderate to good enantioselectivities [101]. The chiral phosphoramidates used in this study and tested in many other enantioselective reactions (aldol reaction [102], Michael addition [103], Diels–Alder reaction [104], Friedel–Crafts alkylation [105]) illustrate the use of phosphoramidates as organocatalysts. These phosphoramidates were not synthesized by an AT reaction. Instead, the reaction of an amine with an electrophilic phosphorus species (P–Cl based compounds) afforded the phosphoramidates. Only a few examples (shown in Scheme 32-ii,iii) of chiral phosphoramidates were synthesized with the AT reaction likely due to the commercial accessibility of some chlorophosphine or chlorophosphate that render the AT reaction pathway less attractive. However, as reported in Scheme 32-ii, some chiral phosphoramidates and thiophosphoramidates can be readily synthesized with the AT reaction in high yield (85–88%) from dimethyl phosphite or *O*,*O*-dimethyl thiophosphite [106]. When the chiral amine was functionalized with a thiol group (Scheme 32-iii), the expected phosphoramidate was jointly isolated with 5 to 10% of thiophosphoramidate resulting from a cyclization reaction. The chiral phosphoramidates (Scheme 32-ii and iii) were tested as a chiral catalyst for the nucleophilic addition of diethylzinc [107] on benzaldehyde or for the asymmetric borane reduction of a prochiral ketone. The phosphoramidate (Scheme 32-iii) was the most efficient catalyst for these two reactions (ee: 95–98%, conversion 87–98%).

In relation with asymmetric synthesis, the determination of the enantiomeric excess (ee) is usually achieved by different methodologies including chiral HPLC or CPG. In a recent study, Montchamp et al. used the AT reaction for the determination of the ee of P-chiral H-phosphinates by the formation of diastereoisomers (Scheme 33) [108]. The ee determined by this method, which can be achieved directly in the NMR tube before recording $^{31}$P NMR spectra, was consistent with those determined by other methods (e.g., chiral HPLC).

## 4.2 Flame retardants

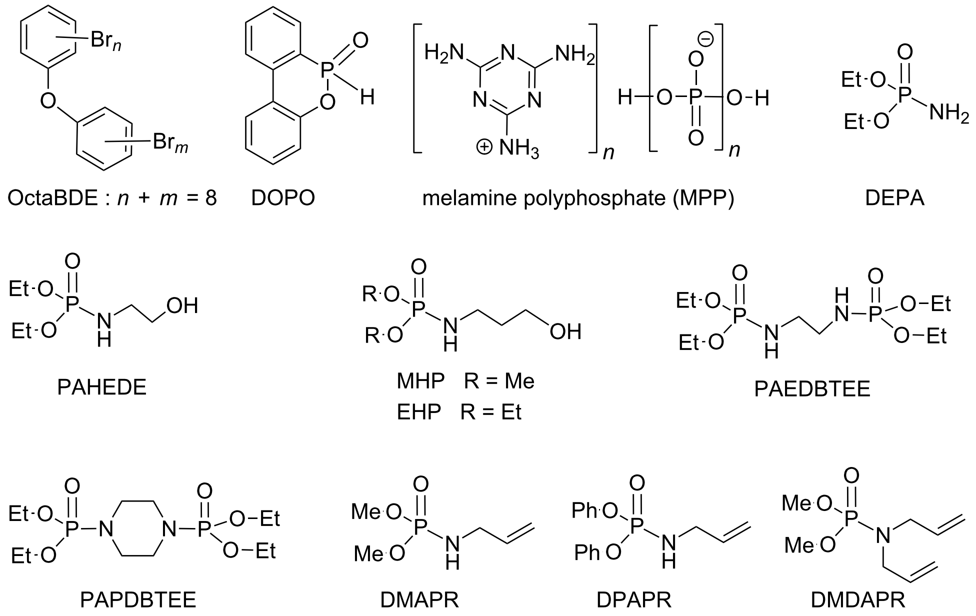
Since the early age of the development of synthetic fibers, the production of flame retardants became an industrial and academic challenge aiming to identify efficient compounds for this purpose but also to elucidate the mechanisms involved in the burning process of polymers. This goal was also extended, for evident safety reasons, to natural fibres (e.g., cotton). Halogen-based flame retardants were extensively employed (e.g., OctaBDE) but for safety reasons that pointed out carcinogenic risks and/or to the production of toxic fumes when burning (e.g., HBr) several of these halogenated flame retardants were withdrawn from the market (e.g., octaBDE) [109]. Phosphorus-based compounds [110] are another class of flame retardants. This type of compounds contributes to the extinction of the flame by, at least, two distinct mechanisms. First, some phosphorus compounds (e.g., DOPO, Scheme 34) act on the gas phase by the production of non-flammable compounds (e.g., water) or by the production of reactive species that act as hydroxyl radical scavengers. Alternatively, phosphorus-based flame retardants may act on the solid phase by forming a thermal barrier between the solid phase and the gaseous phase. This charring process results from the formation of polyphosphoric acid derivatives. Interestingly, the association of phosphorus and nitrogen-based flame retardants proved to be efficient probably due to synergic effects. Melamine polyphosphate (MPP, Scheme 34), illustrates this possibility: melamine decomposes endothermically and produces $NH_3$ when burning (a gas-phase active agent), while polyphosphate, which is simultaneously produced, favors the charring process. The synergic effects of phosphorus and nitrogen-based flame retardants led scientists to investigate the synthesis of organic compounds characterized by the presence of these two elements. Accordingly, phosphoramidates constitute an interesting family of potential flame retardants and the AT reaction is an efficient tool for the production of this type of compounds.

Phosphoramidate derivatives were investigated as flame retardants for many years [111,112]. However, some recent studies,



(*R*)-BINAP: 16% ee (HPLC); 15% de ($^{31}$P NMR assay)
rac BINAP: 1.9% ee (HPLC); 2.3% de ($^{31}$P NMR assay)

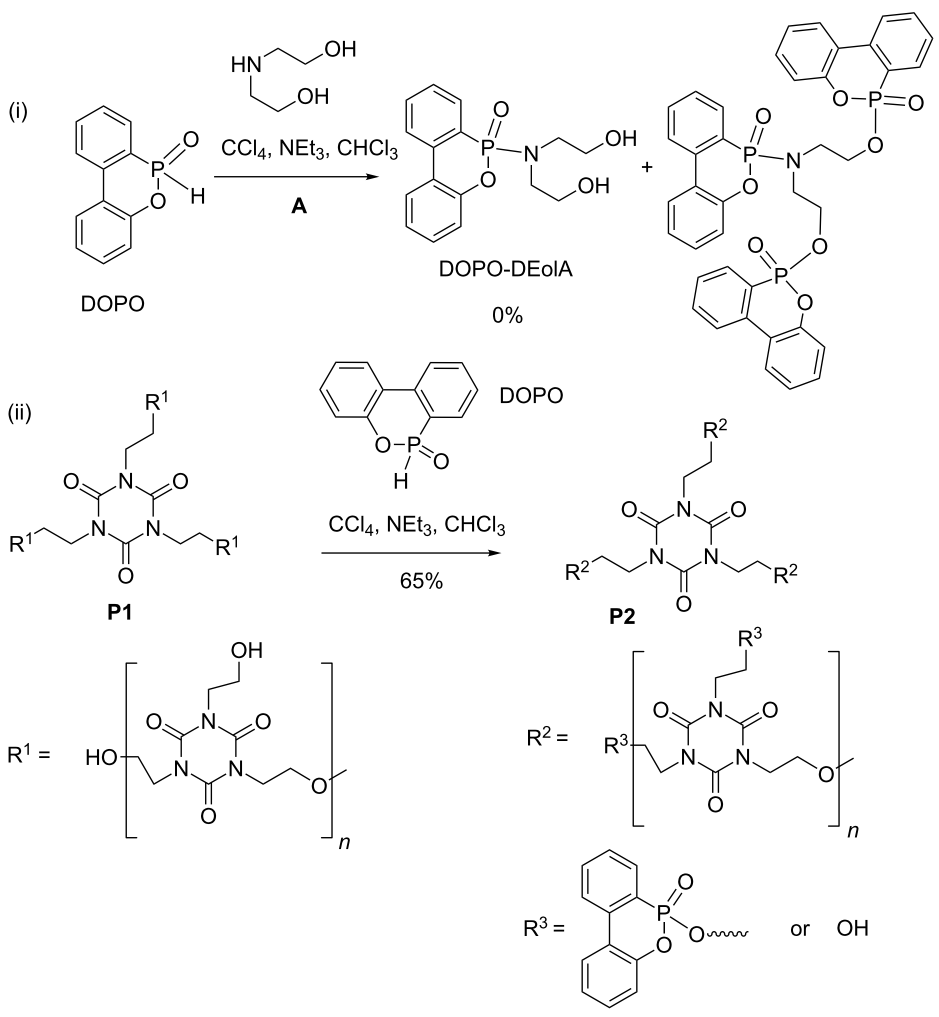
**Scheme 33:** Determination of ee of H-phosphinate by the application of the AT reaction with a chiral amine (adapted from [108]).



**Scheme 34:** Chemical structure of selected flame retardants synthesized by AT reactions; (BDE: polybrominated diphenyl ether; DOPO: 9,10-dihydro-9-oxa-10-phosphaphenanthrene-10-oxide; DEPA: diethyl phosphoramidate; PAHEDE: phosphoramidic acid-*N*-(2-hydroxyethyl) diethyl ester; EHP: diethyl 3-hydroxypropylphosphoramidate; MHP: dimethyl 3-hydroxypropylphosphoramidate; PAEDBTEE: phosphoramidic acid-1,2-ethanediylbis-tetraethyl ester; PAPDBTEE: phosphoramidic acid-1,4-piperazinediyl tetraethyl ester; DMAPR: dimethyl allylphosphoramidate; DPAPR: diphenyl allylphosphoramidate; DMAPR: dimethyl diallylphosphoramidate).

which will be discussed below, have reinvestigated the use of this type of compounds. We focus on the synthetic procedures of phosphoramidates. These derivatives can be divided in two broad categories depending on the presence of polymerizable groups. When polymerizable groups are present, the fire-resistant molecule can be included in polymers by copolymerization or can act as a crosslinking agent. This type of compounds is also employed for the surface modification of fibers or polymers (e.g., plasma technique). Without a polymerizable group, phosphoramidates can be used as an additive in polymers. Gaan et al. [113] have studied the thermal decomposition of cotton cellulose treated with different phosphoramidates. More specifically, they have shown that a secondary phosphoramidate (e.g., PAHEDE) was more efficient than a primary phosphoramidate (DEPA; Scheme 34). Additional results reported by Rupper et al. [114] indicated that PAHEDE produced phosphoric acid moieties at the surface of cellulose after burning. Moreover, cellulose interacts with phosphoramides to produce C–O–P bonds. In these studies, secondary phosphoramidate (e.g., PAHEDE) was synthesized by reacting diethyl phosphite with ethanolamine in $CCl_4$ and with one equivalent of triethylamine. After filtration and concentration, the phosphoramidate was isolated in quantitative yield after distillation. It is noteworthy that the synthesis is readily achieved and can be applied to large-scale productions. More recently, the comparison of the flame-retardant properties of MHP and EHP (Scheme 34), led to the conclusion that phosphoramidate with two methoxy groups (MHP) was more efficient [115]. The mechanism of degradation states that the MHP produced covalent bonds with cotton cellulose while the diethyl analogue (EHP) did not produce any such bonds. In this study, MHP was produced by an AT reaction as reported for PAHEDE [113]. For the synthesis of MHP, the aminoalcohol engaged in the AT reaction exhibited complete chemoselectivity since no trace amount of phosphate was reported. Some bis(phosphoramidates) were also considered as flame retardants. PAEDBTAEE and PAPBDTEE (Scheme 34) were compatible with cotton acetate and enhance the formation of char [116]. These two bis(phosphoramidates) were produced at a 0.1 mol scale (31 g of pure PAEDBTEE) with the AT reaction carried out in THF with a stoichiometric amount of $CCl_4$ (0.2 mol) and diethylphosphite (0.2 mol). Yields greater than 95% were reported for these crystalline solids.

Other studies reported the modification of DOPO (a flame retardant in epoxy resins, Scheme 35-i) with the aim to react the P–H bond (phosphinate) to incorporate either nitrogen or oxygenated groups. Attempts to produce P–N bonds by using the AT reaction with diethanolamine (DEolA) failed because no chemoselectivity was observed between the secondary amine and the primary alcohol [117], whereas in other studies involving dialkyl phosphite a chemoselectivity was observed [107]. It can therefore be concluded that the phosphinate modifies the reactivity of the phosphorus group leading to this



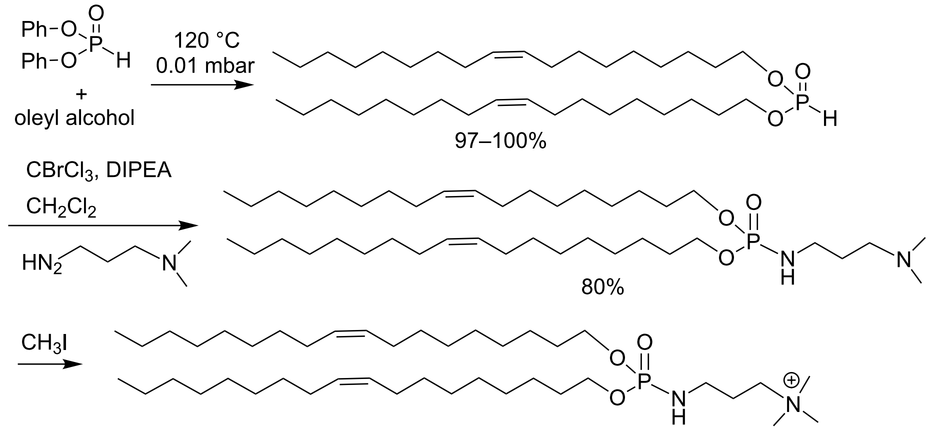
**Scheme 35:** Transformation of DOPO (i) and synthesis of polyphosphonate (ii) by the AT reaction (adapted from [117] and [118]).

absence of selectivity. This surprising reactivity of DOPO with alcohol functional groups inspired the authors to produce cyclic phosphonates with the AT reaction. Accordingly, polymer P1, obtained by polycondensation was functionalized by an AT reaction to produce polymer P2 in 65% yield (Scheme 35-ii) [118].

All these recent studies, which report flame-retardant properties of phosphorus-based compounds illustrate that the AT reaction is easy to implement and, interestingly, high yields are usually obtained. Accordingly, phosphoramidates are cheap to manufacture and we assume that this reaction will be employed to design novel flame retardants.

## 4.3. Phosphorus-based amphiphiles and biological applications

Cationic lipids are a promising class of compounds with the capacity to carry nucleic acids (DNA, RNA) for both in vitro and in vivo transfection assays. For the synthesis of cationic lipids, simple, efficient, modular procedures must be developed because the current applications require multifunctional carrying systems. Indeed, many nano-carriers are designed to respond to a specific stimulus (pH, red/ox, light) to trigger the drug release. To achieve the synthesis of polyfunctional amphiphilic compounds, the synthetic scheme must therefore be efficient, flexible and versatile. The AT reaction, which was used as a key step for the synthesis of neutral or cationic lipids, matches several of these properties. As a first example, cationic lipophosphoramidates can be produced in a three-step sequence that includes an AT reaction (Scheme 36). First, dioleyl phosphite can be readily prepared by a transesterification-like reaction between diphenyl phosphite and oleylalcohol. This reaction tolerates a large panel of lipid alcohol. These phosphite intermediates can be produced on a large scale (more than 50 g) and can be stored for a long period of time without any degradation in contrast to dialkyl chlorophosphate (another possible



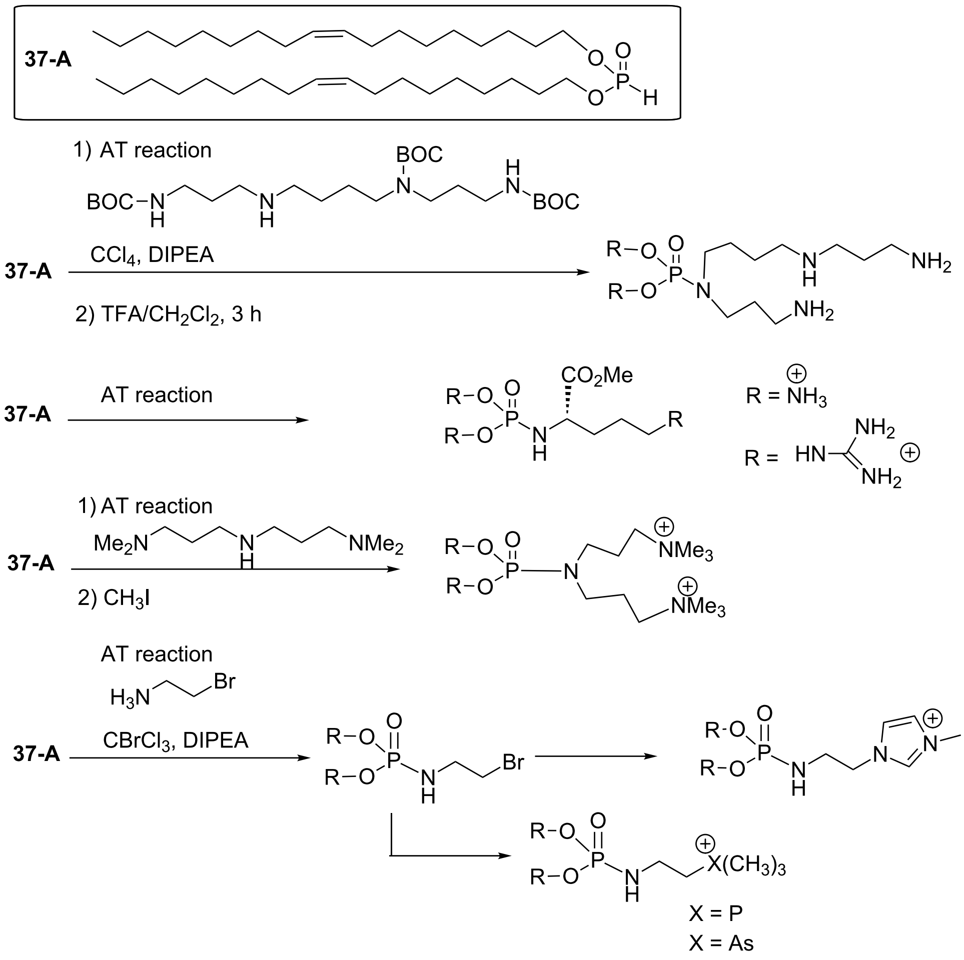
**Scheme 36:** Synthesis of lipophosphite (bisoleyl phosphite) and cationic lipophosphoramidate with an AT reaction (adapted from [119]).

intermediate to produce amphiphilic compounds), which are water sensitive. In a second step, these phosphites can be engaged in the AT reaction as illustrated in Scheme 36. Bisoleyl phosphite was reacted with dimethylaminopropylamine to produce the expected phosphoramidate in good yield (80%) [119]. The reaction is carried out by adding DIPEA to a mixture of dioleyl phosphite, the nucleophilic amine and $CBrCl_3$ in anhydrous dichloromethane. This addition was conducted at 5 °C followed by stirring the solution at 5 °C for 1 h. The concentration and extraction with a low polar solvent (hexane, diethyl ether), produced the expected phosphoramidate in almost quantitative yield. Purification was then achieved by column chromatography. In the last step, the cationic lipid was produced by reacting the tertiary amine functional group with iodomethane. Again, a simple washing (e.g., $Et_2O$/water) produced the expected cationic phosphoramidate with good purity and in good yield (>80%).

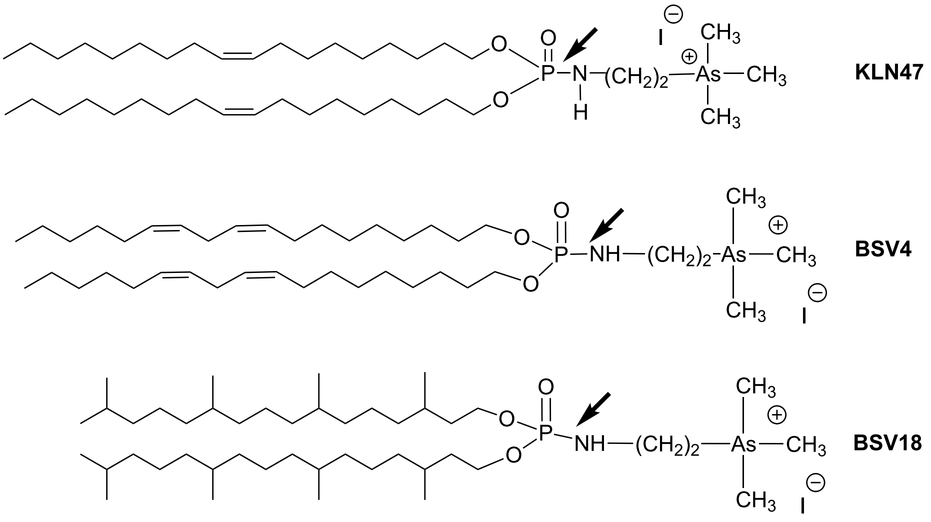
In this sequence (Scheme 36) the AT reaction occupies a central place and with some adaptations a series of cationic lipids were synthesized, each of which characterized by different polar heads. These cationic lipids interact with nucleic acids mainly by electrostatic interactions, while the hydrophobic domains help to produce supramolecular aggregates (lipoplexes). Ideally, these aggregates must be as strong as possible to protect and to compact nucleic acids when these lipoplexes are localized in the systemic circulation (in vivo experiments) or in the supernatant media (in vitro experiments). However, after cell internalization, presumably by endocytosis processes, these lipoplexes must be as fragile as possible in order to escape lysosomal degradation. Consequently, the stability of the lipoplexes must be carefully tuned. The nature of the cationic polar head is one of the molecular features of the cationic lipids which directly influence the stability of lipoplexes by acting on the strength of the ionic interactions with the anion charge of the phosphate groups from the nucleic acids. The replacement of trimethylammonium with either trimethylphosphonium or trimethylarsonium offers better transfection efficacies probably owing to a better compromise between the stability and the instability of lipoplexes [120]. The synthesis of trimethylarsonium-based phosphoramidate was also achieved by using the AT reaction which proved to be an efficient tool to link the lipid part with the polar head region of the cationic lipid as exemplified in Scheme 37. With the same synthetic scheme, guanidinum-based lipophosphoramidates [121] obtained from natural amino acids, methylimidazolium [122], spermine-based amphiphile [123], dicationic lipophosphoramides [119] and arsonium or phosphonium [120] cationic lipids were synthesized.

The lipid domain of lipophosphoramidates also influences the transfection process by acting on the physic-chemical properties of the supramolecular aggregates. Indeed, it was observed that bisphytanyl derivative BSV18 was particularly efficient for in vivo experiments. Presumably, this efficacy is based on the formation of an inverted hexagonal phase [124]. Once more, the AT reaction is a versatile reaction that allows for the production of a large panel of cationic lipids with unsaturated (e.g., KLN47 [125,126]), polyunsaturated (e.g., BSV4 [127]) or substituted alkyl chains (BSV18 [124]) as shown in Scheme 38.

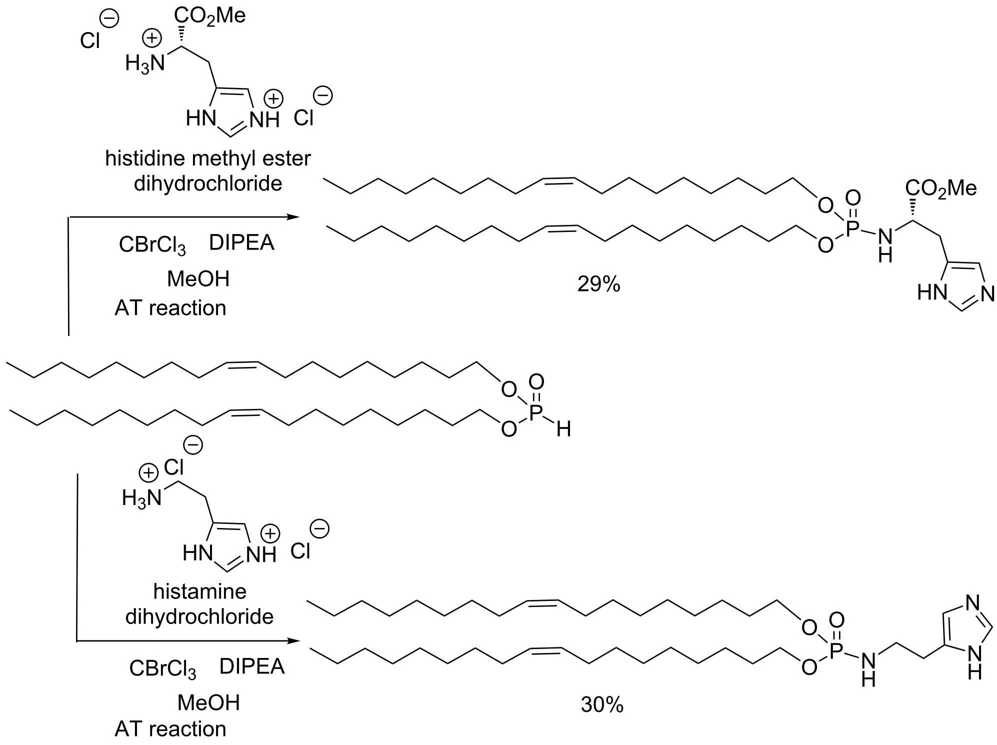
In association with cationic lipids, helper lipids are frequently added to liposomal solutions with the aim to enhance transfection efficacies. DOPE (1,2-dioleyl-*sn*-glycero-3-phosphoethanolamine) is a natural phospholipid that was frequently employed as a helper lipid, since it favors the formation of a hexagonal phase at a pH of 6 [128,129]. In addition to natural helper lipids synthetic co-lipids were also developed. Neutral lipophosphoramidates were synthesized by AT reactions (Scheme 39) [130]. These helper lipids were obtained in a one-step reaction with 29–30% yield from dioleyl phosphite. The



**Scheme 37:** Use of AT reactions to produce cationic lipids characterized by a trimethylphosphonium, trimethylarsonium, guanidinium and methylimidazolium polar head.



**Scheme 38:** Cationic lipid synthesized by the AT reaction illustrating the variation of the structure of the lipid domain. The arrows indicate the bond formed by the AT reaction.



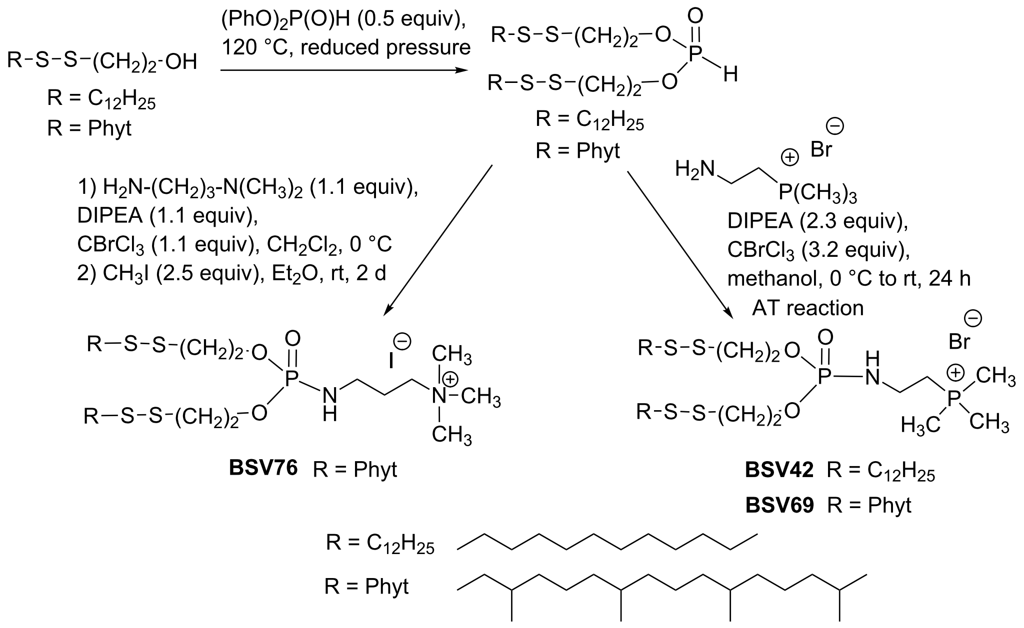
**Scheme 39:** Helper lipids for nucleic acid delivery synthesized with the AT reaction (adapted from [130]).

low yield was explained by the low solubility of the amine, which imposed the use of methanol as a solvent. Consequently, methanol acts as a second nucleophilic agent competing with the amine (histidine methyl ester or histamine). These yields can be improved (up to 50%) by reducing the volume of methanol used as a solvent in this reaction [131]. Interestingly, the liposomal solutions which incorporated the histamine-based helper lipid were also efficiently used to prepare lipopolyplexes (association of cationic lipid, cationic polymers and nucleic acid) employed for pDNA [132], RNA [133] and siRNA delivery [134].

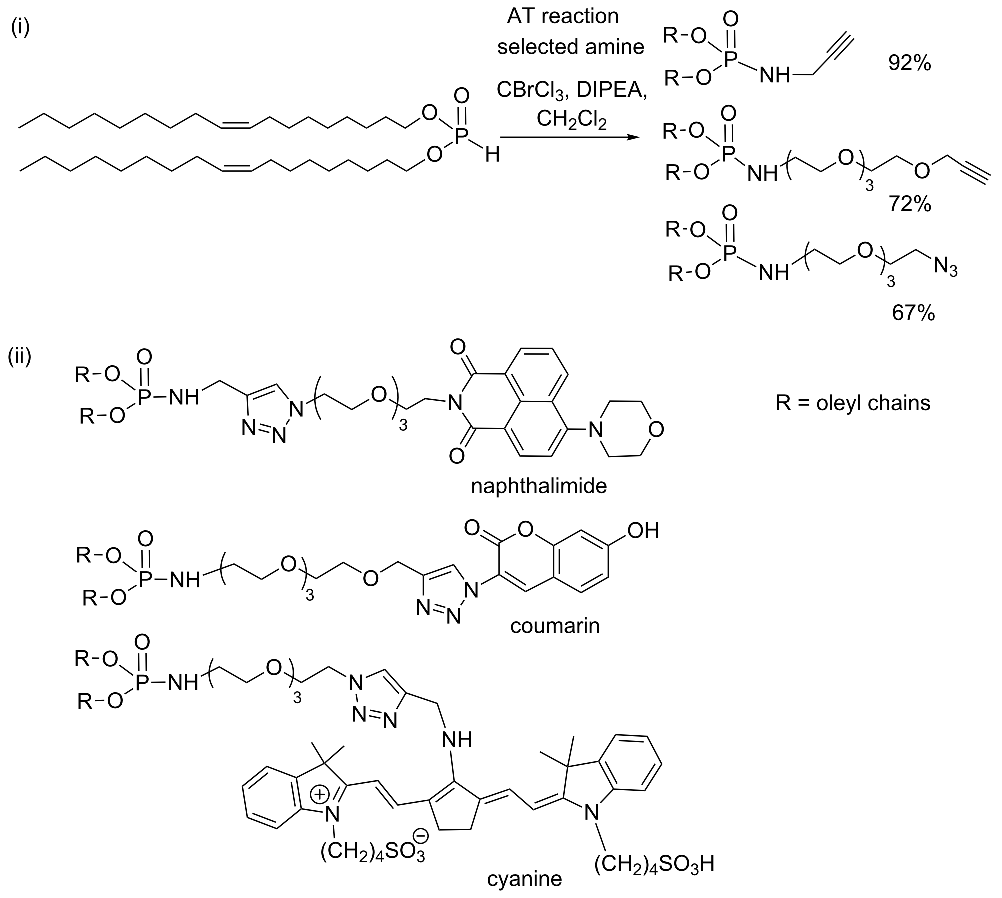
The question of the destabilization of lipoplexes after cell internalization can also be addressed by designing red/ox-sensitive cationic lipids. Accordingly, the incorporation of a disulfide bond, which can be cleaved by reducing agents naturally present in cytosol (glutathione), can induce a destabilization of the supramolecular aggregates. The AT reaction was also used for the synthesis of such red/ox-sensitive amphiphiles as illustrated in Scheme 40 [135]. The synthesis of lipophosphites incorporating two disulfide moieties was a key step. These phosphites were then engaged in the AT reaction to produce ammonium (BSV76) or phosphonium (BSV42 and BSV69) red/ox-sensitive cationic lipids in one or two steps. It was subsequently shown that lipoplexes prepared from these cationic lipids were destabilized in the presence of a reducing agent presumably caused by the breakdown of the S–S bond.

The introduction of a lipid domain on a molecule exhibiting specific properties (e.g., fluorescent or targeting group) is another goal needed to design tools for vectorization purposes. The use of click reactions for the production of polyfunctional amphiphiles (e.g., Huisgen cycloaddition) is very attractive. The combination of the AT reaction and click reaction (CuAAC) was reported to produce fluorescent lipids. The ‘clickable’ lipids ($N_3$ or alkyne-functionalized phosphoramidates) were obtained by an AT reaction (Scheme 41-i). These intermediates were isolated with moderate to good yields (67–92%) at a 1 g scale after a purification step on silica gel [136]. These intermediates were then engaged in copper-catalyzed Huisgen cycloaddition to produce efficiently a series of fluorescent lipids like those shown in Scheme 41-ii.

Recently, Le Gall et al. [137] have reported that some lipophosphoramidates synthesized by AT reactions exhibited a remarkable bactericidal effect even on clinically relevant strains (*S. aureus* N315). Interestingly, the bactericidal effect was independent of the resistance profile of bacteria (e.g., MRSA). In a structure–activity study it has been shown that the presence of a trimethylarsonium polar head combined with a lipid domain



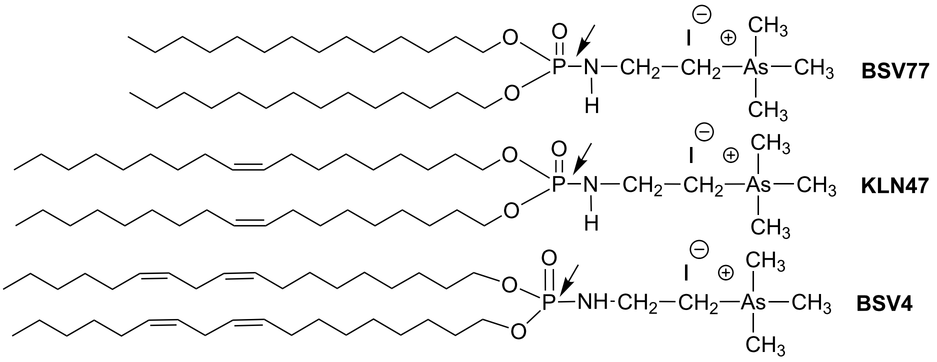
**Scheme 40:** AT reaction used to produce red/ox-sensitive cationic lipids (adapted from [135]).



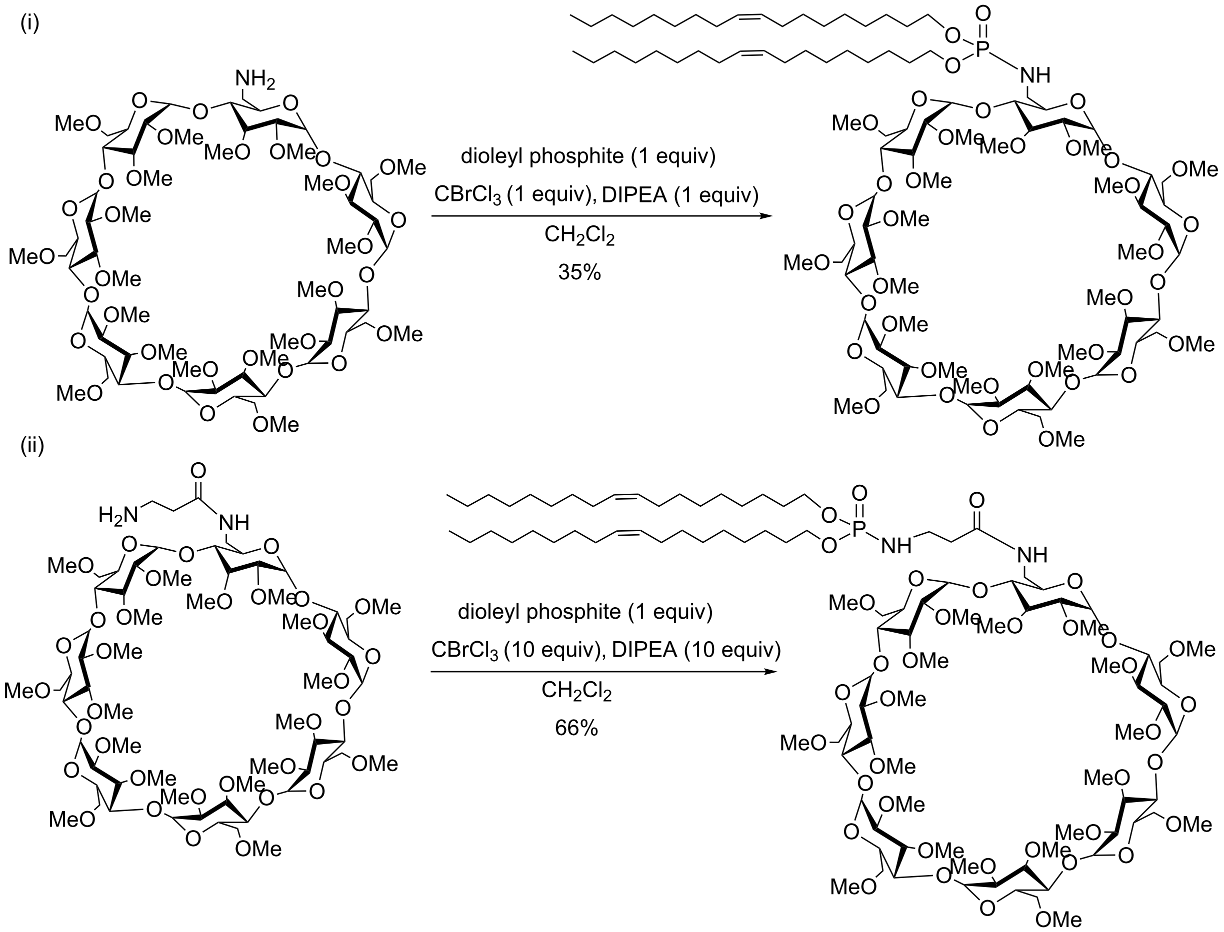
**Scheme 41:** Alkyne and azide-functionalized phosphoramidate synthesized by AT reactions,(i); illustration of some fluorescent lipids synthesised from these intermediates, (ii) (adapted from [136]).

were two structural features deeply influencing the bactericidal efficacies. The most efficient bactericidal agents were BSV77 and BSV4 (Scheme 42). Moreover, it was shown that lipoplexes, formed by the association of pDNA with BSV4, kept its bactericidal action. Additional experiments demonstrated that BSV4-based lipoplexes were able to simultaneously have a toxic effect on bacteria (bactericidal action) and a transfection capability for eukaryotic cells [137].

β-Cyclodextrin (β-CD) is another molecular platform that was chemically modified with a lipid moiety introduced by an AT reaction [138]. As exemplified in Scheme 43, Djedaïni-Pilard et



**Scheme 42:** Cationic lipids exhibiting bactericidal action – arrows indicate the bond formed by the AT reaction (adapted from [137]).

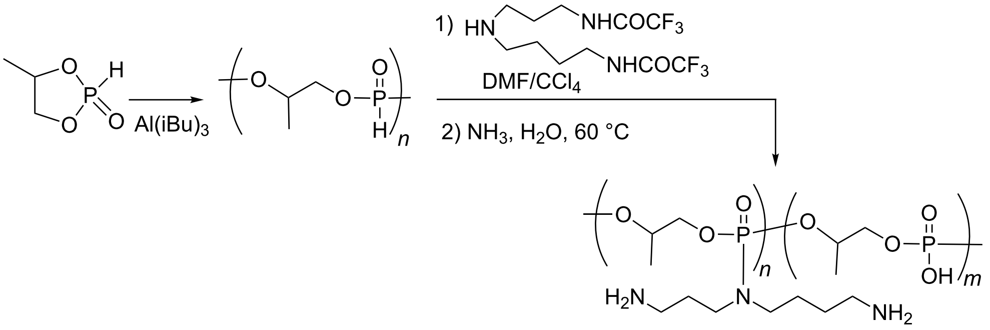


**Scheme 43:** β-Cyclodextrin-based lipophosphoramidates (adapted from [138]).

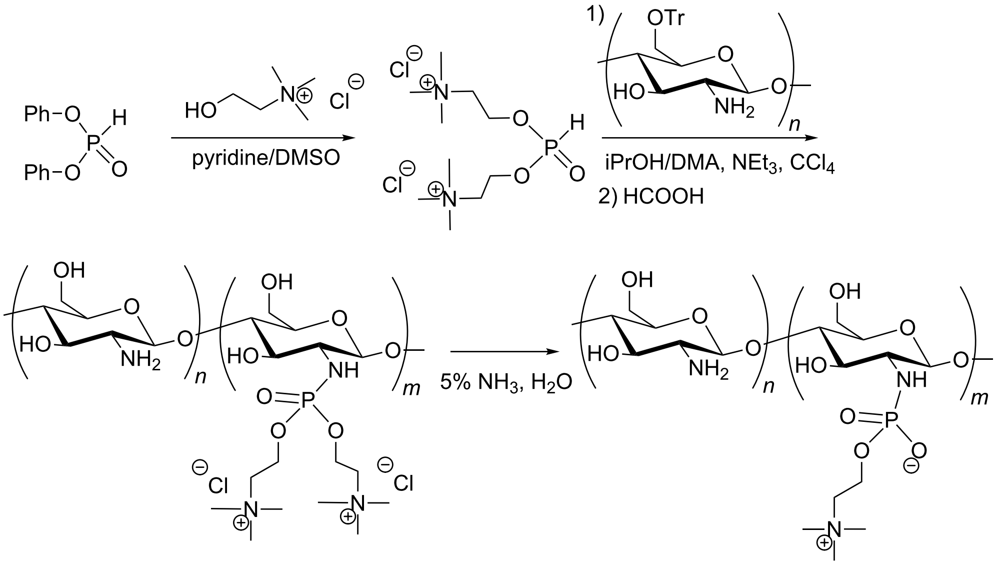
al. reported the use of the AT reaction to introduce a lipophosphoramidate fragment on a permethylated β-cyclodextrin possessing one primary amine (Scheme 43-i). After purification on silica gel, the expected lipophosphoramidate was isolated with 35% yield. The use of a spacer placed between the lipophosphoramide and the β-CD moiety (Scheme 43-ii) produced another permethylated β-CD with a better yield (66%). It is noteworthy that for this last reaction, an excess of $CBrCl_3$ and DIPEA was used, which might explain the better yield. Finally, the same reaction achieved on non-methylated β-CD produced the lipophosphoramidate with very low yield (4%). It is probable that the alcohol functions and the residual water molecules compete as nucleophilic species in the AT reaction.

The AT reaction was also employed for the functionalization of polymeric materials that were subsequently used as a gene carrier. A polyphosphite was synthesised by ring-opening polymerization of 4-methyl-2-oxo-2-hydro-1,3,2-dioxaphopsholane with triisopropylaluminium (Scheme 44) [139]. Then, the AT reaction was carried out in a mixture of $DMF/CCl_4$ with doubly protected spermidine (protection with trifluoroacetamide groups) as a nucleophile to produce a polyphosphoramidate. The deprotection of the primary amine with $NH_3$ yielded the polyphosphoramidate branched with polyamine, which was subsequently used as a gene carrier. The functionalization of the polyphosphite with the AT reaction was compatible with a large panel of primary and secondary amines [140]. The post-functionalization of this polyphosphoramidate with monosaccharide or disaccharide groups has also been reported as a better transfection agent, especially for hepatocytes [141].

Chitosan is another type of polymer functionalized with an AT reaction as shown in Scheme 45 [142]. The primary alcohol functions of chitosan were first protected with a trityl group. Then, the protected chitosan was engaged in an AT reaction that



**Scheme 44:** Polyphosphate functionalized by an AT reaction (adapted from [139]).



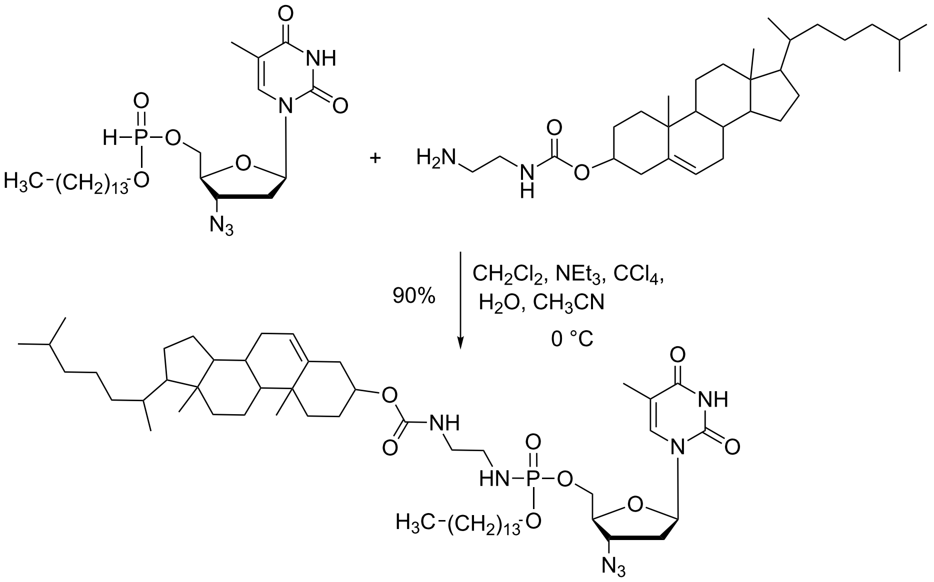
**Scheme 45:** Synthesis of zwitterionic phosphocholine-bound chitosan (adapted from [142]).

used a mixture of solvent (isopropanol/DMA), triethylamine as a base and $CCl_4$ as a halogenating agent. The deprotection of the trityl group under basic conditions ($NH_3$, $H_2O$) led to the loss of one choline moiety.

The AT reaction was also used to produce prodrugs as exemplified by the works of Zhao et al (Scheme 46), who reported the synthesis of phosphoramidates that included two lipid chains and one AZT moiety [143]. All phosphoramidates produced by this synthetic scheme exhibited high anti-HIV activities. The AT reaction can also be used to produce nucleoside phosphoramidate monoester [144] or thiophosphoramidates-based dinucleotides [77]. Other prodrugs were prepared by functionalization of polymers via a phosphoramidate tether. Yang et al. have reported the synthesis of chitosan functionalized with d4T (stavudine), a nucleoside reverse transcriptase inhibitor [145,146].

## Conclusion

The discovery of the reaction of dialkyl phosphite with amine in the presence of a base and $CCl_4$ by Atherton, Openshaw and Todd in 1945 opened the way to a series of studies, which were initially focused on the investigation of the mechanism of this reaction. The most likely mechanism produced chloro- or bromophosphate as intermediate reactive species. This intermediate reacts in situ with a nucleophile in the presence of a base, which is involved to trap hydrochoride or hydrobromide, the byproducts of the AT reaction. The synthetic conditions were improved by employing stoichiometric quantities of $CCl_4$ or $CBCl_3$ instead of using them as a solvent. AT reactions can be used by chemists as a tool to activate phenol or amine functional groups, which may subsequently be engaged in reactions such as cyclization, reduction, cross coupling, the production of organometallic species or for the synthesis of arylphosphonates. Beside these synthetic applications, phosphoramidates or phosphates produced by AT reactions can be used for a variety of applications including organocatalysis, improvement of the fire resistance of polymers, prodrugs, and vectorization purposes. Among the recent published works, we would like to point out two promising domains, in which the AT reaction seems exceptionally attractive and worthwhile to be studied in depth. First, the current developments of vectorization systems aiming at being applied in the realm of personalized medicine require the synthesis of amphiphilic derivatives with several functionalities, e.g., fluorescent moieties, targeting groups, and PEG fragments, to produce stealthy nanoparticles. The accessibility of phosphite with two lipid chains renders the AT reaction very attractive for the incorporation of hydrophobic domains and thus provides a synthetic path to functionalized amphiphilic compounds. The second domain concerns the activation of small molecules like $CO_2$ as recently illustrated by Y. F. Zhao et al. In these works, hydrospirophosphorane reacts with $CO_2$ and a secondary amine to produce a phosphorylated carbamate derivative. Currently, the hydrospirophosphorane is used stoichiometrically. The development of a catalytic system characterized by hydrospirophosphorane or analogues acting as organocatalyst represents an alternative to organometallic catalysis in the field of $CO_2$-based chemistry.



**Scheme 46:** Synthesis of AZT-based prodrug via an AT reaction (adapted from [143]).

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# Synthesis of ethoxy dibenzooxaphosphorin oxides through palladium-catalyzed $C(sp^2)$–H activation/C–O formation

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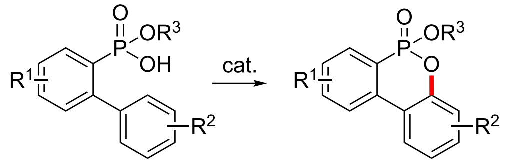
## Abstract

We report an efficient Pd-catalyzed $C(sp^2)$–H activation/C–O bond formation for the synthesis of ethoxy dibenzooxaphosphorin oxides from 2-(aryl)arylphosphonic acid monoethyl esters under aerobic conditions.

## Introduction

Unreactive $C(sp^2)$–H and $C(sp^3)$–H bonds are ubiquitous in organic compounds [1-7], so that the development of methods for the transition metal-catalyzed C–H activation is one of the challenging goals in organic synthesis. Especially, the development of synthetic methods of C–heteroatom bond formation via C–H activation has received attention owing to the omnipresence of heterocyclic compounds in nature [8]. Recently, it has been demonstrated that the intramolecular bond formation between a heteroatom and a vicinal unreactive C–H is an efficient method for the synthesis of heterocycles [9-17]. Although C–H activation/C–N formation has been widely used for the synthesis of azaheterocycles, the preparation of oxaheterocycles via C–H activation/C–O formation has been described a lot less, because the energy correlation between the HOMO of the Pd–O bond and the LUMO of the Pd–C bond is unfavorable and the Pd–O bond has a significantly ionic character [18-23]. To expand this scope, we are interested in the development of C–H activation/C–O formation by means of new directing groups. Recently, a variety of C–H activations by using new phosphoryl-related directing groups have been reported by our

[24-32] and other groups [33-41]. More recently, we developed a method allowing for synthetic access to benzoxaphosphole 1- and 2-oxides starting from phosphonic and phosphinic acids via Pd-catalyzed C(sp$^2$ and sp$^3$)–H activation/C–O formation [42]. In this context, we herein report the synthetic method of alkoxy dibenzooxaphosphorin oxides from 2-(aryl)arylphosphonic acid monoesters via Pd-catalyzed C(sp$^2$)–H activation/C–O formation (Scheme 1).



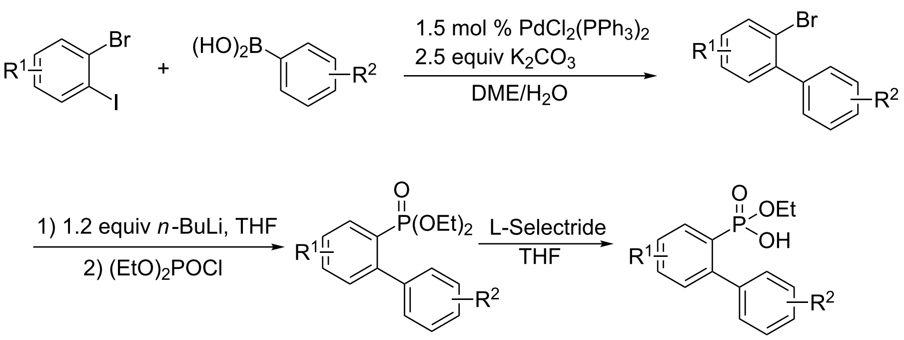
**Scheme 1:** Synthesis of alkoxy dibenzooxaphosphorin oxides by C(sp$^2$)–H activation/C–O formation.

## Results and Discussion

First, a wide range of 2-(aryl)arylphosphonic acid monoethyl esters were efficiently prepared by a Suzuki reaction of 2-bromoiodoarenes with arylboronic acids, a lithium bromide exchange reaction of 2-bromobiaryls followed by diethylphosphinylation with diethyl chlorophosphate, and the C–O cleavage of diethyl 2-(aryl)arylphosphonates by using L-Selectride (Scheme 2).

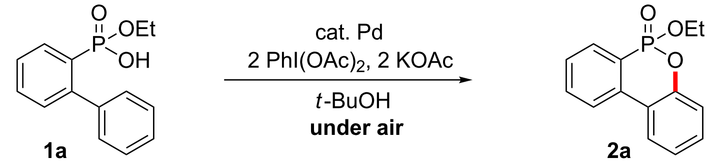
The C–H activation/C–O formation of 2-(phenyl)phenylphosphonic acid monoethyl ester (**1a**) was examined with a variety of oxidants and bases in the presence of Pd(OAc)$_2$. A multitude of oxidants such as $K_2S_2O_8$, BQ, benzoyl peroxide, PhI(TFA)$_2$, Cu(OAc)$_2$, CuCl$_2$, CuBr, AgOAc, Ag$_2$CO$_3$ and Ag$_2$O did not produce the cyclized product **2a** (see Supporting Information File 1). However, PhI(OAc)$_2$, which is an efficient oxidant for the Pd(II)/Pd(IV) catalytic cycle, gave **2a** in 30% yield in *t*-butanol (80 °C for 16 h; Table 1, entry 1) [19,43-47]. In addition, various bases were examined. Although NaOAc, CsOAc, CsF and CsOPiv afforded **2a** in yields ranging from 42% to 52%, KOAc gave the best result (57%) in the presence of PhI(OAc)$_2$ in *tert*-butanol (see Supporting Information File 1). *tert*-Butanol gave the best result among the solvents DCE, dioxane, ACN, *t*-AmOH, DMF, HFIP, THF, toluene, TFA and MeOH (see Supporting Information File 1). With this preliminary result in hand, we investigated a variety of organic acids as ligands in an effort to improve the catalytic efficiency (Scheme 3). However, these attempts provided no improvement (Table 1, entries 2–4). Finally, we discovered that easily accessible monoprotected amino acids, which have recently been established as efficient ligands in C–H activations [48-50], increased the yield (Table 1, entries 5–10). Among the investigated ligands, *N*-acetyl-*L*-leucine (L9) gave the best results (Table 1, entry 10). After examination of the reaction temperature (Table 1, entries 11–13) and time (Table 1, entries 14–16), the oxidative cyclization using PhI(OAc)$_2$ (2 equiv) and KOAc (2 equiv) in the presence of Pd(OAc)$_2$ (10 mol %) and L9 (30 mol %) gave the best result under aerobic conditions, affording **2a** in 61% yield (isolated yield 55%, Table 1, entry 16). Both Pd(TFA)$_2$ and Pd(OTf)$_2$·H$_2$O gave inferior results compared to Pd(OAc)$_2$ (Table 1, entries 17 and 18).

To ascertain the scope of the Pd-catalyzed C–H activation followed by the C–O formation, a wide range of 2-(aryl)phenylphosphonic acid monoethyl esters **1** were examined under the optimized reaction conditions (Scheme 4). Phenylphosphonic acid monoethyl ester **1b** with a 2-methyl group on the phenyl ring was transformed to the desired dibenzooxaphosphorin oxide **2b** in 53% yield. Phenylphosphonic acid monoethyl esters (**1c**) with a 3-methyl group were selectively converted to the cyclized products (**2c**) in 66% yield due to steric effects. In the case of 4-*tert*-butyl, the desired product



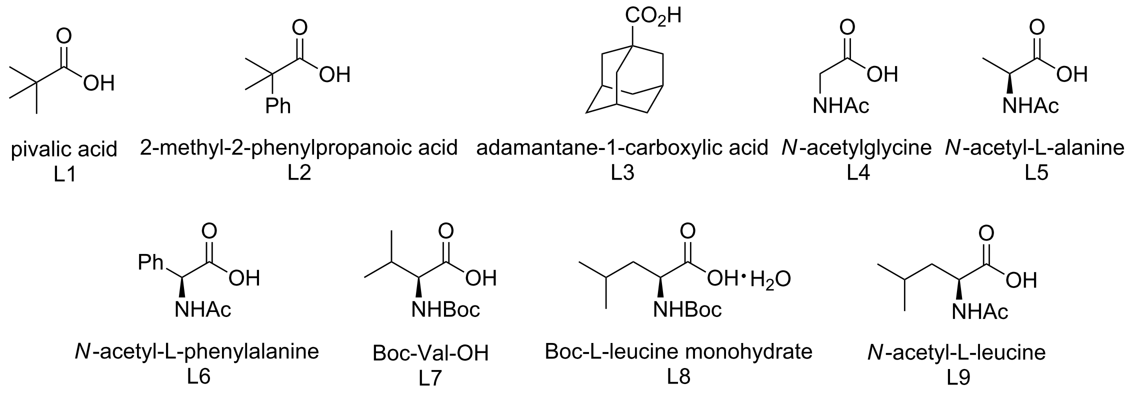
**Scheme 2:** Preparation of 2-(aryl)arylphosphonic acid monoethyl esters.

**Table 1:** Optimization studies for the cyclization of 2-(phenyl)phenylphosphonic acid monoethyl esters.



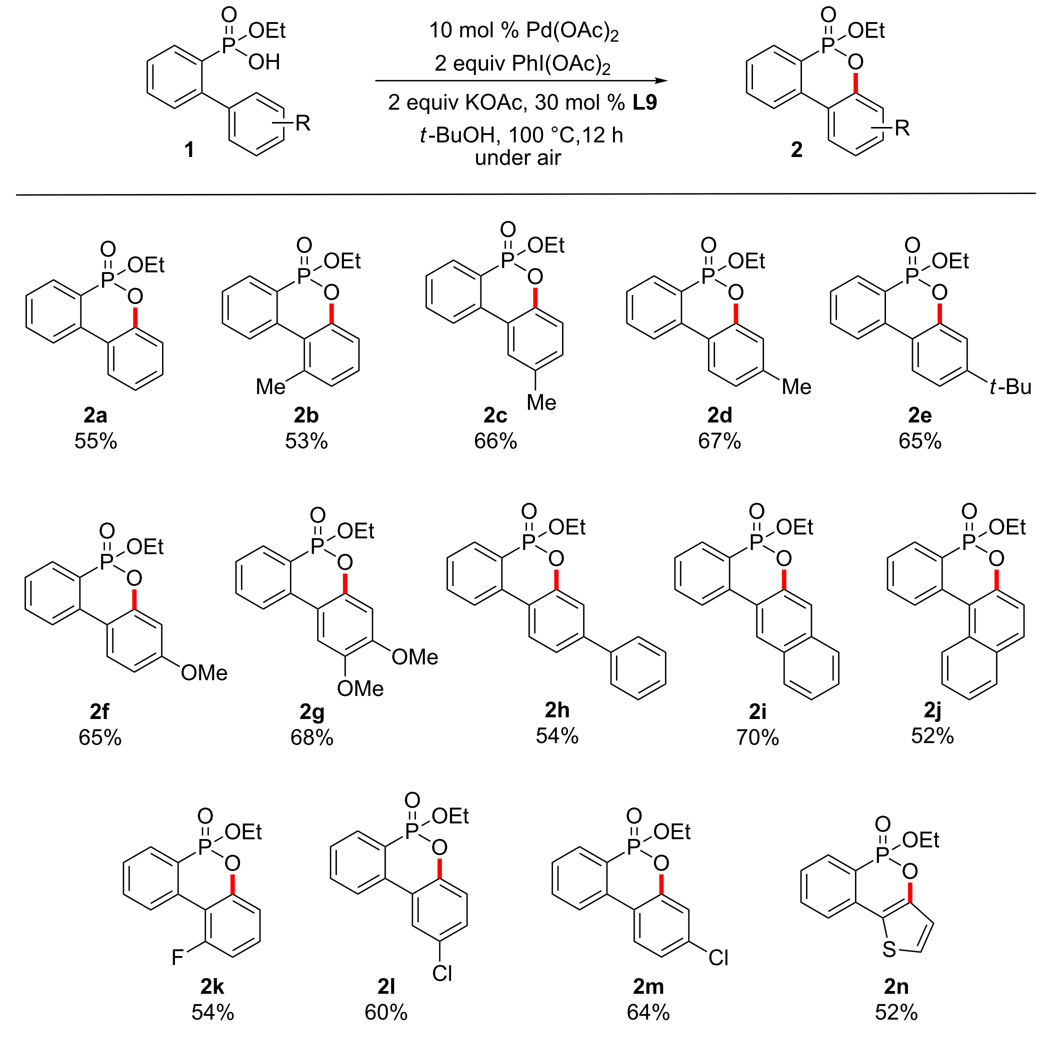
| entry | cat. Pd | ligand | *T* [°C] | *t* [h] | yield[a] [%] |
|---|---|---|---|---|---|
| 1 | 10 mol % Pd(OAc)$_2$ | — | 80 | 16 | 30 |
| 2 | 10 mol % Pd(OAc)$_2$ | 30 mol % L1 | 80 | 16 | 23 |
| 3 | 10 mol % Pd(OAc)$_2$ | 30 mol % L2 | 80 | 16 | 34 |
| 4 | 10 mol % Pd(OAc)$_2$ | 30 mol % L3 | 80 | 16 | 28 |
| 5 | 10 mol % Pd(OAc)$_2$ | 30 mol % L4 | 80 | 16 | 48 |
| 6 | 10 mol % Pd(OAc)$_2$ | 30 mol % L5 | 80 | 16 | 48 |
| 7 | 10 mol % Pd(OAc)$_2$ | 30 mol % L6 | 80 | 16 | 54 |
| 8 | 10 mol % Pd(OAc)$_2$ | 30 mol % L7 | 80 | 16 | 53 |
| 9 | 10 mol % Pd(OAc)$_2$ | 30 mol % L8 | 80 | 16 | 51 |
| 10 | 10 mol % Pd(OAc)$_2$ | 30 mol % L9 | 80 | 16 | 57 |
| 11 | 10 mol % Pd(OAc)$_2$ | 30 mol % L9 | 60 | 16 | 20 |
| 12 | 10 mol % Pd(OAc)$_2$ | 30 mol % L9 | 100 | 16 | 61 |
| 13 | 10 mol % Pd(OAc)$_2$ | 30 mol % L9 | 120 | 16 | 50 |
| 14 | 10 mol % Pd(OAc)$_2$ | 30 mol % L9 | 100 | 4 | 45 |
| 15 | 10 mol % Pd(OAc)$_2$ | 30 mol % L9 | 100 | 8 | 51 |
| **16** | **10 mol % Pd(OAc)$_2$** | **30 mol % L9** | **100** | **12** | **61(55)** |
| 17 | 10 mol % Pd(TFA)$_2$ | 30 mol % L9 | 100 | 12 | 53 |
| 18 | 10 mol % Pd(OTf)$_2$·H$_2$O | 30 mol % L9 | 100 | 12 | 45 |

[a]Yields were determined by $^1$H NMR with $CH_2Br_2$ as an internal standard. The number in parentheses is the isolated yield.



**Scheme 3:** A variety of organic acids and monoprotected amino acids as ligands.

**2e** was obtained in 65% yield. Substrate **1f**, characterized by an electron-donating 4-methoxy group, was cyclized to dibenzooxaphosphorin oxide **2f** in 65% yield under aerobic conditions. The present method worked equally well with 3,4-dimethoxyphenyl-substituted phenylphosphonic acid monoethyl ester **1g**. Phenylphosphonic acid monoethyl ester **1h** with a 4-phenyl group on the phenyl ring turned out to be compatible with the reaction conditions. As anticipated, 2-naphthyl-substituted phenylphosphonic acid monoethyl ester **1i** underwent the Pd-catalyzed oxidative cyclization regioselectively at the sterically less hindered position to afford the desired dibenzooxaphosphorin oxide **2i** in 70% yield. We were pleased to

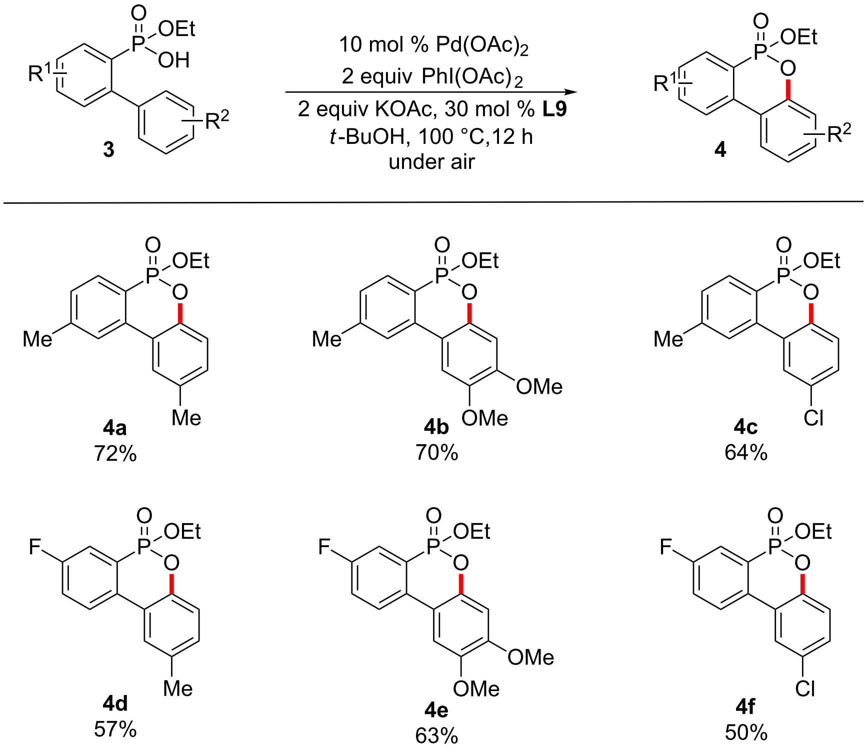


**Scheme 4:** Cyclization of 2-arylphenylphosphonic acid monoethyl esters.

obtain **2j** by a Pd-catalyzed oxidative cyclization of 1-naphthyl-substituted phenylphosphonic acid monoethyl ester **1j**. 2-(Aryl)phenylphosphonic acid monoethyl esters **1k**, **1l** and **1m** with an electron-withdrawing fluoro or chloro group on the phenyl ring were subjected to the oxidative cyclization to deliver the desired products **2k**, **2l** and **2m** in yields ranging from 54% and 64%. In particular, the tolerance of the chloro groups may be of importance for a subsequent catalytic cross-coupling reaction. Substrate **1n**, which contains a 2-thiophenyl moiety, was subjected to the cyclization affording **2n** in 52% yield. The preparation of 2-arylphenylphosphonic acid monoethyl esters with a nitro, difluoro, or ethoxycarbonyl group failed.

Next, the Pd-catalyzed oxidative cyclization of 2-(aryl)arylphosphonic acid monoethyl esters **3** were examined to demonstrate the efficiency of the present method (Scheme 5). 4-Methylphenylphosphonic acid monoethyl esters **3a** and **3b** with a 3-methyl- and 3,4-dimethoxyphenyl group at 2-position turned out to be compatible with the Pd-catalyzed oxidative cyclization. There are no regioisomers formed due to steric effects. Substrate **3c** bearing a chloro group was selectively cyclized to afford **4c** in 64% yield. To our delight, the present method worked equally well even if a fluoro group on the phenyl ring is present. 3-Fluorophenylphosphonic acid monoethyl esters **3d**, **3e** and **3f** with 3-methyl-, 3,4-dimethoxy and 3-chlorophenyl groups at the 2-position selectively underwent the oxidative cyclization to give the corresponding cyclized products **4d**, **4e** and **4f** in yields ranging from 50% and 63%.

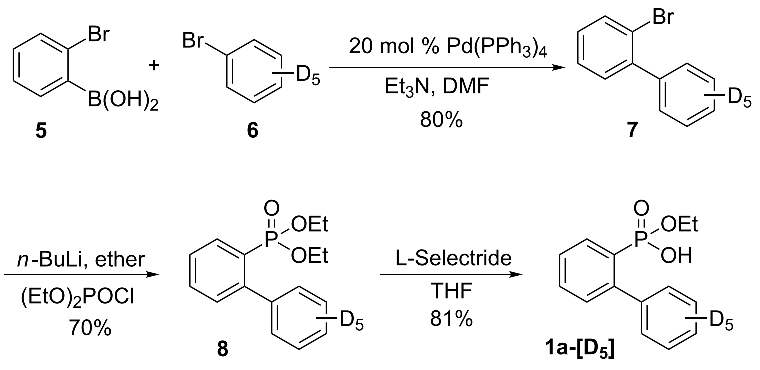
We carried out kinetic isotope effect (KIE) studies to prove the reaction mechanism (see Scheme 8). The required deuterium-labeled 2-(phenyl)phenylphosphonic acid monoethyl ester



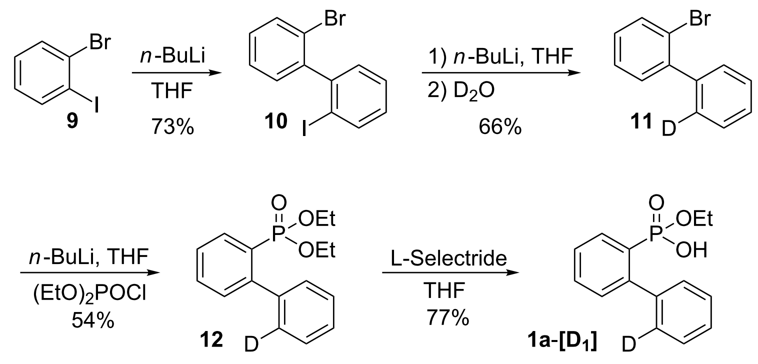
**Scheme 5:** Cyclization of 2-(aryl)arylphosphonic acid monoethyl esters.

**1a-[D$_5$]** was efficiently prepared by a Suzuki reaction of deuterated bromobenzene (**6**) with 2-bromophenylboronic acid (**5**), a lithium bromide exchange reaction of 2-bromo deuterated biphenyl **7** followed by diethylphosphinylation with diethyl chlorophosphate, and C–O cleavage of diethyl 2-(phenyl)-phenylphosphonate by using L-Selectride (Scheme 6). In addition, the deuterium-labeled 2-(phenyl)phenylphosphonic acid monoethyl ester **1a-[D$_1$]** was obtained by the lithium bromide exchange reaction of 2‘-bromo-2-iodo-1,1‘-biphenyl (**10**) and the treatment of $D_2O$, diethylphosphinylation with diethyl chlorophosphate, and C–O cleavage of diethyl 2-(phenyl)-phenylphosphonate by using L-Selectride (Scheme 7).

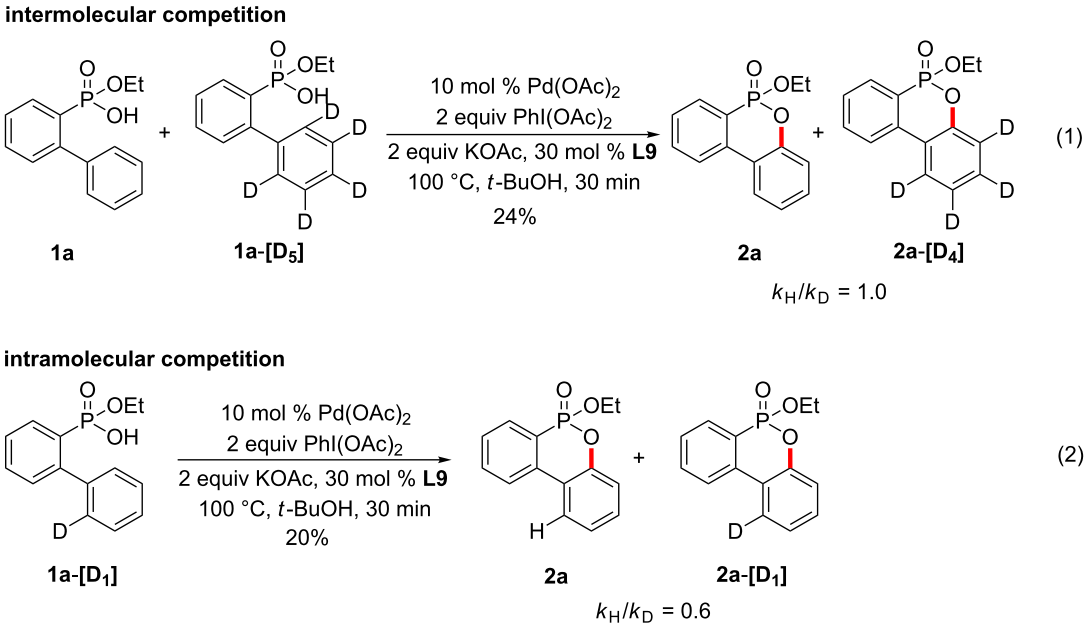
In the case of an intermolecular competition reaction using **1a** and **1a-[D$_5$]**, a KIE was detected ($k_H/k_D = 1.0$; Scheme 8, reaction 1) [51,52]. Also, an intramolecular competition reaction



**Scheme 6:** Preparation of **1a**-**[D$_5$]**.



**Scheme 7:** Preparation of **1a-[D$_1$]**.



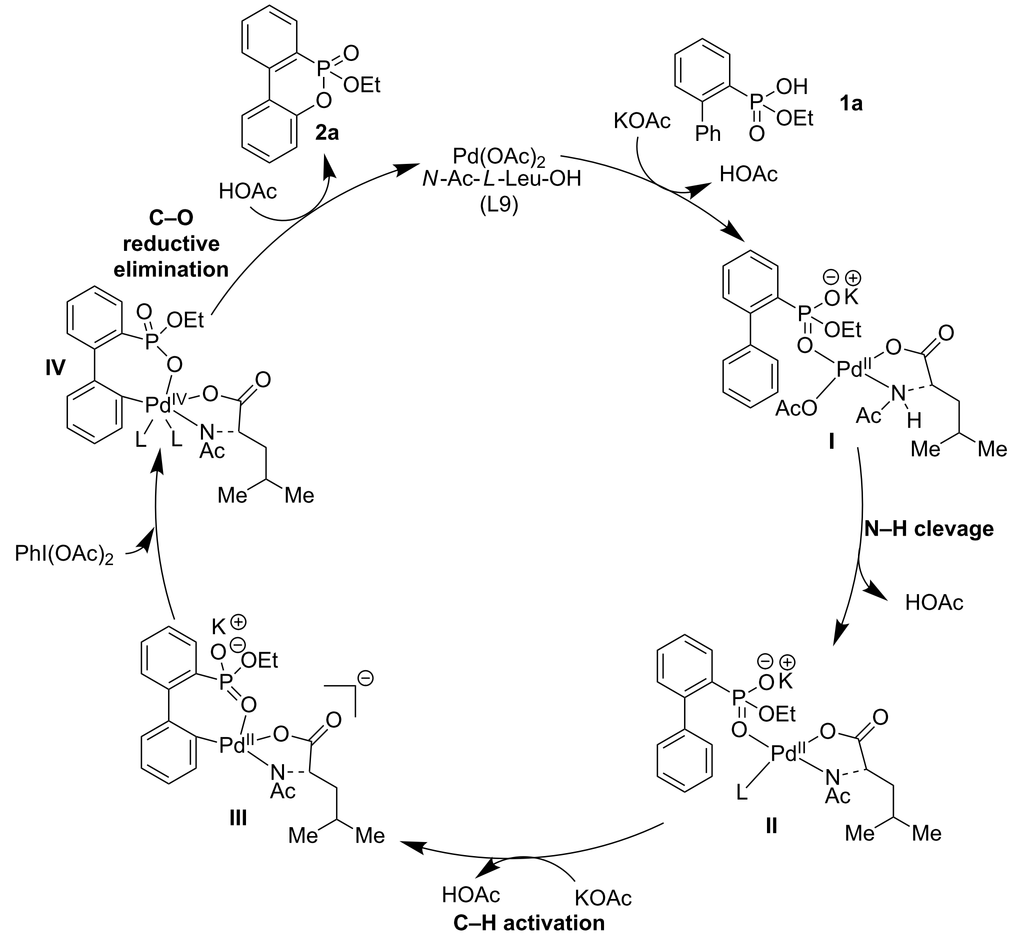
**Scheme 8:** Studies with isotopically labelled compounds.

using **1a-[D$_1$]** was carried out to give KIE ($k_H/k_D$ = 0.6; Scheme 8, reaction 2). These results indicate that the C–H cleavage at the *ortho*-position of 2-(phenyl)phenylphosphonic acid monoethyl ester is not involved in the rate-limiting step and the C–H bond metallation is reversible.

To elucidate the mechanism of the present reaction, the reaction was conducted with a stoichiometric amount of $Pd(OAc)_2$ and without the oxidant $PhI(OAc)_2$. However, no cyclized product was observed. This result indicates that the C–O reductive elimination from Pd(II) is not favorable. Because both the intermolecular and intramolecular competition experiments exhibited no significant kinetic isotope effect ($k_H/k_D$ = 1.0 and 0.6; Scheme 8), we hypothesize that the C–O reductive elimination step is the rate-determining step. A feasible mechanism involving the Pd(II)/Pd(IV) catalytic cycle is described in Scheme 9. The C–H activation might be efficiently accelerated by the N–H activation propelled by *N*-Ac-*L*-Leu-OH (L9) as a ligand [53-55], resulting in the formation of palladacycle **III**. Thereafter, ethoxy dibenzooxaphosphorin oxide **2a** is obtained from the oxidation of the Pd(II) to Pd(IV) species **IV** and the subsequent C–O reductive elimination.

## Conclusion

In this paper, we have developed an efficient synthetic method for a wide range of ethoxy dibenzooxaphosphorin oxides



**Scheme 9:** A plausible mechanism.

starting from 2-(aryl)arylphosphonic acid monoethyl esters and employing Pd-catalyzed C($sp^2$)–H activation/C–O formation under aerobic conditions. Oxidative cyclization by means of a Pd(II)/Pd(IV) catalytic cycle might play a role in the mechanism of the present reaction.

## Supporting Information

### Supporting Information File 1

Experimental procedures, characterization data, and $^1$H and $^{13}$C NMR spectra of new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-120-S1.pdf]

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# Synthesis of 1-[bis(trifluoromethyl)phosphine]-1’-oxazolinylferrocene ligands and their application in regio- and enantioselective Pd-catalyzed allylic alkylation of monosubstituted allyl substrates

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Full Research Paper

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## Abstract

A class of novel, easily accessible and air-stable 1-[bis(trifluoromethyl)phosphine]-1’-oxazolinylferrocene ligands has been synthesized from ferrocene. It became apparent that these ligands can be used in the regio- and enantioselective Pd-catalyzed allylic alkylation of monosubstituted allyl substrates in a highly efficient manner. Excellent regio- and enantioselectivity could be obtained for a wide range of substrates.

## Introduction

The palladium-catalyzed asymmetric allylic alkylation (AAA) reaction is now becoming an efficient method for the construction of carbon–carbon bonds [1-5]. Despite extensive investigation and noteworthy advances in this field, several challenges remain to be solved. For instance, with monosubstituted allyl substrates, the palladium-catalyzed allylic substitution reaction prefers to give linear products rather than the branched ones [6-9] (Scheme 1). Accordingly, the regio- and enantioselective allylic substitution reaction of monosubstituted allylic substrates to preferably obtain the branched products is one of the continuing challenges. To our knowledge, there are several cases in which high levels of both regio- and enantioselectivity have been realized by introducing special ligands [10-34] (Figure 1). Hayashi and coworkers reported a sterically bulky chiral monophosphine ligand (MeO-MOP) could be used for the Pd-catalyzed alkylation of branched monosubstituted allyl acetate favoring the branched products. However, linear products were favored when the linear allyl substrates were employed [23,24]. The chiral oxazoline–phosphite ligands introduced by Pfaltz and coworkers proved to be highly efficient for regio- and enantiocontrol in the Pd-catalyzed allylic alkylation reaction. Excellent results were obtained for the bulky and electron-rich aryl allyl substrates [25-27]. In 2001, Dai, Hou and their coworkers synthesized a new class of 1,1’-ferrocene-based *P*,*N*-ligands, namely SiocPhox. The application of these SiocPhox ligands in the Pd-catalyzed allylic substitution led to excellent regio- and enantioselectivities for a wide range of substrates in both allylic alkylation and amination reactions despite of the electronic properties of the allylic substrates [28-33]. Recently, Shen and co-workers reported an elegant synthesis of bis(perfluoroalkyl)phosphine-oxazoline ligands where small but strongly electron-withdrawing substituents were introduced at the phosphorus [34]. 1,2-Ferrocene based *P*,*N*-ligands were synthesized and gave excellent regio- and enantioselectivities in the Pd-catalyzed allylic alkylation reactions of monosubstituted allylic substrates. Inspired by these pioneering studies above and as our continuing interests in the transition metal-catalyzed asymmetric allylic alkylation reaction [35-38], we envisaged that the 1-[bis(trifluoromethyl)phosphine]-1’-oxazolinylferrocene ligands, a straightforward combination of the features of SiocPhox and Shen’s ligand, should be highly efficient for the Pd-catalyzed allylic alkylation reactions of monosubstituted allyl substrates. Herein, we report the synthesis of 1-[bis(trifluoromethyl)phosphine]-1’-oxazolinylferrocene ligands and their application in Pd-catalyzed allylic alkylation reactions of monosubstituted allyl substrates with excellent regio- and enantioselectivity.

## Results and Discussion

As depicted in Scheme 2, ligands **L1a–L1d** were synthesized from known compounds **3**, which were obtained from ferrocene in three steps according to the reported procedures [39-41]. The commercially available ferrocene was dilithiated with *n*-BuLi and then quenched with dibromoterafluoroethane to give dibromoferrocence **1**. Treatment of **1** with *n*-BuLi at −20 °C followed by trapping with $CO_2$ afforded compound **2**. Treatment of compound **2** with $(COCl)_2$ and then chiral amino alcohols yielded the amide intermediates which were transformed to their corresponding 1-bromo-1’-oxazolinylferrocenes **3**. Eventually, lithium–bromide exchange of **3** with *n*-BuLi at −78 °C, followed by quenching with $P(OPh)_3$, provided the phosphonite intermediates which were used without further purification. Subsequently, trifluoromethylation provided the ligands **L1a–d** in moderate yields, upon treatment with Ruppert’s reagent ($TMSCF_3$) and CsF [42-45]. Notably, ligands **L1a–d** are moisture and air-stable, and their NMR spectra show no change even after being stored over six months under ambient atmosphere.

To test the suitability of these 1-[bis(trifluoromethyl)phosphine]-1’-oxazolinylferrocene ligands in Pd-catalyzed allylic alkylation reactions, we began our study by choosing methyl cinnamyl carbonate and dimethyl malonate as the model

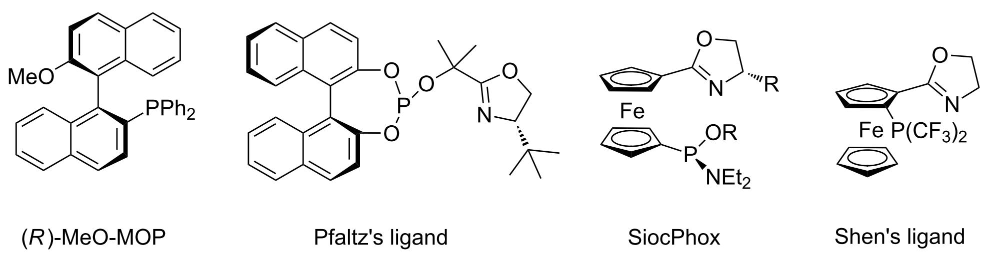
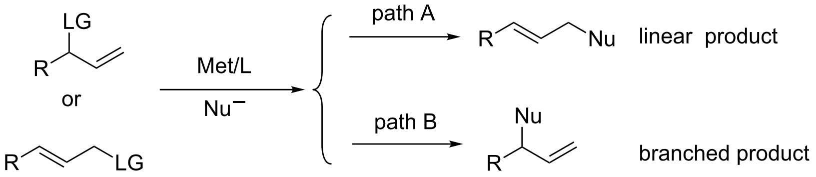
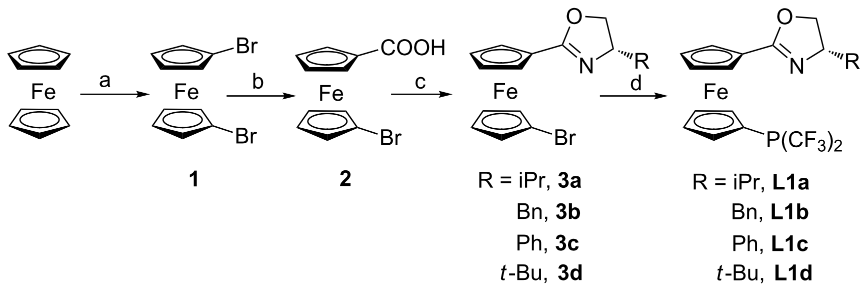


**Figure 1:** Representative ligands developed for the regio- and enantioselective Pd-catalyzed allylic alkylation.



**Scheme 1:** Transition metal-catalyzed allylic substitution reactions with monosubstituted allyl substrates.

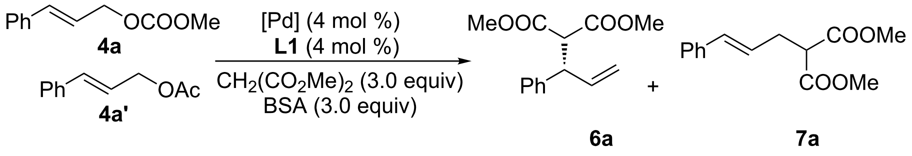


**Scheme 2:** Preparation of 1-[bis(trifluoromethyl)phosphine]-1'-oxazolinylferrocene ligands. Reagents and conditions: (a) (i) *n*-BuLi, TMEDA, $Et_2O$, rt; (ii) $(BrCF_2)_2$, −78 °C. (b) *n*-BuLi, $CO_2$, THF, −20 °C. (c) (i) $(COCl)_2$, DCM, rt; then TEA, amino alcohol, DCM, rt; (ii) $Ph_3P$, $CCl_4$, TEA, $CH_3CN$, rt. (d) (i) *n*-BuLi, TMEDA, $P(OPh)_3$, $Et_2O$, −78 °C; (ii) $TMSCF_3$, CsF, $Et_2O$, rt.

substrates, along with the catalysts derived from $Pd_2(dba)_3$ and ligands **1a–d**. The results are summarized in Table 1. Ligands **L1a–d** were screened in the reaction using bis(trimethylsilyl)acetamide (BSA) as the base and LiOAc as the additive. The results suggested that ligands **L1a–d** were effective for this reaction with full conversion and high selectivities (entries 1–4, Table 1). The catalyst derived from **L1d** gave the highest selectivities [b/l (branched/linear): 95/5, 82% ee; entry 4, Table 1]. With ligand **L1d**, different reaction parameters including the Pd precursor and solvent were further optimized. The utilization of $[Pd(C_3H_5)Cl]_2$ as Pd precursor or DCM as solvent resulted in slightly lower selectivities (entries 5–6, Table 1). Further screening of the additives revealed that NaOAc was the optimal one (b/l: 97/3, 85% ee, entry 7, Table 1). Running the reaction at 0 °C resulted in an increased enantioselectivity (b/l: 96/4, 88% ee, entry 9, Table 1). When the reaction was run at −30 °C, only a trace amount of product was formed. As for the leaving groups of allyl substrates, the cinnamyl acetate could also be tolerated to give a similar level of regio- and enantioselectivity (entry 11, Table 1). The absolute configuration of the product was assigned as (*S*) by comparing the sign of the optical rotation with that reported in literature [28].

Under the optimized reaction conditions (2 mol % of $Pd_2(dba)_3$, 4 mol % of **L1d**, 300 mol % of $CH_2(COOMe)_2$, 300 mol % of BSA and 3 mol % of NaOAc in DCE at 0 °C; entry 9, Table 1), the substrate scope was examined to test the generality of the reaction (Table 2). We first compared the reaction of branched

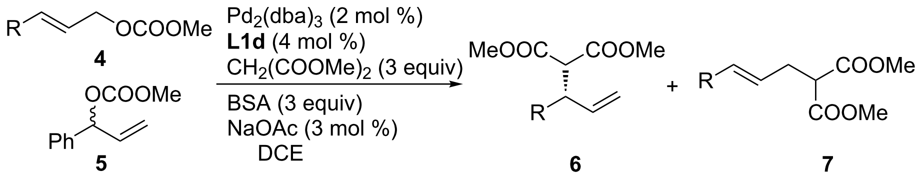
**Table 1:** Evaluation of the ligands and optimization of the reaction conditions.[a]



| entry | **4** or **4a'** | [Pd] | **L1** | Additive | Solvent | *T* (°C) | Yield (%)[b] | **6a/7a**[c] | ee (%)[d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **4a** | $Pd_2(dba)_3$ | **L1a** | LiOAc | DCE | rt | 95 | 84/16 | 68 |
| 2 | **4a** | $Pd_2(dba)_3$ | **L1b** | LiOAc | DCE | rt | 96 | 93/7 | 68 |
| 3 | **4a** | $Pd_2(dba)_3$ | **L1c** | LiOAc | DCE | rt | 91 | 85/15 | 80 |
| 4 | **4a** | $Pd_2(dba)_3$ | **L1d** | LiOAc | DCE | rt | 95 | 95/5 | 82 |
| 5 | **4a** | $[Pd(C_3H_5)Cl]_2$ | **L1d** | LiOAc | DCE | rt | 93 | 90/10 | 76 |
| 6 | **4a** | $Pd_2(dba)_3$ | **L1d** | LiOAc | DCM | rt | 91 | 83/17 | 76 |
| 7 | **4a** | $Pd_2(dba)_3$ | **L1d** | NaOAc | DCE | rt | 90 | 97/3 | 85 |
| 8 | **4a** | $Pd_2(dba)_3$ | **L1d** | KOAc | DCE | rt | 91 | 91/9 | 82 |
| 9 | **4a** | **$Pd_2(dba)_3$** | **L1d** | **NaOAc** | **DCE** | **0** | **95** | **96/4** | **88** |
| 10[e] | **4a** | $Pd_2(dba)_3$ | **L1d** | NaOAc | DCE | −30 | trace | nd | nd |
| 11[e] | **4a'** | $Pd_2(dba)_3$ | **L1d** | NaOAc | DCE | rt | 80 | 95/5 | 87 |

[a]Reagents and conditions: 2.0 mol % $Pd_2(dba)_3$, 4.0 mol % ligand, 0.2 mmol allyl substrate, 0.6 mmol dimethyl malonate, 0.6 mmol BSA, 3.0 mol % additive, solvent (2 mL). [b]Isolated yield after 12 h. [c]Determined by $^1H$ NMR of the crude reaction mixture. [d]Determined by HPLC. [e]Reaction for 24 h.

**Table 2:** Regio- and enantioselective allylic alkylation of monosubstituted allyl substrates.[a]

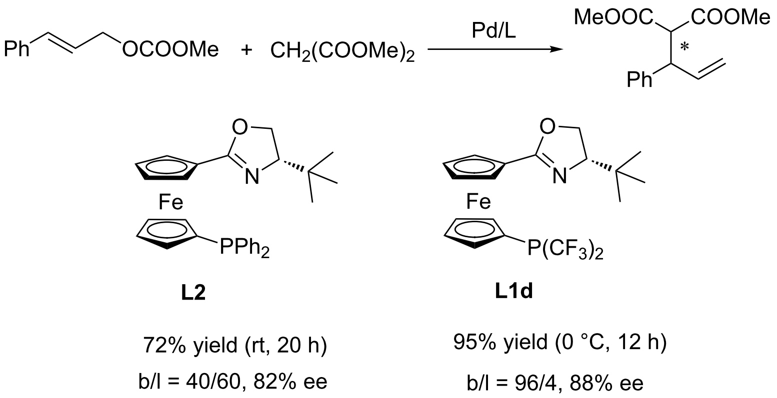


| entry | R | *T* (°C) | Yield (%)[b] | **6/7**[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | **4a**, Ph | 0 | 95 | 96/4 | 88 |
| 2 | **5** | 0 | 93 | 95/5 | 87 |
| 3 | **4b**, 1-naphthyl | 0 | 95 | 99/1 | 92 |
| 4 | **4c**, 4-$MeC_6H_4$ | 0 | 93 | 95/5 | 85 |
| 5 | **4d**, 4-$MeOC_6H_4$ | 0 | 96 | 95/5 | 82 |
| 6 | **4e**, 2-thienyl | 0 | 94 | 98/2 | 70 |
| 7 | **4f**, 2-furyl | rt | 90 | 83/17 | 65 |
| 8 | **4g**, 4-$ClC_6H_4$ | 0 | 91 | 96/4 | 83 |
| 9 | **4h**, 4-$BrC_6H_4$ | 0 | 90 | 99/1 | 83 |
| 10 | **4i**, 2-$FC_6H_4$ | rt | 90 | 93/7 | 81 |
| 11 | **4j**, 2-$MeOC_6H_4$ | 0 | 95 | 99/1 | 92 |
| 12 | **4k**, 2-$MeC_6H_4$ | 0 | 91 | 97/3 | 94 |
| 13 | **4l**, 3-$ClC_6H_4$ | 0 | 90 | 93/7 | 88 |
| 14[e] | **4m**, methyl | 0 | 96 | 81/19 | ND |

[a]Reagents and conditions: 2.0 mol % $Pd_2(dba)_3$, 4.0 mol % **L1d**, 0.5 mmol allyl substrate, 1.5 mmol dimethyl malonate, 1.5 mmol BSA, 3.0 mol % NaOAc, DCE (5 mL). [b]Isolated yield after 12 h. [c]Determined by $^1H$ NMR of the crude. [d]Determined by HPLC. [e]$[Pd(C_3H_5)Cl]_2$ as the Pd precursor.

substrate **5** with the linear substrate **4a**. Nearly identical results were obtained indicating that the reaction proceeds via the formation of the same Pd-π-allyl intermediate. Substrates bearing either an electron-donating group or electron-withdrawing group on the aromatic ring of the aryl allyl carbonates all proceeded smoothly in full conversion within 12 h. In all cases, the reactions gave excellent regioselectivity favoring the formation of the branched products in good to excellent enantioselectivity (b/l: 93/7–99/1, 81–94% ee). It is known that the regioselectivity could be strongly influenced by electronic properties of the allyl substrates and the formation of branched products was dramatically reduced for substrates bearing electron-withdrawing groups [21]. Fortunately, with our catalytic system, substrates bearing electron-withdrawing groups were well tolerated with excellent regioselectivity and preferred formation of the branched products (b/l: 93/7–99/1, entries 8–10, and 13, Table 2). Reactions of sterically hindered 1-naphthyl allyl carbonate, 2-MeO and 2-Me-substituted cinnamyl carbonates occurred smoothly to give excellent regio- and enantioselectivity (b/l: up to 99/1, up to 94% ee, entries 3, 11, 12, Table 2). In addition, heteroaryl allyl carbonates **4e** and **4f** also gave good regioselectivity with slightly lower enantioselectivity (entries 6 and 7, Table 2). Good regioselectivity (b/l: 81/19) was obtained with 2-buten-3-yl carbonate as a substrate (entry 14, Table 2).

We conducted some control experiments to probe the effect of the bis(trifluoromethyl) group in the ligands (Scheme 3). With ferrocence-based biphenyl phosphine-oxazoline **L2** as the ligand, the Pd-catalyzed allylic alkylation of cinnamyl carbonate with dimethyl malonate afforded the linear product as the major product (b/l: 40/60). Whereas the corresponding ligand **L1d** with two $CF_3$ groups (instead of two phenyl groups) at the P atom improved the regioselectivity significantly (b/l: 96/4). A preliminary explanation was described in Figure 2. In addition to the effect of different metals, there are at least two additional factors controlling the regioselectivity of the allylic alkylation reaction. The steric factor favors path a since the terminal allylic carbon is less hindered. In contrast, when the R group has the ability to stabilize the carbocation, the electronic factor would favor the formation of the branched product (path b). The phosphorus atom has a stronger *trans* effect comparing with the oxazoline nitrogen, indicating that the carbon *trans* to phosphorus atom bears more electropositivity [46]. This fact may be responsible for the preferred placement of the substituted allylic carbon in the *trans* position to the phosphorus atom to better stabilize the electropositivity of the carbon. When the nucleophile attacks the more electropositive substituted allylic carbon terminus, a branched product will be formed. The introduction of the $CF_3$ group on the phosphorus atom further increases the *trans* influence of the $P(CF_3)_2$ moiety and



**Scheme 3:** Comparison of the effect of ligands in the reaction.

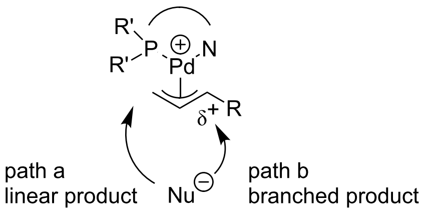


**Figure 2:** Preliminary explanation of the regioselectivity.

enhances the electronic factor, providing a better branched-product selectivity. Further experimental studies and computational investigation are still needed to confirm this hypothesis.

## Conclusion

In summary, we have synthesized a class of novel and efficient bis(trifluoromethyl)phosphine-oxazolines as π-acceptor ligands which have shown good to excellent regio- and enantioselectivity for the Pd-catalyzed asymmetric allylic alkylation reaction of monosubstituted allyl carbonates. Further studies on the synthesis of 1-[bis(perfluoroalkyl)phosphine]-1’-oxazolinylferrocene ligands and their applications in asymmetric catalysis are ongoing in our lab.

## Supporting Information

### Supporting Information File 1

Experimental, characterization data and spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-126-S1.pdf]

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# Synthesis of chiral *N*-phosphoryl aziridines through enantioselective aziridination of alkenes with phosphoryl azide via Co(II)-based metalloradical catalysis

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Full Research Paper

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## Abstract

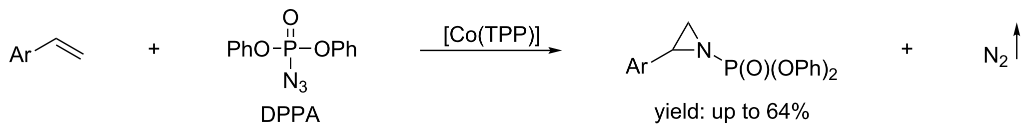
The Co(II) complex of a new $D_2$-symmetric chiral porphyrin 3,5-DiMes-QingPhyrin, [Co(**P6**)], can catalyze asymmetric aziridination of alkenes with bis(2,2,2-trichloroethyl)phosphoryl azide (Tcep$N_3$) as a nitrene source. This new Co(II)-based metalloradical aziridination is suitable for different aromatic olefins, producing the corresponding *N*-phosphorylaziridines in good to excellent yields (up to 99%) with moderate to high enantioselectivities (up to 85% ee). In addition to mild reaction conditions and generation of $N_2$ as the only byproduct, this new metalloradical catalytic system is highlighted with a practical protocol that operates under neutral and non-oxidative conditions.

## Introduction

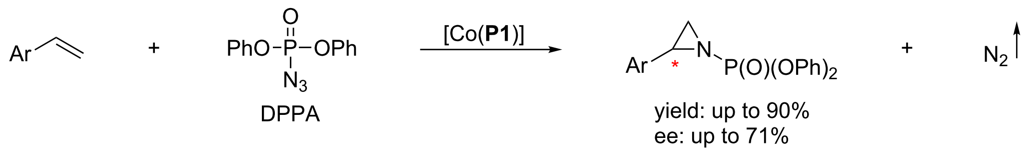
Aziridines, the smallest three-membered nitrogen-containing heterocycles, are highly valuable heterocyclic compounds that are widely used in organic synthesis and pharmaceuticals [1,2]. As a result, tremendous efforts have been made for the construction of this class of nitrogen-containing three-membered ring compounds [3-8]. Among synthetic methodologies, catalytic aziridination of alkenes with nitrene sources via "C2 + N1" addition has received the most attention because of the abundance of both alkenes and nitrene sources [9-12]. The enantioselective olefin aziridination is of particular significance due to the streamlined approach for the installation of chiral aziridines, which are versatile intermediates in organic synthesis. To date, several different types of transition metal-based chiral catalysts, such as Mn, Fe, Cu, Rh, Ru and Co complexes, have been demonstrated as effective catalysts in asymmetric olefin aziridination with various nitrene sources, including the widely used iminoiodanes and their in situ variants, chloramine-T, bromamine-T, tosyloxycarbamates and organic azides [9-15]. Among them, the organic azides have recently emerged as attractive alternative nitrene sources for metal-catalyzed aziridination because of many advantages such as ease of preparation, structural diversity, and $N_2$ gas as the only byproduct [13-15]. While sulfonyl and aryl azides have been effectively employed for metal-catalyzed asymmetric aziridination [16-19], the catalytic system based on other types of azides, such as phosphoryl azides, remains underdeveloped.

Phosphoryl azides, a family of common organic azides that can be directly synthesized from commercially available phosphoryl chlorides, have been recently explored as nitrene sources for transition metal-catalyzed nitrene transfer reactions [20-23]. Their use in a catalytic asymmetric aziridination would provide an attractive approach for the synthesis of valuable chiral phosphorous-containing aziridines, producing nitrogen gas as the only and also environmentally friendly byproduct. Chiral phosphorylated aziridines and their derivatives have been demonstrated with pharmaceutical and other important synthetic applications. In addition to the fundamental and practical significance of the phosphorous-containing aziridines, the easy deprotection of phosphoryl groups makes them even more synthetically useful [24-27]. However very few catalytic systems are available for the direct asymmetric olefin aziridination with phosphoryl azides. In this regard, our group initially reported in 2006 a racemic olefin aziridination system with diphenylphosphoryl azide (DPPA) using Co(II) complexes of common porphyrin ligands as catalysts, including [Co(TPP)] (Scheme 1) [20]. Despite the first demonstration of DPPA as a new nitrene source, this Co(II)-based catalytic transformation, however, suffered from low-yielding formation of the desired aziridine products. To improve the efficiency and control the enantioselectivity of the nitrene transfer process, we then developed a new Co(II)-based metalloradical catalytic system by employing $D_2$-symmetric chiral amidoporphyrins as the supporting ligands [28]. It was shown that the chiral metalloradical catalyst [Co(**P1**)] (**P1** = 3,5-Di$^t$Bu-ChenPhyrin) could catalyze the formation of optically enriched phosphoryl aziridine through direct aziridination of alkenes with DPPA (Scheme 2) [21]. While this [Co(**P1**)]/DPPA catalytic system represented the first asymmetric version of olefin aziridination with phosphoryl azide, both the yields and enantioselectivities were moderate even using 10 mol % catalyst loading. It would be desirable if a more effective Co(II)-based metalloradical system could be developed for asymmetric aziridination of alkenes with phosphoryl azides with both improved reactivity and enantioselectivity.

The stable 15e-metalloradicals Co(II) complexes of $D_2$-symmetric chiral amidoporphyrins ([Co($D_2$-Por*)]) represent a new type of chiral catalysts that have been demonstrated to be effective for asymmetric olefin aziridination using different types of nitrene sources, particularly with sulfonyl and aryl azides [16,18]. Computational and experimental studies have provided increasing evidences to suggest a stepwise radical mechanism for the Co(II)-catalyzed metalloradical aziridination that involves an unprecedented Co(III)–nitrene radical intermediate [29-34]. It is worthy to note the importance of dual functions of the chiral amide units of the $D_2$-symmetric chiral amidoporphyrin ligands played in the Co(II)-based metalloradical catalysis (MRC): the rigid amide spacers do not only support and orient the chiral environments toward the cobalt metalloradical center, but also function as potential donors to engage in hydrogen bonding with acceptors located at the nitrene moiety in the Co(III)–nitrene radical intermediate [18,35,36]. These secondary hydrogen bonding interactions are expected to lower the energy barrier of the transition state and thus lead to acceleration of the reaction rate as well as improvement of the stereoselectivity [18,29]. Given that the



**Scheme 1:** [Co(TPP)]-catalyzed olefin aziridination with DPPA.



**Scheme 2:** [Co(**P1**)]-catalyzed asymmetric olefin aziridination with DPPA.

P=O group can serve as a potential hydrogen bond acceptor, we hypothesized that the resulting Co(III)–nitrene radical intermediate from activation of phosphoryl azides would benefit from a similar hydrogen bonding interaction (Figure 1).

With this assumption in mind, we have carried out a systematic study to identify more effective phosphoryl azides and to employ Co(II) complexes of suitable $D_2$-symmetrical chiral porphyrin ligands ([Co(Por*)]) (Figure 2) for the development of Co(II)-based asymmetric aziridination via MRC to improve

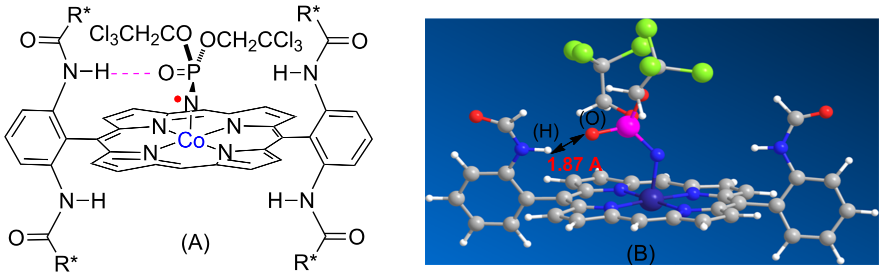


**Figure 1:** (A) Potential H-bonding interaction in postulated nitrene radical complex of [Co($D_2$-Por*)]. R* represents a chiral unit. (B) Geometry corresponding to the minimum energy from simplified computer modeling by molecular mechanics with Spartan 10. The P=O···H–N distance of (1.87 Å) suggests possible existence of significant hydrogen bonding interaction. However, besides computer modeling there is no direct experimental evidence for such interactions. For clarity, the other two *meso*-groups of the porphyrin are omitted in both (A) and (B). In addition, the other two amido units below the porphyrin ring are also omitted in (B).

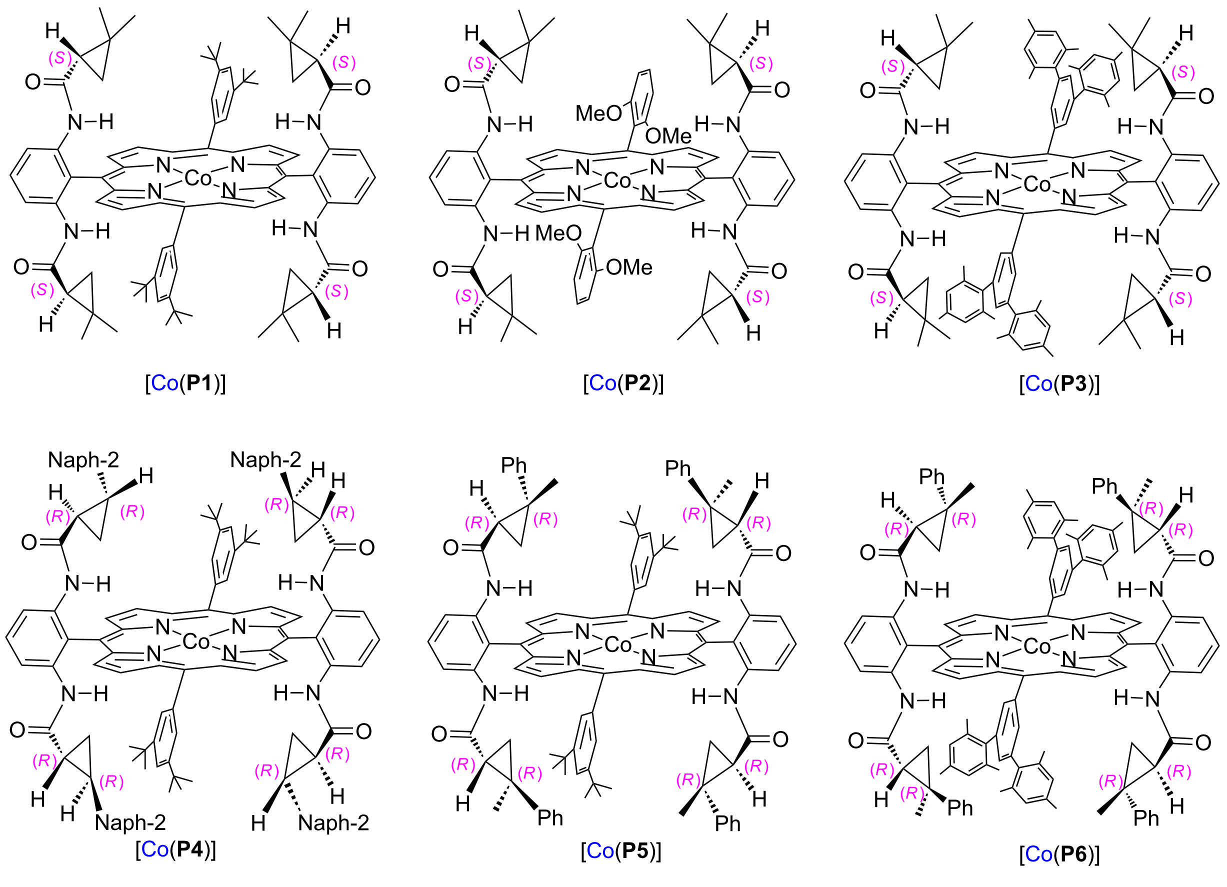


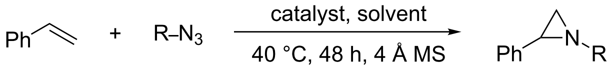
**Figure 2:** Structures of $D_2$-symmetric chiral cobalt(II) porphyrins.

the reactivity and selectivity. As the result of this study, herein we wish to report an effective catalytic system for asymmetric olefin aziridination based on the use of bis(2,2,2-trichloroethyl)phosphoryl azide (TcepN$_3$) as nitrene source and the employment of new generation of chiral Co(II) metalloradical catalysts. The aziridination via Co(II)-based MRC is applicable for a broad range of aromatic olefins, producing the corresponding *N*-phosphorylated aziridines in good to excellent yields with moderate to high enantioselectivities. In addition to generating N$_2$ as the only byproduct, the new metalloradical aziridination process is highlighted by a practical protocol that operates under neutral and non-oxidative reaction conditions without the need of any additives.

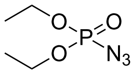
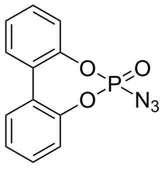
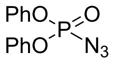
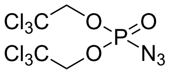
## Results and Discussion

Our initial study was focused on the aziridination reaction of styrene (**1a**) as a model reaction and [Co(TPP)] (TPP = 5,10,15,20-tetraphenylporphyrin) as catalyst to search for a more effective phosphoryl azide (Table 1). In the presence of 10 mol % of [Co(TPP)], the phosphoryl azides **2a–c** were found to be ineffective nitrene sources for the catalytic reaction, with no detectable aziridine product but remaining of the starting azides (Table 1, entries 1–3). It should be noted that azide **2c** was previously shown to be a productive nitrene source for the catalytic aziridination reaction only at a high temperature of 80 °C [20]. Afterwards, we were pleased to find that the phosphoryl azide bis(2,2,2-trichloroethyl)phosphoryl azide (TcepN$_3$, **2d**) was an effective nitrene source even at low temperature. For instance, at 40 °C, styrene could be aziridinated with the phosphoryl azide TcepN$_3$ in low but significant yield when using [Co(TPP)] as the catalyst (Table 1, entry 4). Subsequent experiments showed that Co(II) complexes of *D*$_2$-amidoporphyrin ligands (Figure 2) were more effective catalysts to activate TcepN$_3$ for the aziridination reaction. For example, under

**Table 1:** Optimization of catalytic aziridination of styrene with phosphoryl azides by Co(II)-based metalloradical catalysts.[a]



**1a** **2** **3**

| entry | R–N$_3$ | catalyst | solvent | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1[d] | <br>**2a** | [Co(TPP)] | PhCl | 0 | – |
| 2[d] | <br>**2b** | [Co(TPP)] | PhCl | 0 | – |
| 3[d] | <br>**2c** | [Co(TPP)] | PhCl | 0 | – |
| 4[d] | <br>**2d** | [Co(TPP)] | PhCl | 11 | – |
| 5 | **2d** | [Co(**P1**)] | PhCl | 77 | 53 |
| 6 | **2d** | [Co(**P2**)] | PhCl | <5 | nd |
| 7 | **2d** | [Co(**P3**)] | PhCl | 99 | 40 |
| 8 | **2d** | [Co(**P4**)] | PhCl | 7 | 65 |
| 9 | **2d** | [Co(**P5**)] | PhCl | 23 | 81 |
| 10 | **2d** | [Co(**P6**)] | PhCl | 98 | 75 |
| 11 | **2d** | [Co(**P6**)] | PhCF$_3$ | 75 | 77 |
| 12 | **2d** | [Co(**P6**)] | C$_6$H$_6$ | 98 | 81 |
| 13[e] | **2d** | [Co(**P6**)] | C$_6$H$_6$ | 99 | 82 |

[a]Reaction conditions: 2 mol % of catalyst; olefin:azide = 5:1; [azide] = 0.1 M. [b]Isolated yield. [c]Determined by chiral HPLC. [d]10 mol % of catalyst. [e]at 35 °C in 36 h.

the similar conditions, the reaction catalyzed by [Co(**P1**)] (**P1** = 3,5-Di$^t$Bu-ChenPhyrin) [28], gave the desired aziridine in 77% yield and 53% ee even using only 2 mol % of catalyst loading (Table 1, entry 5). The dramatic difference observed in the catalytic performance between [Co(**P1**)] and [Co(TPP)] is in accordance with N-H···O=P hydrogen bonding which we assume to play an important role in activating the phosphoryl azide (Figure 1). Further studies showed that the Co(II) complex of the more sterically hindered amidoporphyrin ligand [Co(**P2**)] (**P2** = 2,6-DiMeO-ChenPhyrin) gave almost no reaction (Table 1, entry 6), signifying the steric demand of the catalytic process. Gratifyingly, [Co(**P3**)], in which the 3,5-positions of the *meso*-phenyl rings of the porphyrin were installed with mesityl groups, was found extremely effective in catalyzing this olefin aziridination reaction with TcepN$_3$, producing the desired aziridine product in almost quantitative yield although with lower enantioselectivity (Table 1, entry 7). Further improvement in enantioselectivity was achieved when [Co(**P4**)] (**P4** = 3,5-Di$^t$Bu-Xu(2'-Naph)Phyrin), a second-generation MRC catalyst that was previously shown to be optimal for asymmetric olefin aziridination with aryl azides [18], was used as a catalyst, reaching 65% ee but in a poor yield (Table 1, entry 8). To our delight, the use of catalyst [Co(**P5**)] (**P5** = 3,5-Di$^t$Bu-QingPhyrin), which was shown to be effective in asymmetric intramolecular olefin cyclopropanation [37], led to significant further improvement in enantioselectivity to 81% ee although the yield for the aziridination reaction with TcepN$_3$ remained to be low (Table 1, entry 9). These studies on the relationship between catalytic reactivity and the porphyrin ligand structure indicate the importance of both the chiral amido units and the non-chiral substituents of the porphyrin ligand in influencing the catalytic performance of the Co(II) metalloradical center. Accordingly, we designed and synthesized a new $D_2$-symmetric amidoporphyrin 3,5-DiMes-QingPhyrin (**P6**), whose Co(II) complex [Co(**P6**)] was shown to be the optimal catalyst for this reaction, producing the desired aziridine in 98% yield and 75% ee using only 2 mol % of catalyst loading (Table 1, entry 10). After screening various solvents, it was found that benzene was the solvent of choice for the catalytic process, giving the desired product with high enantioselectivity (81% ee) while maintaining the excellent yield (98%) (Table 1, entries 10–12). Some reduction in reaction temperature (from 40 °C to 35 °C) and time (from 48 h to 36 h) was shown to have no obvious effect on both product yield and enantioselectivity (Table 1, entry 13). However, the catalytic reaction became significantly slower as the temperature further decreased.

Under the optimized reaction conditions, we then investigated the scope and limitation of the [Co(**P6**)]/TcepN$_3$-based catalytic system for asymmetric olefin aziridination. The Co(II)-catalyzed asymmetric aziridination was shown to be effective for a variety of styrene derivatives with varied electronic and steric properties (Table 2). Similar to styrene, the styrene derivatives with electron-donating groups, such as the *para*-methylated styrene **1b** could be effectively aziridinated to afford the corresponding *N*-phosphoryl aziridine in a high yield with good enantioselectivity (Table 2, entries 1 and 2). In addition to the electron-rich aromatic olefins, styrenes with electron-deficient substituents at various positions were found to be suitable substrates as well for the Co(II)-based asymmetric aziridination. For instance, the *meta*-nitro-substituted styrene **1c** could be aziridinated in a moderate yield and good enantioselectivity (Table 2, entry 3). Interestingly, when the nitro group is located at the *para*-position as in the case of olefin **1d**, the corres-

**Table 2:** Enantioselective aziridination of olefins with TcepN$_3$ catalyzed by [Co(**P6**)].[a]

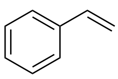
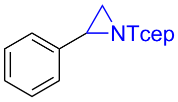
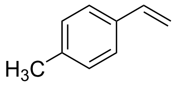
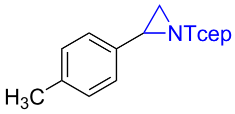
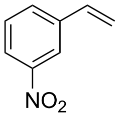
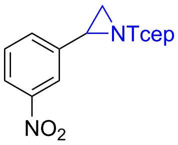
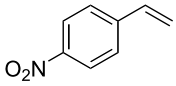
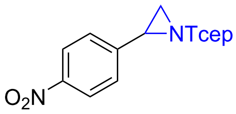
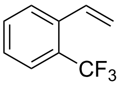
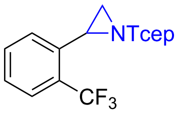
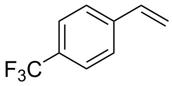
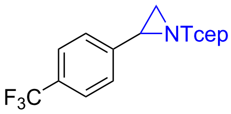
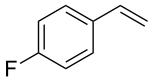
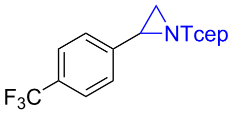
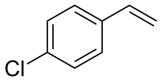
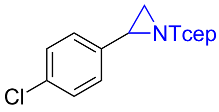
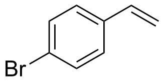
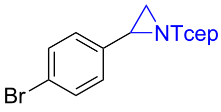
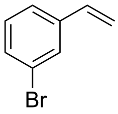
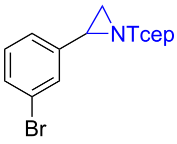
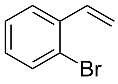
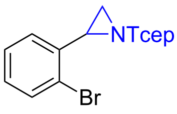
| entry | olefin | aziridine | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | <br>**1a** |  <br>**3a** | 99 | 82 |
| 2[d] |  <br>**1b** |  <br>**3b** | 86 | 76 |
| 3 |  <br>**1c** |  <br>**3c** | 66 | 66 |

**Table 2:** Enantioselective aziridination of olefins with $\text{TcepN}_3$ catalyzed by [Co(**P6**)].[a] (continued)

| | | | | |
|---|---|---|---|---|
| 4 | <br>**1d** | <br>**3d** | 90 | 23 |
| $5^e$ | <br>**1e** | <br>**3e** | 98 | – |
| 6 | <br>**1f** | <br>**3f** | 64 | 48 |
| 7 | <br>**1g** | <br>**3g** | 98 | 85 |
| $8^d$ | <br>**1h** | <br>**3h** | 74 | 74 |
| 9 | <br>**1i** | <br>**3i** | 98 | 72 |
| $10^d$ | <br>**1j** | <br>**3j** | 85 | 66 |
| 11 | <br>**1k** | <br>**3k** | 99 | 85 |

[a] Reaction conditions: 2 mol % of catalyst in the presence of 4 Å MS; olefin:azide = 5:1; [azide] = 0.1 M, benzene as solvent; 35 °C in 36 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] At 40 °C in 48 h. [e] The enantiomers could not be resolved.

ponding aziridine was produced in an excellent yield but in low enantioselectivity (Table 2, entry 4). An excellent yield was also achieved for the catalytic aziridination reaction of the sterically hindered substrate *o*-trifluoromethylstyrene (**1e**) (Table 2, entry 5). When *p*-trifluoromethylstyrene (**1f**) was used as the substrate, however, a decrease in reaction yield was observed (Table 2, entry 6). Furthermore, [Co(**P6**)] could effectively catalyze the aziridination reactions of various halogenated styrenes. For example, under similar conditions, *p*-fluorostyrene (**1g**) could be aziridinated with $\text{TcepN}_3$ in 98% yield with 85% ee (Table 2, entry 7). Like *p*-fluorostyrene, the *p*-chlorostyrene (**1h**) and *p*-bromostyrene (**1i**) were also effective substrates for the metalloradical aziridination system, forming the corresponding chiral aziridines in good yields and enantioselectivities (Table 2, entries 8 and 9). In addition to *p*-bromostyrene, both *m*-bromostyrene (**1j**) and *o*-bromostyrene (**1k**) could also be productively aziridinated (Table 2, entries 10 and 11). Similar to the case of *o*-$\text{CF}_3$-subtituted styrene **1e** (Table 2, entry 5), the catalytic reaction of the sterically demanding *o*-Br-substituted olefin **1k** gave the desired aziridine in almost quantitative yield as well as high enantioselectivity (Table 2, entry 11). It is worthy to mention that the aryl halide units of these chiral aziridines may be further functionalized via other transformations such as palladium-catalyzed cross-coupling reactions.

## Conclusion

In summary, we have shown that the Co(II) complex of the new $D_2$-symmetric chiral porphyrin 3,5-DiMes-QingPhyrin, [Co(**P6**)], is an effective metalloradical catalyst for asymmetric olefin aziridination with bis(2,2,2-trichloroethyl)phosphoryl azide ($TcepN_3$) as a new nitrene source. This [Co(**P6**)]/$TcepN_3$-based new aziridination system, which can be operated under neutral and non-oxidative conditions without the need of any additives, is suitable to various aromatic olefins. The resultant enantioenriched *N*-phosphorylaziridines may find potential applications in stereoselective synthesis of both nitrogen- and phosphorous-containing compounds. Efforts are underway to employ phosphoryl azides as effective nitrene sources for other types of organic transformations via Co(II)-based metalloradical catalysis (MRC).

## Supporting Information

### Supporting Information File 1

Experimental procedures and characterization data. Copies of $^1H$, $^{13}C$, and $^{31}P$ NMR spectra and HPLC data for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-129-S1.pdf]

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# Rasta resin–triphenylphosphine oxides and their use as recyclable heterogeneous reagent precursors in halogenation reactions

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Letter

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Appel reaction; halogenation; organophosphorus; polymer-supported reagent; rasta resin; triphenylphosphine oxide

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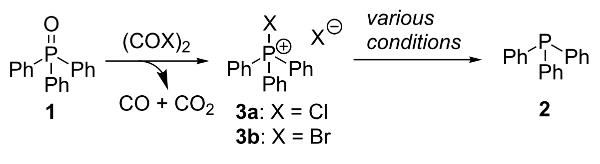
## Abstract

Heterogeneous polymer-supported triphenylphosphine oxides based on the rasta resin architecture have been synthesized, and applied as reagent precursors in a wide range of halogenation reactions. The rasta resin–triphenylphosphine oxides were reacted with either oxalyl chloride or oxalyl bromide to form the corresponding halophosphonium salts, and these in turn were reacted with alcohols, aldehydes, aziridines and epoxides to form halogenated products in high yields after simple purification. The polymer-supported triphenylphosphine oxides formed as a byproduct during these reactions could be recovered and reused numerous times with no appreciable decrease in reactivity.

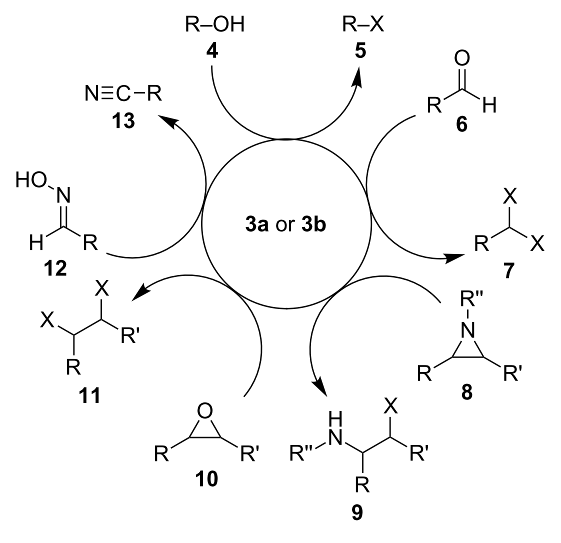
## Introduction

One of the major drawbacks of the Wittig [1] and Mitsunobu [2,3] reactions is that they result in the formation of a stoichiometric quantity of triphenylphosphine oxide (**1**) as a byproduct. From an atom economy perspective this is less than ideal, and from an environmental point of view it would be good if **1** could be simply reduced to triphenylphosphine (**2**) for reuse [4]. In this regard Tanaka and co-workers have studied the possibility of applying the reaction first reported by Masaki and Fukui [5] in which **1** can be treated with oxalyl chloride (or bromide) to form halophosphonium salt **3a** (or **3b**), which in turn can be reduced to **2** under more mild reaction conditions than can **1** (Scheme 1) [6,7].

In addition to being relatively easily reduced, halophosphonium salts **3a**,**b** are also useful reagents in a wide range of reactions, such as those illustrated in Scheme 2: (1) the conversion



**Scheme 1:** The Masaki–Fukui reaction and halophosphonium salt reduction.

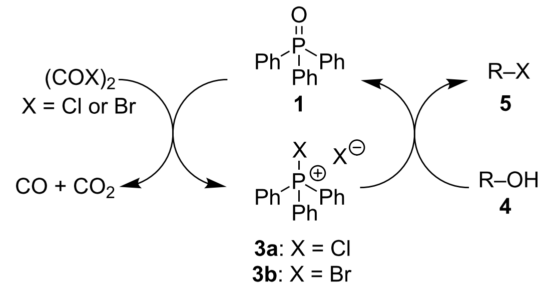


**Scheme 2:** Representative reactions involving halophosphonium salts **3a**,**b**.

of alcohols **4** to alkyl halides **5** (the Appel reaction), (2) the conversion of aldehydes **6** to 1,1-dihaloalkanes **7**, (3) halogenation of aziridines **8** to form 2-haloamines **9**, (4) halogenation of epoxides **10** to form 1,2-dihaloalkanes **11**, (5) and the dehydration of oximes **12** to form nitriles **13**.

Capitalizing on the fact that **1** is formed as a byproduct from **3a**,**b** in each of these reactions, Denton and co-workers have recently combined the Masaki–Fukui reaction with many of the functional group transformation outlined in Scheme 2, in one-pot processes in which the role of **1** is referred to as that of a catalyst [8-12]. For example, catalytic Appel reactions were achieved by slowly adding separate solutions of oxalyl chloride and alcohols **4** to a solution of **1** (Scheme 3) [8,9]. In these reactions, the simultaneous slow addition of oxalyl chloride and alcohol substrate **4** to a sub-stoichiometric quantity of **3a** was necessary in order to minimize formation of undesired ester side-products formed by the reaction of **4** with the acid chloride. Furthermore, chromatographic purification of the alkyl halide product **5** was required. Thus, while the procedures reported by Denton et al. might be conceptually interesting, they may not be particularly convenient to perform, especially on larger scales than what was originally reported.

We have had a long-term interest in the use of organic polymers as supports for reagents and catalysts [13], and have reported the use of various polymer-supported phosphines as reagents, organocatalysts, and ligands in order to simplify product isolation [14-18]. Most recently we have studied the use of the rasta resin polystyrene architecture [19-26] as a platform for reagents and catalysts [27-33], and have used easily synthesized rasta resin–Ph$_3$P (**14**) in various Wittig reactions that required only filtration and solvent removal for product purification (Figure 1) [27-29]. Additionally, **14** was converted into phosphonium salt **15**, which proved to be an efficient and highly recyclable catalyst for aldehyde and ketone cyanosilylation reactions from which the products could also be obtained pure after only filtration and solvent removal [30]. It should be noted that the grafts of the rasta resins reported are random co-polymers, and the structures drawn for them are not mean to indicate that they are block co-polymers. The format for their presentation is used merely to indicate their monomer incorporation ratios.



**Scheme 3:** Catalytic Appel reactions reported by Denton and co-workers.

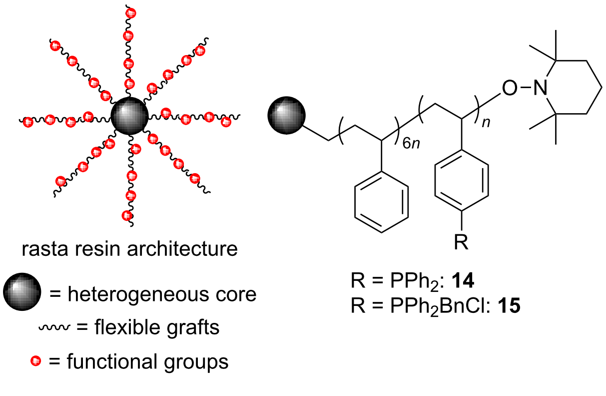


**Figure 1:** Rasta resins **14** and **15**.

Thus, considering our prior success in using **14** and **15**, we wanted to oxidize **14** to **16**, and in turn use this as a heterogeneous precursor to reagents **17a**,**b** for use in the halogenation reactions described in Scheme 2. We anticipated that using a full equivalent **17a**,**b** generated in situ would eliminate the need for slow addition of the oxalyl halide to form the halophosphonium salt, and thus allow for the reactions to be performed more conveniently than in the catalytic procedures of Denton and co-workers. Furthermore, since **16** would be the byproduct of the reactions, it could be recovered by filtration at the end of the reactions and reused directly. Herein we report the realization of this strategy and describe simple procedures for alcohol, aziridine, aldehyde and epoxide halogenation reactions from which the desired products are easily isolated and the phosphine oxide byproduct is readily recycled.

## Results and Discussion

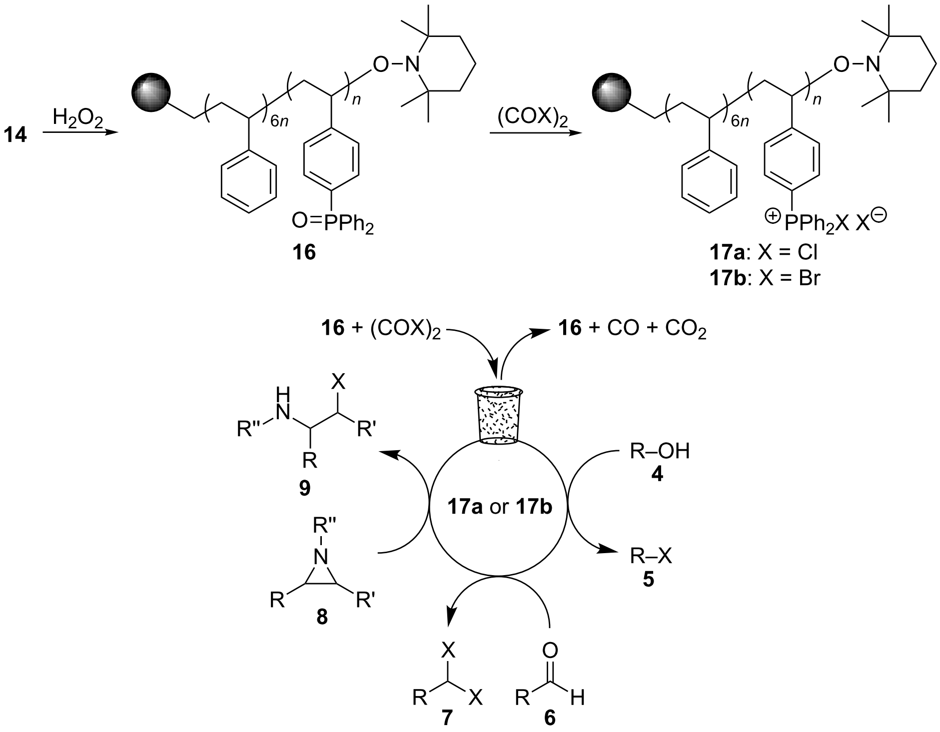
Rasta resin **16** was prepared by oxidation of **14**, which was prepared as previously reported [28], using $H_2O_2$ (Scheme 4). The loading level of **16** was determined by elemental analysis to be 0.97 mmol/g, and gel-phase $^{31}P$ NMR spectroscopic analysis of **16** showed only a single peak at 29.4 ppm, indicating that the phosphine groups were completely oxidized.

### Appel reactions using 16

With **16** in hand, we initially used it to perform Appel reactions by first converting it into either **17a** or **17b** in situ (Scheme 4). To do this, **16** was suspended/swollen in dichloromethane, and then the appropriate oxalyl halide was added. Once gas evolution ceased, alcohol **4** was added, and the reaction mixture was heated to reflux. Progress of the reactions was monitored by TLC analysis, and they were all finished in 4–7 hours. Upon completion, the reaction mixtures were cooled to room temperature and then filtered. Finally, the filtrates were concentrated at reduced pressure to afford the desired products that were essentially pure based on $^1H$ and $^{13}C$ NMR spectroscopic analyses. Chromatographic purification of the resultant alkyl halide products was not required. As can be seen in Table 1, both primary (entries 1–8) and secondary (entries 9 and 10) benzylic alcohols with various substituents all afforded excellent yield of the corresponding chloride and bromide using this procedure. Similar high yields were also obtained from reactions using primary (Table 1, entries 11–14) and secondary aliphatic alcohols (Table 1, entries 15 and 16). A reaction performed on a scale ten times larger afforded excellent yield as well (Table 1, entry 17). The recovered polymer was washed sequentially with water, MeOH, THF, diethyl ether and hexane. After drying, $^{31}P$ NMR spectroscopy confirmed its identity as **16**.

### Aldehyde halogenation reactions using 16

With the success of the Appel reactions, we further examined the utility of **16** by studying its use in aldehyde halogenation reactions. As before, **16** was converted into **17a** or **17b** in situ, and aldehyde **6** was added upon cessation of gas evolution.

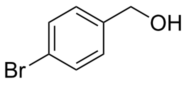
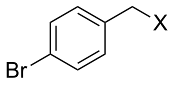
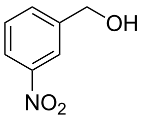
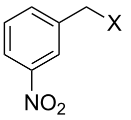
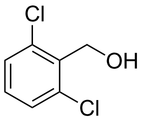
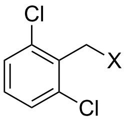
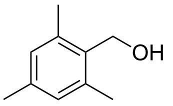
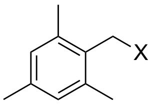
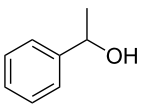
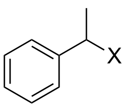
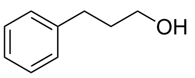
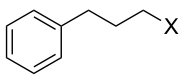
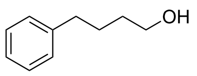
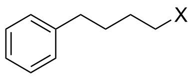
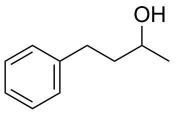
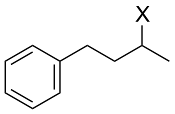


**Scheme 4:** Synthesis and applications of rasta resins **16** and **17a**,**b**.

**Table 1:** Appel reactions using **16**.[a]

$$\mathbf{16} \xrightarrow[\text{CH}_2\text{Cl}_2\text{, rt}]{(\text{COX})_2} \xrightarrow[\text{reflux}]{\mathbf{4}} \mathbf{5} + \mathbf{16}$$

X = Cl or Br

| Entry | Starting material | | Product | | Yield (%) |
|---|---|---|---|---|---|
| 1 |  | **4A** |  | **5Aa**, X = Cl | 98 |
| 2 | | | | **5Ab**, X = Br | 92 |
| 3 |  | **4B** |  | **5Ba**, X = Cl | 93 |
| 4 | | | | **5Bb**, X = Br | 91 |
| 5 |  | **4C** |  | **5Ca**, X = Cl | 93 |
| 6 | | | | **5Cb**, X = Br | 90 |
| 7 |  | **4D** |  | **5Da**, X = Cl | 98 |
| 8 | | | | **5Db**, X = Br | 93 |
| 9 |  | **4E** |  | **5Ea**, X = Cl | 85 |
| 10 | | | | **5Eb**, X = Br | 89 |
| 11 |  | **4F** |  | **5Fa**, X = Cl | 95 |
| 12 | | | | **5Fb**, X = Br | 90 |
| 13 |  | **4G** |  | **5Ga**, X = Cl | 98 |
| 14 | | | | **5Gb**, X = Br | 92 |
| 15 |  | **4H** |  | **5Ha**, X = Cl | 95 |
| 16 | | | | **5Hb**, X = Br | 91 |
| 17[b] | | | | **5Ha**, X = Cl | 92 |

[a]Reaction conditions: 0.6 mmol **16**, 0.6 mmol oxalyl halide, 0.5 mmol **4** in 5 mL $CH_2Cl_2$, reflux. [b]Reaction conditions: 6 mmol **16**, 6 mmol oxalyl halide, 5 mmol **4** in 50 mL $CH_2Cl_2$, reflux.

After 72 hours at reflux, the reactions were stopped, filtered and the products were purified by column chromatography (Table 2). Unlike the Appel reactions discussed above, some of these reactions did not proceed to completion, even when the reaction time was lengthened. Generally, it was observed that the bromination reactions afforded higher product yields than did the corresponding chlorination reactions (Table 2, entries 1–8), except when electron-rich aldehyde starting materials were used (Table 2, entries 9–12). These results are generally similar to what was previously reported by Denton and co-workers when similar substrates were used [12].

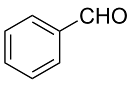
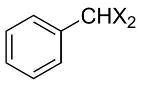
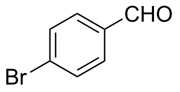
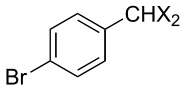
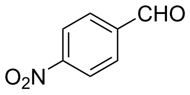
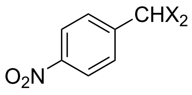
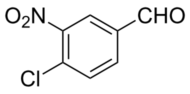
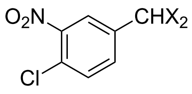
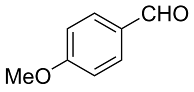
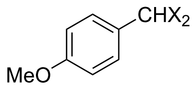
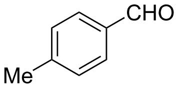
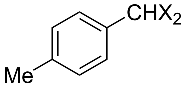
## Aziridine halogenation reactions using **16**

We next examined the use of **16** as a precursor to **17a** and **17b** in aziridine halogenation reactions [34]. Using reaction conditions similar to those used for the Appel and aldehyde halogenation reactions, a variety of *N*-tosyl aziridines **8** were successfully converted into the corresponding chloro- or bromotosylamides **9** in excellent yields (Table 3). The trans configurations of the **9Ba** and **9Bb** were confirmed by X-ray diffraction analysis of the isolated products, and as was true for the Appel reactions described above, all the products were obtained in high purity simply by filtration to remove the polymer, and

**Table 2:** Halogenation reactions of aldehydes using **16**.[a]

$$\mathbf{16} \xrightarrow[\text{CHCl}_3\text{, rt}]{(\text{COX})_2} \xrightarrow[\text{reflux}]{\mathbf{6}} \mathbf{7} + \mathbf{16}$$

X = Cl or Br

| Entry | Starting material | | Product | | Yield (%) |
|---|---|---|---|---|---|
| 1 |  | **6A** |  | **7Aa**, X = Cl | 54[b] |
| 2 | | | | **7Ab**, X = Br | 75[b] |
| 3 |  | **6B** |  | **7Ba**, X = Cl | 65[b] |
| 4 | | | | **7Bb**, X = Br | 83[b] |
| 5 |  | **6C** |  | **7Ca**, X = Cl | 64[b] |
| 6 | | | | **7Cb**, X = Br | 89[b] |
| 7 |  | **6D** |  | **7Da**, X = Cl | 61[b] |
| 8 | | | | **7Db**, X = Br | 93[b] |
| 9 |  | **6E** |  | **7Ea**, X = Cl | 94[c] |
| 10 | | | | **7Eb**, X = Br | 20[d] |
| 11 |  | **6F** |  | **7Fa**, X = Cl | 85[b] |
| 12 | | | | **7Fb**. X = Br | 77[b] |

[a]Reaction conditions: 0.3 mmol **16**, 0.3 mmol oxalyl halide, 0.1 mmol **6** in 3 mL $CHCl_3$, reflux. [b]Isolated yield after flash silica gel column chromatography. [c]Isolated yield after filtration and concentration under reduced pressure. [d]Determined by $^1H$ NMR spectroscopy.

concentration of the filtrate. Our procedure was also successfully performed on a gram-scale (Table 3, entry 5), and substrates **8** possessing a single aryl substituent were halogenated as the less hindered position (Table 3, entries 10–13).

## Recovery and reuse of 16

After demonstrating that **16** could effectively serve as a precursor to **17a,b**, and realizing that it was returned as the byproduct of the above reactions, we next examined its recyclability in the chlorination of alcohol **4H** and aziridine **8B**. The results of these studies are shown in Table 4 and Table 5, respectively. In these experiments, the polymer recovered by filtration of the reaction mixture was washed and dried, and then used directly for the next reaction cycle. Excellent yields were successfully obtained for 8 runs with both **4H** and **8B**. Gel-phase $^{31}P$ NMR analysis of **16** recovered at the end of these experiments indicated no change in its oxidation state.

## Epoxide halogenation reactions

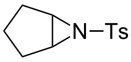
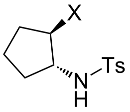
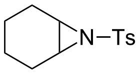
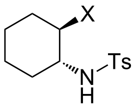
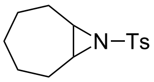
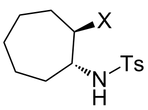
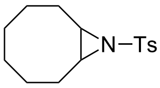
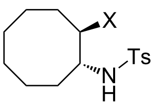
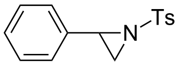
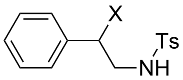
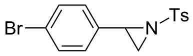
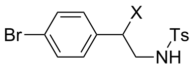
With the versatility and excellent reactivity of **16** established, we were encouraged to examine our method in the epoxide halogenation reactions shown in Scheme 2. Since these reactions require the use of a base, we designed a bifunctional rasta resin, RR-NBniPr$_2$-PPh$_3$=O **18** (Scheme 5), which bears both triphenylphosphine oxide and tertiary amine moieties, in order to increase the efficiency and appeal of our method. We have extensive experience in preparing functionalized resins with two different catalytic groups [35-38], and prepared **18** by oxidation of **19**, which we previously used as a bifunctional reagent in one-pot Wittig reactions [29]. Gel-phase $^{31}P$ NMR spectroscopic analysis of **18** indicated that oxidation of the phosphine groups was complete, and elemental analysis was used to determine the loading level of phosphine oxide and amine groups to be 1.07 mmol/g and 1.06 mmol/g, respectively. It should be noted that a test reaction between *N*,*N*-diisopropylbenzylamine and $H_2O_2$ under similar reaction conditions does not result in amine oxidation, and this seems to indicate that only the phosphine groups of **19** are oxidized during its conversion to **18**.

Having successfully synthesized polymer **18**, we examined its reactivity in epoxide halogenation reactions (Table 6). As

**Table 3:** Halogenation reactions of aziridines using **16**.[a]

$$\mathbf{16}\ \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{rt}]{(\text{COX})_2}\ \xrightarrow[\text{reflux}]{\mathbf{8}}\ \mathbf{9} + \mathbf{16}$$

$$X = \text{Cl or Br}$$

| Entry | Starting material | | Product | | Yield (%) |
|---|---|---|---|---|---|
| 1 |  | **8A** |  | **9Aa**, X = Cl | 95 |
| 2 | | | | **9Ab**, X = Br | 93 |
| 3 |  | **8B** |  | **9Ba**, X = Cl | 89 |
| 4 | | | | **9Bb**, X = Br | 92 |
| 5[b] | | | | **9Ba**, X = Cl | 95 |
| 6 |  | **8C** |  | **9Ca**, X = Cl | 96 |
| 7 | | | | **9Cb**, X = Br | 98 |
| 8 |  | **8D** |  | **9Da**, X = Cl | 93 |
| 9 | | | | **9Db**, X = Br | 92 |
| 10 |  | **8E** |  | **9Ea**, X = Cl | 91 |
| 11 | | | | **9Eb**, X = Br | 93 |
| 12 |  | **8F** |  | **9Fa**, X = Cl | 93 |
| 13 | | | | **9Fb**, X = Br | 95 |

[a]Reaction conditions: 0.6 mmol **16**, 0.6 mmol oxalyl halide, 0.5 mmol **8** in 5 mL $CH_2Cl_2$, reflux. [b]Reaction conditions: 6 mmol **16**, 6 mmol oxalyl halide, 5 mmol **8** in 50 mL $CH_2Cl_2$, reflux.

**Table 4:** Recycling of **16** in the chlorination of **4H**.[a]

$$\mathbf{16}\ \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{rt}]{(\text{COCl})_2}\ \xrightarrow[\text{reflux}]{\mathbf{4H}}\ \mathbf{5Ha} + \mathbf{16}$$

| Run | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Yield of **5Ha** (%) | 94 | 95 | 93 | 98 | 94 | 95 | 95 | 93 |
| Recovery of **16** (%) | 99 | 99 | 99 | 99 | 98 | 95 | 93 | 91 |

[a]Reaction conditions: 0.6 mmol **16**, 0.6 mmol oxalyl chloride, 0.5 mmol **4H** in 5 mL $CH_2Cl_2$, reflux.

**Table 5:** Recycling of **16** in the chlorination of **8B**.[a]

$$\mathbf{16}\ \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{rt}]{(\text{COCl})_2}\ \xrightarrow[\text{reflux}]{\mathbf{8B}}\ \mathbf{9Ba} + \mathbf{16}$$

| Run | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Yield of **9Ba** (%) | 93 | 92 | 95 | 93 | 87 | 91 | 91 | 90 |
| Recovery of **16** (%) | 96 | 97 | 95 | 95 | 96 | 95 | 90 | 92 |

[a]Reaction conditions: 0.6 mmol **16**, 0.6 mmol oxalyl chloride, 0.5 mmol **8B** in 5 mL $CH_2Cl_2$, reflux.

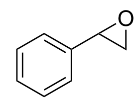
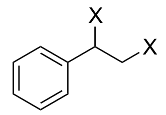
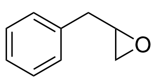
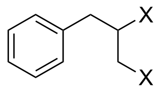
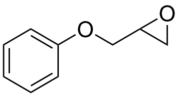
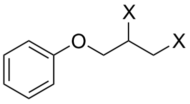
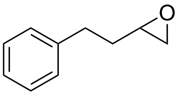
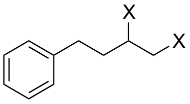
before, **18** was suspended/swollen in solvent prior to addition of the oxalyl halide. Once gas evolution ceased, epoxide **10** was added, and the reaction mixture was heated to reflux. When TLC analysis indicated that the reactions were complete, 3–4 hours, the reaction mixtures were filtered and the filtrates were concentrated to afford products that were essentially pure according to both $^1$H and $^{13}$C NMR analysis. Reactions with epoxides bearing phenyl (Table 6, entries 1 and 2), benzyl (Table 6, entries 3 and 4), and alkyl substutients (Table 6, entries 5–8) all proceeded to completion, and afforded the corresponding 1,2-dihalides in excellent yields.

We also examined the recyclability of **18** in the halogenation of epoxide **10C** (Table 7). As was the case for **16**, bifunctional

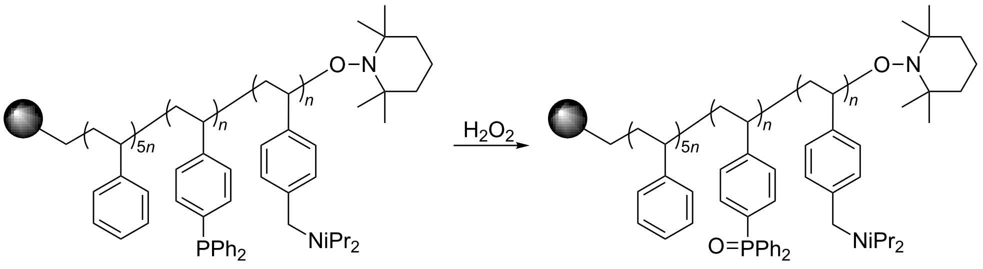
**Table 6:** Halogenation reactions of epoxides using **18**.[a]

$$\mathbf{18} \xrightarrow[\text{CHCl}_3\text{, rt}]{(\text{COX})_2} \xrightarrow[\text{reflux}]{\mathbf{10}} \mathbf{11} + \mathbf{18}$$

X = Cl or Br

| Entry | Substrate | | Product | | Yield (%) |
|---|---|---|---|---|---|
| 1 |  | **10A** |  | **11Aa**, X = Cl | 95 |
| 2 | | | | **11Ab**, X = Br | 93 |
| 3 |  | **10B** |  | **11Ba**, X = Cl | 89 |
| 4 | | | | **11Bb**, X = Br | 92 |
| 5 |  | **10C** |  | **11Ca**, X = Cl | 95 |
| 6 | | | | **11Cb**, X = Br | 96 |
| 7 |  | **10D** |  | **11Da**, X = Cl | 98 |
| 8 | | | | **11Db**, X = Br | 92 |

[a]Reaction conditions: 1.2 mmol **18**, 1.1 mmol oxalyl halide, 0.5 mmol **10** in 5 mL $CHCl_3$, reflux.



**19**

**18**

**Scheme 5:** Synthesis of bifuncitonal rasta resin **18**.

polymer **18** could be repeatedly recovered and reused without an observable decrease in its reactivity. However, whereas **16** could be reused directly after recover, reusing **18** required washing it with an aqueous solution of $Na_2CO_3$ after each reaction.

## Conclusion

In summary, we have designed and synthesized recyclable heterogeneous rasta resin-supported triphenylphosphine oxide **16**, and have applied it as a phosphonium halide salt precursor in a wide range of halogenation reactions from which it is readily recovered and reused. The reusability of this polymer

**Table 7:** Recycling of **18** in the chlorination of **10c**.[a]

$$\mathbf{18} \xrightarrow[\text{CHCl}_3\text{, rt}]{(\text{COCl})_2} \xrightarrow[\text{reflux}]{\mathbf{10C}} \mathbf{11Ca} + \mathbf{18}$$

| Run | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Yield of **11Ca** (%) | 94 | 91 | 93 | 94 | 93 | 92 | 90 |
| Recovery of **18** (%) | 98 | 98 | 97 | 98 | 95 | 93 | 90 |

[a]Reaction conditions: 1.2 mmol **18**, 1.1 mmol oxalyl chloride, 0.5 mmol **10C** in 5 mL $CHCl_3$, reflux.

was demonstrated by the fact that all of the reactions reported herein involving **16** were performed by repeatedly reusing a single batch of it. We also prepared bifunctional rasta resin **18** which bears amine groups in addition to the phosphine oxide moieties for use in epoxide halogenation reactions. The products of all of these reactions, except for the aldehyde halogenation reactions, can be easily separated from the phosphine oxide functionalized polymer simply by filtration, and isolated directly in high purity. Thus, the use of polymers **16** or **18** as reagent precursors represents a convenient alternative to the "phosphine oxide-catalyzed" methods of Denton and co-workers, which generally require slow addition of the oxalyl halide and chromatographic purification of the product. In order to assess the overall utility of **16** and **18**, we are currently examining their applications as organocatalysts [39-43], and will report results of these studies in due course.

## Experimental

**General procedure for Appel reactions using 16:** Polymer **16** (0.6 g, 0.6 mmol) was suspended in dichloromethane (5 mL), and the oxalyl halide (0.6 mmol) was added. Upon cessation of gas evolution, alcohol **4** (0.5 mmol) was added, and the reaction mixture magnetically stirred and heated to reflux. After the reaction was completed as monitored by TLC, the mixture was cooled to room temperature and filtered. The solid on funnel was washed with dichloromethane (10 mL × 3). The solvent of filtrate was removed under reduced pressure to afford the desired product **5** in an essentially pure state based on $^{1}$H and $^{13}$C NMR spectroscopic analyses.

**General procedure for aldehyde halogenation reactions using 16:** Polymer **16** (0.3 g, 0.3 mmol) was suspended in chloroform (3 mL), and the oxalyl halide was added (0.3 mmol). Upon cessation of gas evolution, aldehyde **6** (0.1 mmol) was added, and the reaction mixture was magnetically stirred and heated to reflux. After 72 hours, the reaction was cooled to room temperature and filtered. The solid on funnel was washed with dichloromethane (5 mL × 3). The solvent of filtrate was removed under reduced pressure. The resulting crude product **7** was purified by flash silica gel column chromatography using ethyl acetate and hexane as eluent mixture.

**General procedure for aziridine halogenation reactions of using 16:** Polymer **16** (0.6 g, 0.6 mmol) was suspended in dichloromethane (5 mL), and the oxalyl halide was added (0.6 mmol). Upon cessation of gas evolution, aziridine **8** (0.5 mmol) was added, and the reaction mixture was magnetically stirred and heated to reflux. After the reaction was completed as monitored by TLC, the mixture was cooled to room temperature and filtered. The solid on funnel was washed with dichloromethane (10 mL × 3). The solvent of filtrate was removed under reduced pressure to afford the desired product **9** in an essentially pure state based on $^{1}$H and $^{13}$C NMR spectroscopic analyses.

**General procedure for epoxide halogenation reactions using 18:** Polymer **18** (1.3 g, 1.2 mmol) was suspended in chloroform (10 mL) and the oxalyl halide was added (1.1 mmol). Upon cessation of gas evolution, epoxide **10** (0.5 mmol) was added, and the reaction was magnetically stirred and heated to reflux. After the reaction was completed as monitored by TLC, the mixture was cooled to room temperature and filtered. The solid on funnel was washed with dichloromethane (10 mL × 3). The solvent of filtrate was removed under reduced pressure to afford the desired product **11** in an essentially pure state based on $^{1}$H and $^{13}$C NMR spectroscopic analyses.

**General procedure for recovery and reuse of 16 and 18:** After being separated from the reaction mixture by filtration, the polymer, **16** or **18**, was rinsed sequentially using deionized water (30 mL), dichloromethane (50 mL), MeOH (50 mL), THF (50 mL), diethyl ether (50 mL), hexane (50 mL). It was then dried under vacuum at 60 °C prior to use in the next reaction cycle. Furthermore, **18** was initially washed with a saturated aqueous solution of $Na_2CO_3$ in order to ensure that it was deprotonated and ready for use in the next reaction cycle.

## Note Added in Proof

After the initial submission of our manuscript we became aware of a recent report by Denton and co-workers regarding similar work using polystyrene-supported halophosphonium salts in Appel and dehydration reactions [44]. This work utilized a commercially available polymer-supported phosphine oxide based on the Merrifield resin architecture, and it is noteworthy that the reactions reported in this manuscript required a 6-fold excess of the halophosphonium salt compared to the substrate. Use of our rasta resins **16** and **18** required only a 20 mol % excess.

## Supporting Information

### Supporting Information File 1

Additional experimental details and characterization data of synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-143-S1.pdf]

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# Rational design of cyclopropane-based chiral PHOX ligands for intermolecular asymmetric Heck reaction

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Full Research Paper

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asymmetric catalysis; chiral phosphine ligands; cyclopropane; Heck reaction; organophosphorus; transition metal catalysis

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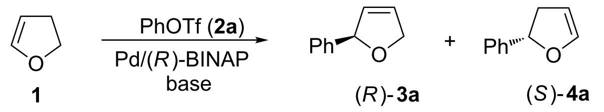
## Abstract

A novel class of chiral phosphanyl-oxazoline (PHOX) ligands with a conformationally rigid cyclopropyl backbone was synthesized and tested in the intermolecular asymmetric Heck reaction. Mechanistic modelling and crystallographic studies were used to predict the optimal ligand structure and helped to design a very efficient and highly selective catalytic system. Employment of the optimized ligands in the asymmetric arylation of cyclic olefins allowed for achieving high enantioselectivities and significantly suppressing product isomerization. Factors affecting the selectivity and the rate of the isomerization were identified. It was shown that the nature of this isomerization is different from that demonstrated previously using chiral diphosphine ligands.

## Introduction

The asymmetric Heck reaction is one of the most powerful and versatile processes for the enantioselective construction of new carbon–carbon bonds. Intramolecular versions of this reaction catalysed by palladium complexes with BINAP and related diphosphine ligands [1,2] allow for efficient installation of tertiary and quaternary chiral centres leading to a rapid increase of molecular complexity [3-5]. To date, various modes of this transformation are being successfully employed in the synthesis of complex organic molecules [6-14].

Considerable achievements have also been made towards the application of BINAP-type ligands in the intermolecular asymmetric Heck reaction [15]. This reaction was pioneered by Hayashi [16], who demonstrated the arylation of dihydrofuran (**1**) with phenyl triflate (**2a**) (Scheme 1) in the presence of (*R*)-BINAP [16-18] produced isomeric dihydrofurans **3a** and **4a**, with the latter being the major product, due to substantial isomerization of the double bond. Depending on the reaction conditions, moderate to good selectivities toward formation of



**Scheme 1:** Intermolecular asymmetric Heck reaction by Hayashi [16].

**4a** were observed. Remarkably, the obtained products, "normal" **3a** and "isomerized" **4a**, had the opposite absolute configurations of the stereogenic center at C2. Moreover, it was found that the enantioselectivity improved during the reaction course. The mechanistic rationale proposed by Hayashi [16] fully accounts for the observed stereoselectivity change (Scheme 2). The catalytic cycle begins with the oxidative addition of Pd(0) species **5** into the aryl triflate **2** resulting in the formation of cationic complex **6**. The latter can coordinate to either of the prochiral faces of dihydrofuran (**1**) affording diastereomeric η$^2$-complexes **7** and **10**. Subsequent carbopalladation, followed by β-hydride elimination, produces species **9** and **12**, respectively. It was proposed that the diastereomeric complex **12** has a higher propensity toward further hydropalladation than **9**. Accordingly, the latter species releases the (*S*)-enantiomer of 2,5-dihydrofuran **3** (path I), while the former undergoes a series of reversible hydropalladations and β-hydride eliminations, resulting in the formation of a thermodynamically more favoured η$^2$-complex **14**, which ultimately produces the (*R*)-enantiomer of the isomeric product **4**.

Later, a number of research groups pursued the design of alternative diphosphine ligands to achieve better regio- and enantioselectivity in the intramolecular Heck reaction. Several derivatives of BINAP [19,20] and other chiral diphosphines [21-27] including TMBTP [28-31], BIPHEP [32-34], BITIANP [30,35] (Figure 1) were tested, some of which provided improved selectivity. Nevertheless, in all cases predominant or exclusive formation of the isomerized product **4** was observed.

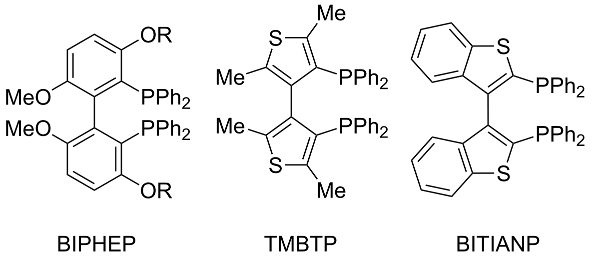
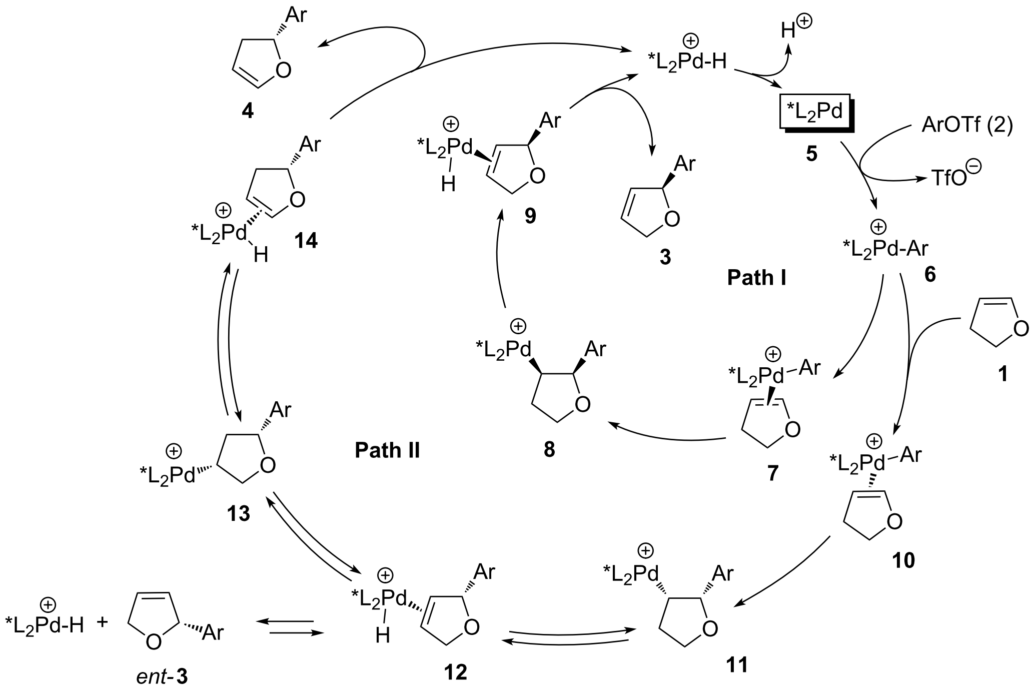


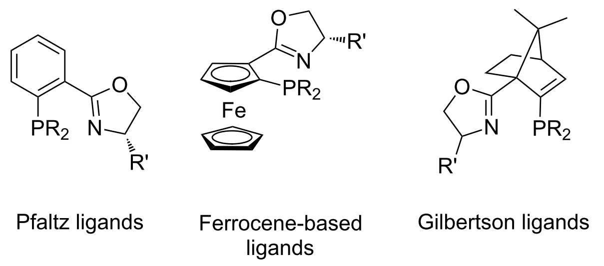
**Figure 1:** Chiral diphosphine ligands used for intermolecular asymmetric Heck reaction.

At the same time, several mixed hetereoatom ligands of the P–S [36,37], P–O [38], and N–N [39,40] type have also been explored in the intermolecular Heck arylation; however, they demonstrated in most cases only marginal regio- and enantioselectivities. On the other hand, superior results were obtained



**Scheme 2:** Mechanistic rationale of asymmetric Heck reaction.

using chiral ligands of the P,N-type [15,41-44]. Particularly, excellent enantioselectivities were achieved using different variations of phosphanyl-oxazoline (PHOX) ligands [45-52], originally introduced by Pfaltz (Figure 2) [53,54]. The remarkable, yet not fully understood feature of PHOX ligands is their low tendency to promote C=C-bond isomerization [45-52]. Thus, in contrast to the diphosphines, PHOX ligands produced dihydrofuran **3** with very high selectivity. Structural modification of the flat ortho-phenylene tether in the Pfaltz ligand through the incorporation of additional chirality elements into the ligand backbone allowed for significant improvement of the enantioselectivity. Thus, ferrocene-based ligands introduced by Dai and Hou [55,56], and Guiry [57,58] (Figure 2) were employed in the asymmetric Heck reaction of different cyclic olefins. Furthermore, Gilbertson demonstrated PHOX ligands featuring apobornene backbone (Figure 2) exhibit outstanding activities and selectivities in the arylation and alkenylation of different cyclic substrates [59]. A highly efficient asymmetric arylation in the presence of sugar-derived phosphite-oxazoline ligands was reported by Diéguez and Pàmies [47,48].



Pfaltz ligands

Ferrocene-based ligands

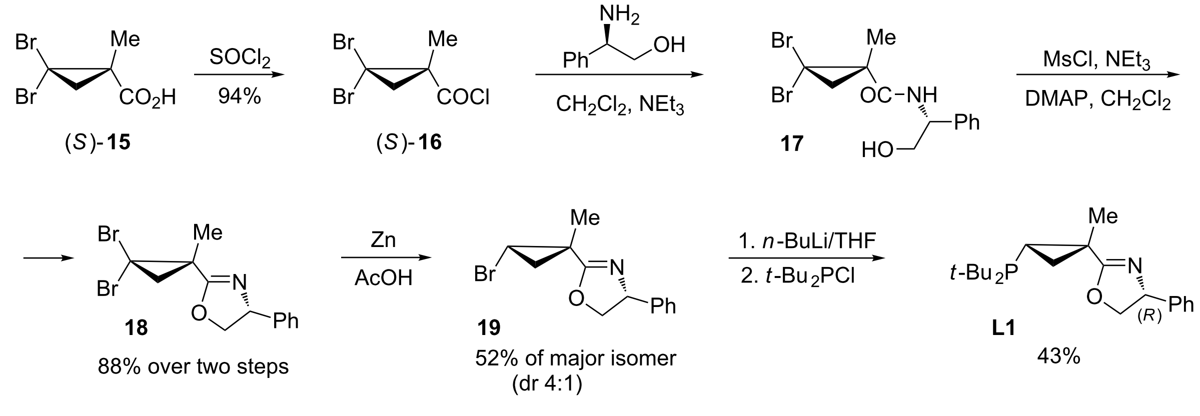
Gilbertson ligands

**Figure 2:** Chiral phosphanyl-oxazoline (PHOX) ligands used for intermolecular asymmetric Heck reaction.

PHOX ligands are very appealing due to their high catalytic potential and modular design, which permits easy preparation of a series of analogues via the same synthetic route. To date, however, general approach to the ligand design has been largely empirical due to a poor understanding of the factors affecting the activity of the corresponding catalytic systems and the operating modes of asymmetric induction imparted by the employed chiral ligands. In our investigation, we decided to benefit from a well-established strategy commonly used in medicinal chemistry. According to this approach conformationally constrained cyclic analogues of biologically active molecules are employed for elucidation of important mechanisms and identifying critical enzyme binding sites. Analogously, we anticipated that incorporation of a three-membered cycle in the ligand structure [60-63] would impart rigidity to the ligand backbone and provide conformationally constrained systems with amplified steric effects, which can be easily modelled and predicted. This, in turn, could be used to rationally design the ligand structure en route to more efficient catalytic systems. In 2008 we communicated the design and synthesis of a novel series of PHOX ligands featuring a chiral cyclopropyl backbone, as well as their employment in the enantioselective intermolecular Heck arylation reaction [64]. Herein we describe the full account on this investigation, including the results of the structure–activity studies and provide our insight into the origins of the enantioselectivity of this transformation and factors controlling the rate of isomerization reaction.

## Results and Discussion

Our approach to the PHOX ligands with a chiral cyclopropyl backbone is presented in Scheme 3. The synthesis began from optically active 1-methyl-2,2-dibromocyclopropanecarboxylic acid (**15**) [65] readily available in both enantiomeric forms. The *S*-enantiomer of acid **15** was converted into acyl chloride (*S*)-



**Scheme 3:** Synthetic scheme for preparation of PHOX ligands with chiral cyclopropyl backbone.

**16**. Subsequent acylation of (*R*)-phenylglycinol with (*S*)-**16** afforded amide **17**, which was subjected to cyclization in the presence of mesyl chloride and a base providing dihydrooxazole **18**. Diastereoselective partial reduction of the dibromocyclopropane moiety with zinc dust in glacial acetic acid produced a 1:4 mixture of *trans*- and *cis*-bromocyclopropanes **19**, which were separated by column chromatography. Lithium to halogen exchange followed by trapping of the resulting cyclopropyllithium species with chlorophosphine produced ligand **L1** (Scheme 3).

Ligand **L1** once obtained, was tested in the asymmetric arylation reaction of 2,3-dihydrofuran under various reaction conditions (Table 1). It was found that the reaction proceeded efficiently, yet with only moderate enantioselectivity, in the presence of palladium acetate and Hünig's base (Table 1, entry 3). Interestingly, the employment of proton sponge as a base resulted in significant isomerization of product **3a** into the more thermodynamically stable dihydrofurans **4a** and **20a**. Close monitoring of the reaction by chiral GC revealed, that the initially formation of "normal" product **3a** is observed (Table 1, entry 4); however, by the time when starting material **1** was completely consumed, the entire amount of **3a** produced was transformed into **4a** (Table 1, entry 5). Remarkably, the absolute configuration at C2 did not change at all through the reaction course; moreover, the optical purity of both products **3a** and **4a** remained constant (Table 1, entries 4 and 5). This feature makes this isomerization mechanistically distinct from the one reported by Hayashi (vide supra).

To better understand the factors affecting the selectivity and efficiency of the asymmetric arylation, we have prepared two more analogues of **L1**: ligand **L2**, possessing a diphenylphosphanyl group and ligand **L3** derived from *tert*-leucinol (Figure 3). Not surprisingly, installation of the less hindered phosphorus moiety in **L2** negatively affected the asymmetric induction: the corresponding product **3a** was obtained in only 78–79% ee (Table 2, entries 3 and 4). However, in contrast to **L1** (Table 2, entries 1 and 2) the selectivity toward **3a** in the reaction using **L2** remained high, regardless of the base used.

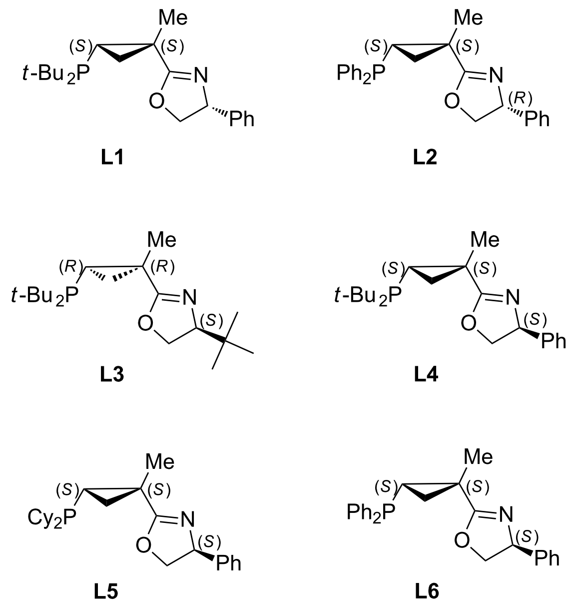
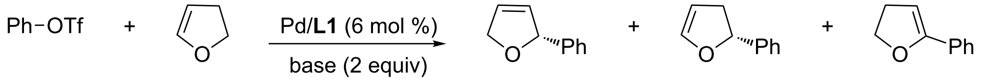


**Figure 3:** PHOX ligands with chiral cyclopropyl backbone employed in this study.

Modification of the dihydrooxazole moiety by installation of a bulky *tert*-butyl group was pursued in attempt to improve the enantioinduction of our catalytic system. Indeed, a number of previously reported PHOX ligands derived from *tert*-leucinol were shown to provide superior enantioselectivities compared to their analogues obtained from less bulky amino alcohols [54,57,59]. However, the arylation carried out in the presence of

**Table 1:** Selected results on optimization of the reaction conditions for asymmetric Heck arylation using **L1**.

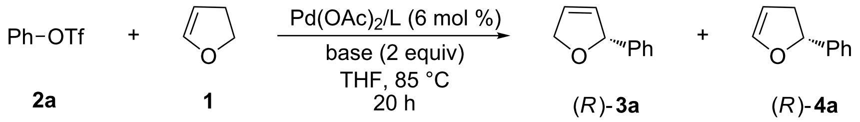


**2a** **1** (*R*)-**3a** (*R*)-**4a** **20a**

| Entry | Pd cat. | Base | Solvent | Time/Temp | **3a**:**4a** | ee, %$^a$ | conv, %$^b$ |
|---|---|---|---|---|---|---|---|
| 1 | $Pd_2dba_3{\cdot}CHCl_3$ | $EtN(iPr)_2$ | benzene | 3 d/70 °C | 19:1 | 90 | 15 |
| 2 | $Pd_2dba_3{\cdot}CHCl_3$ | $EtN(iPr)_2$ | THF | 20 h/85 °C | 10:1 | 85 | 60 |
| 3 | $Pd(OAc)_2$ | $EtN(iPr)_2$ | THF | 20 h/85 °C | 11:1 | 83 | 99 |
| 4 | $Pd(OAc)_2$ | proton sponge | THF | 20 h/60 °C | 10:1 | 88 | 45 |
| 5 | $Pd(OAc)_2$ | proton sponge | THF | 70 h/60 °C | >1:50$^c$ | 85 | 99 |
| 6 | $Pd(OAc)_2$ | proton sponge | THF | 20 h/90 °C | >1:50$^c$ | 82 | 99 |

$^a$Ee's of major regioisomers are listed. $^b$Conversion by GC. $^c$Formation of small amounts of dihydrofuran **20a** was observed.

**Table 2:** Screening of **L1**–**L3** in the asymmetric Heck arylation of dihydrofuran **1**.

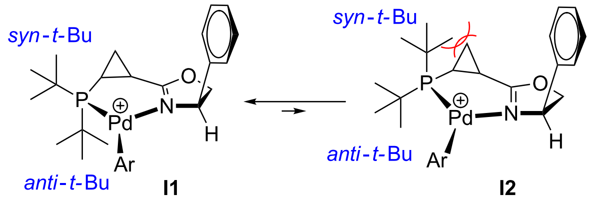


| Entry | Ligand | Base | **3a**:**4a** | ee, %[a] | conv, %[b] |
|---|---|---|---|---|---|
| 1 | **L1**[c] | EtN(iPr)$_2$ | 11:1 | 83 | 99 |
| 2 | **L1**[c] | proton sponge | >1:50 | 82 | 99 |
| 3 | **L2** | EtN(iPr)$_2$ | 20:1 | 79 | 99 |
| 4 | **L2** | proton sponge | 15:1 | 78 | 99 |
| 5 | **L3** | EtN(iPr)$_2$ | 7:1 | 87 | 35 |
| 6 | **L3** | proton sponge | 1.4:1 | 84[d] | 80 |

[a] Enantioselectivity of a major product. [b] Conversions by GC. [c] Results from Table 1. [d] Enantioselectivity of product (*R*)-**4a** was 80%.

**L3** proceeded much more sluggishly (Table 2, entries 5 and 6), and allowed for only insignificant improvement in enantioselectivity (84–87% ee). Most remarkably, the same (*R*)-enantiomer of product **3** was obtained, despite the opposite absolute configuration of **L3** with respect to **L1** (Figure 3). In other words, switching from Ph to *t*-Bu substituent in the dihydrooxazole ring of the ligand resulted in a reversal of enantioselectivity.

Such an unexpected change in the catalyst selectivity motivated us to perform structural analysis of the key intermediate complexes invoked in the catalytic cycle of the Heck arylation. First, we assessed the possibility of conformational equilibrium for the six-membered arylpalladium species bearing **L1** (Scheme 4). The non-planar six-membered palladacycle [66-69] can potentially adopt one of two conformations: **I1**, in which the *syn*-*tert*-butyl substituent at phosphorus assumes a pseudo-equatorial position, whereas the *anti*-*tert*-butyl substituent is pseudo-axial; and **I2**, where this relationship is reversed (Scheme 4). Analysis of these two conformations suggests that steric repulsions between the axial *syn*-substituent and the methylene group in cyclopropane makes conformation **I2** thermodynamically disfavored compared to **I1**. This hypothesis was also supported by a single crystal X-ray analysis of (**L1**)PdCl$_2$ complex (Figure 4). The resolved crystal structure clearly shows that the *syn*-(C14) and *anti*-substituent (C18) at phosphorus



**Scheme 4:** Conformational equilibrium in cationic arylpalladium(II) complexes with chiral ligand **L1**.

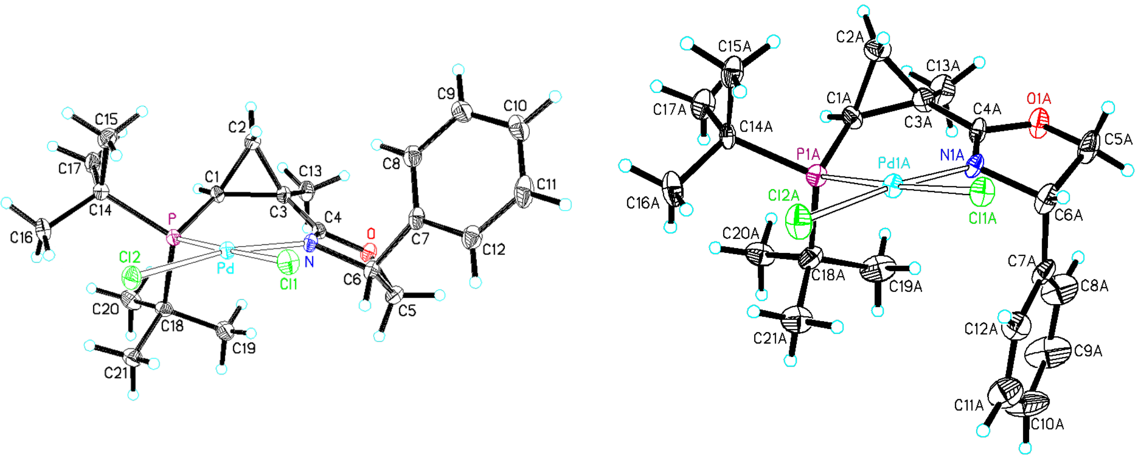
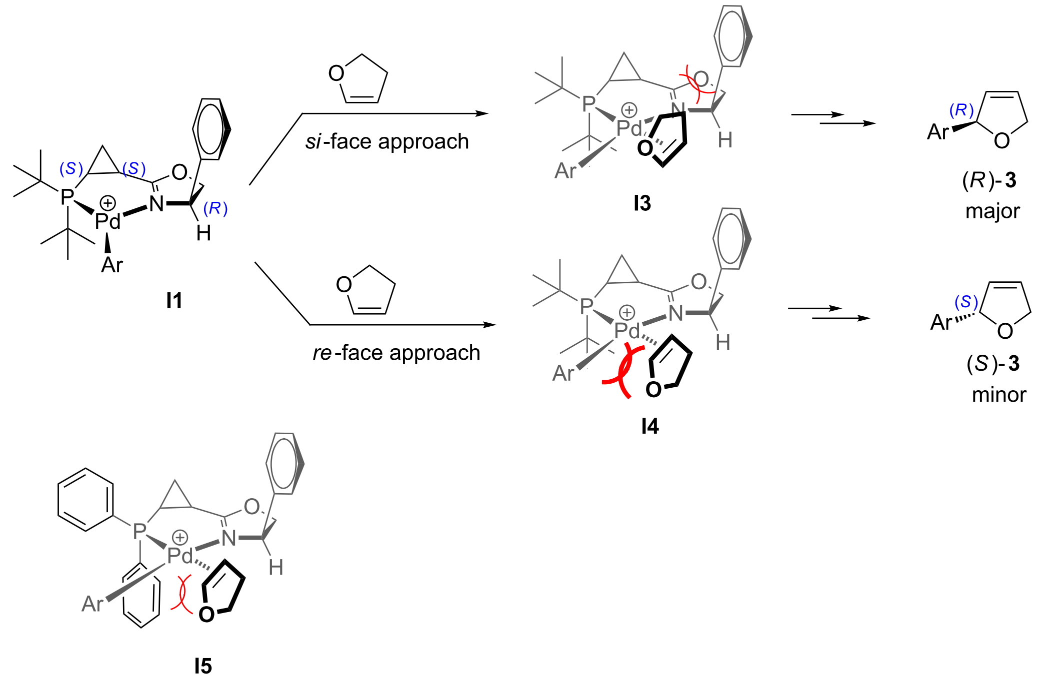


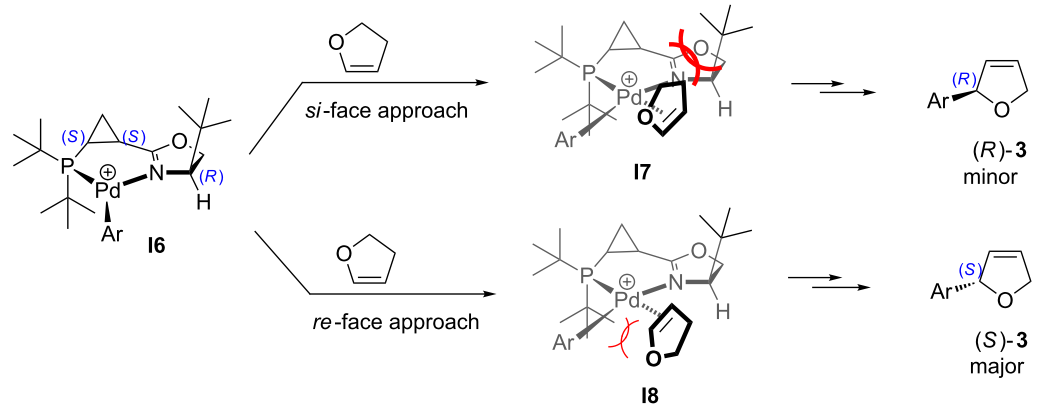
**Figure 4:** X-ray structures of complexes (**L1**)PdCl$_2$ (left) and (**L4**)PdCl$_2$ (right). These structures were originally communicated in [64].

adopt a pseudo-equatorial and a pseudo-axial position, respectively. It would be reasonable to assume that the strained and rigid cyclopropyl backbone renders the six-membered palladacycle particularly inflexible, thus significantly suppressing conformational fluctuations throughout the catalytic cycle. Furthermore, coordination of the soft π-ligand dihydrofuran should take place predominantly *trans* to a soft phosphorus atom [70-72] (Scheme 5). In this case, the *re*-face approach (**I4**) is encumbered by a large pseudo-axial *tert*-butyl group, while the *si*-face approach (**I3**) is also somewhat hindered by a pseudo-axial *syn*-phenyl substituent in dihydrooxazole ring. As a result, the (*R*)-enantiomer of the product was predominantly formed, albeit with moderate enantioselectivity. Analogously, in the intermediate **I5** derived from chiral ligand **L2**, the less bulky pseudo-axial phenyl substituent at phosphorus blocks the *re*-face approach even less efficiently, which ultimately results in a further decrease of enantioselectivity (Scheme 5).

The reversal of enantioselectivity observed in the reaction carried out in the presence of **L3** was explained in a similar fashion (Table 2, entries 5 and 6, Scheme 6). Thus, a bulky *tert*-butyl group in the dihydrooxazole ring creates the increased



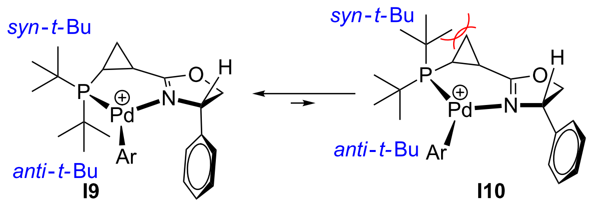
**Scheme 5:** For discussion on asymmetric induction imparted by chiral ligands **L1** and **L2** (originally published in [64]).



**Scheme 6:** For discussion on asymmetric induction imparted by chiral ligands **L3** (originally published in [64]).

steric hindrance, which does not allow for the *si*-face approach resulting in the reaction proceeding predominantly from the *re*-face, providing the (*S*)-enantiomer of **3** (Scheme 6). The fact that in both intermediates **I7** and **I8** dihydrofuran experiences certain impediment on approach to palladium may also be responsible for the observed decrease in the reaction rate.

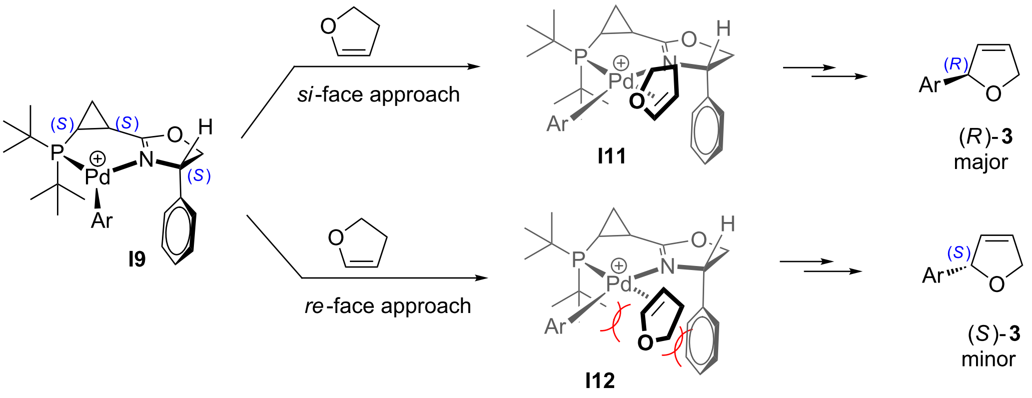
Based on this analysis, we rationalized that the "wrong" relative configuration of the stereogenic centers in ligands **L1**, **L2** and **L3** could be responsible for the observed marginal enantioselectivity of the corresponding catalytic systems. We envisioned that inverting the absolute configuration of the asymmetric center at C4 in the dihydrooxazole ring might potentially help to improve the enantioselectivity of the arylation reaction. Indeed, it is reasonable to propose that the inversion of the stereogenic center in the dihydrooxazole ring should not significantly affect the thermodynamic equilibrium of the corresponding palladacycle conformations **I9** and **I10** (Scheme 7), as compared to **I1** and **I2** (Scheme 4). Thus, the cationic palladacycle with (*S*,*S*,*S*)-ligand **L4** would still predominantly adopt conformation **I9** to avoid the unfavorable steric interaction between the pseudo-axial *syn-tert*-butyl group and the methylene group of the cyclopropane (Scheme 7). Accordingly, a synergistic steric effect of both the axial P–*t*-Bu group and a bulky substituent at C4 in dihydrooxazolyl moiety observed in the alternative (*S*,*S*,*S*)-configuration of the ligand would now provide efficient blocking of the both bottom quadrants thereby completely averting the *re*-face attack (**I12**, Scheme 8). On the other hand, the *si*-face attack should become more favorable after the removal of a bulky group obstructing the top right quadrant (**I11**, Scheme 8 vs **I3**, Scheme 5). Ultimately, if the above assumptions are correct, this change should result in enhanced enantioselectivity of the asymmetric arylation in the presence of ligand **L4** in favor of the (*R*)-enantiomer of the product **3**.



**Scheme 7:** Conformational equilibrium in cationic arylpalladium(II) complexes with chiral ligand **L4**.

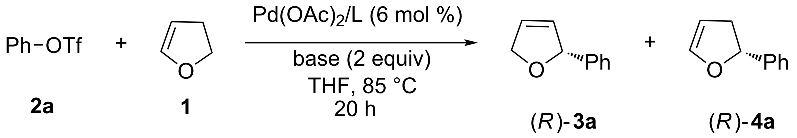
With this idea in mind, we prepared a new series of ligands with the (*S,S,S*)-absolute configuration using the synthetic approach described above (Scheme 3), starting from acid chloride (*S*)-**16** and (*S*)-phenylglycinol. Additional diversification of the ligand structure was achieved by varying the chlorophosphine source. Thus, employment of di-*tert*-butylchlorophosphine, chlorodicyclohexylphosphine, and chlorodiphenylphosphine at the last step of the sequence provided ligands **L4, L5**, and **L6**, respectively (Figure 3). Crystallographic data obtained for the (**L4**)$PdCl_2$ complex (Figure 4) completely confirmed the preference of conformation **I9** vs **I10** (Scheme 7). It should be pointed out, that the resolved crystal structure of (**L4**)$PdCl_2$ complex shows four sets of crystallographically independent molecules. However, all of them have nearly identical palladacycle conformations with the molecule shown in Figure 4 [64]. An overlay of X-ray structures obtained for (**L1**)$PdCl_2$ and (**L4**)$PdCl_2$ complexes demonstrated that all atoms of the palladacycle, cyclopropyl ring, and both *tert*-butyl substituents can be almost perfectly superimposed, which for both ligand configurations, confirms the strong preference of a conformation in which the *syn-tert*-Bu substituent (C14) and the *anti-tert*-Bu substituent (C18) at phosphorus assume pseudo-equatorial and pseudo-axial positions, respectively. Remarkably, X-ray analysis has also demonstrated that the phenyl substituent at C4 of dihydrooxazole ring adopts a pseudo-axial position thereby completely blocking any potential re-face attack (Scheme 8).

Ligands **L4**, **L5**, and **L6** once obtained were tested in the asymmetric arylation of dihydrofuran **1** (Table 3). Gratifyingly, right along with our expectations, the entire series of (*S*,*S*,*S*)-ligands **L4**–**L6** not only provided a significant improvement in enantioselectivity, but also helped to suppress the unwanted isomerization of **3** into **4**, as compared to the diastereomeric ligand series (**L1**–**L3**, Table 2). Remarkably, changing the absolute configuration of the stereocenter in the dihydrooxazole ring did not cause the change of the absolute configuration of the product. This is in contrast to the reactions performed using most known PHOX ligands, in which configuration of the oxazoline moiety usually determines the stereochemical outcome of the reaction (however, in the reactions using PHOX ligands bearing a very bulky planar or axially chiral backbone, the enantiomeric outcome is controlled by the absolute configuration of the backbone rather than that of the oxazoline ring; for discussion, see [15]). Thus, employment of **L4** and **L5** afforded dihydrofuran (*R*)-**3** with very high enantioselectivity regardless of the base used (Table 3, entries 1–6); however, the reactions proceeded more sluggishly in the presence of Hünig's base (Table 3, entries 2 and 5). Employment of proton sponge helped boost the reaction rate in the arylation catalyzed by both **L4** and **L5** (Table 3, entries 3 and 6). Yet, significant isomerization of **3** into **4** was observed with this base when the reaction catalyzed by Pd/**L4** complex was allowed to run for an additional 20 h (Table 3, note c). Employment of the diphenylphosphanyl ligand **L6** provided lower enantioselectivity (Table 3, entries 7



**Scheme 8:** For discussion on asymmetric induction imparted by chiral ligands **L4** (originally published in [64]).

**Table 3:** Screening of **L4**–**L6** in the asymmetric Heck arylation reaction.



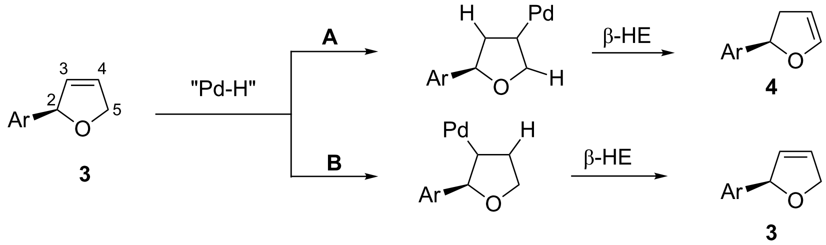
| Entry | Ligand | Base | **3a**:**4a** | ee (**3a**), % | Conv, %$^{a}$ |
|---|---|---|---|---|---|
| 1 | **L4** | $EtN(iPr)_2$ | >50:1 | 98 | 53 |
| 2 | **L4** | $EtN(iPr)_2$ | 16:1 | 98 | 97$^{b}$ |
| 3 | **L4** | proton sponge | >50:1$^{c}$ | 98 | 74 |
| 4 | **L5** | $EtN(iPr)_2$ | >50:1 | 94 | 71 |
| 5 | **L5** | $EtN(iPr)_2$ | 40:1 | 94 | 90$^{b}$ |
| 6 | **L5** | proton sponge | 29:1 | 95 | 99 |
| 7 | **L6** | $EtN(iPr)_2$ | 16:1 | 88 | 76 |
| 8 | **L6** | proton sponge | >50:1 | 86 | 83 |

[a]Conversions by GC. [b]Conversion after 2 days at 85 °C. [c]When the reaction was allowed to stir for an additional 20 h, the product ratio changed to 2:1. The enantioselectivities of products (*R*)-**3a** and (*R*)-**4a** in this case were found to be 98% and 97%, respectively.

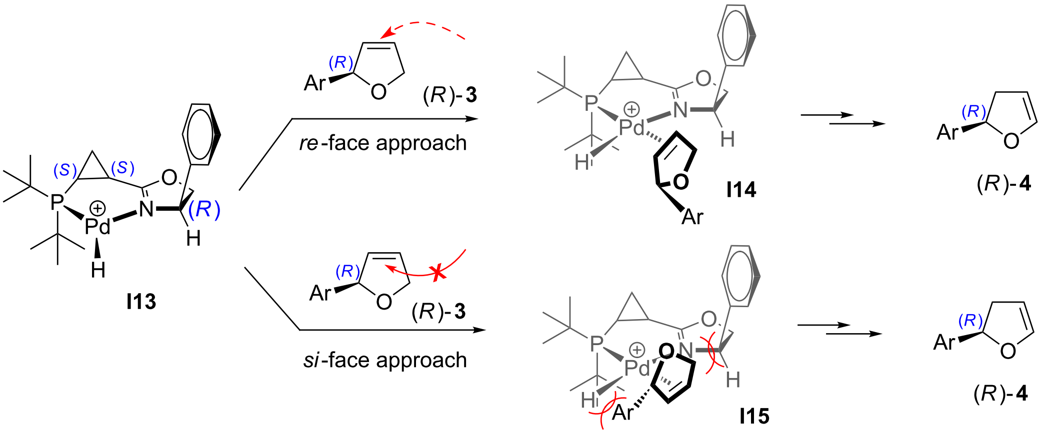
and 8), which can be attributed to decreased steric demands created by phenyl groups at phosphorus as compared to the *tert*-butyl (**L4**) and cyclohexyl (**L5**) substituents.

The different tendencies of Pd/**L1** and Pd/**L4** catalyst systems to promote isomerization of product **3** into **4** can be rationalized as follows. As discussed above (Scheme 2), the isomerization process involves reversible hydropalladation of the double bond of product **3**. The migration of the double bond can be realized only when hydropalladation of **3** occurs with addition of palladium to C4 (Scheme 9, path A), whereas the opposite regioselectivity of hydropalladation would ultimately lead, after the subsequent β-hydride elimination, back to compound **3** (Scheme 9, path B). The diastereoselectivity of the hydropalladation of **3** by Pd/**L1** hydride species **I13** is controlled as shown in Scheme 10. Thus, it seems impossible to realize the *si*-face approach of palladium hydride species **I13** to the double bond of **3** due to severe steric hindrance between the di(*tert*-butyl)phospanyl group of the ligand and the aryl substituent in **3** on one side, and between the phenyl substituent in dihydrooxazole ring and C5-methylene of dihydrofuran **3** on the other (**I15**, Scheme 10). However, the absence of any significant steric interference upon alternative *re*-face approach makes this alternative mechanistic channel available for isomerization (**I14**, Scheme 10).

Two potential pathways for hydropalladation of **3** by the diastereomeric Pd/**L4** hydride species **I16** are shown in Scheme 11. In conjunction with **L1**-derived complex **I15** (Scheme 10), complex **I18** produced via the *si*-face approach

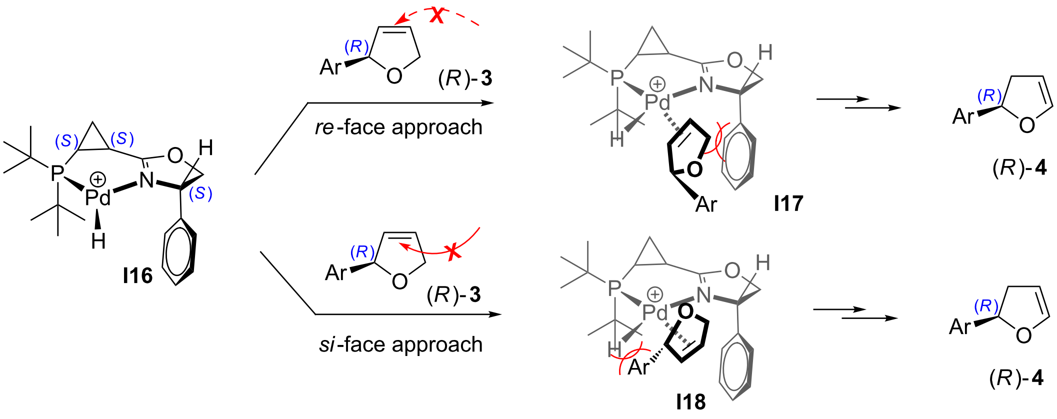


**Scheme 9:** Mechanism of migration of C=C double bond leading to isomerization of product **3** into product **4**.



**Scheme 10:** For discussion on isomerization **3**→**4** imparted by Pd/**L1** complex (originally published in [64]).

should be highly disfavored (Scheme 11). In this case, however, an alternative complex **I17** resulting from the *re*-face attack should also experience steric repulsion between the C5-methylene of dihydrofuran **3** and a pseudo-equatorial phenyl substituent in dihydrooxazole ring (Scheme 11). Accordingly, complex **I17** should be much more unfavorable compared to **L1**-derived complex **I14**, where such interaction does not occur (Scheme 10). As a result, both mechanistic channels for isomerization of compound **3** into **4** should be suppressed in this case. It should be mentioned, however, that electronic density at the phosphine moiety of the ligand also notably affects the propensity of the corresponding catalyst to promote the isomerization. Thus, our experiments indicate that in the series of di(*tert*-butyl)-, dicyclohexyl-, and diphenylphosphanyl-containing ligands (**L4**→**L6**), the former has the highest tendency to induce isomerization while the latter has the lowest (Table 3). A



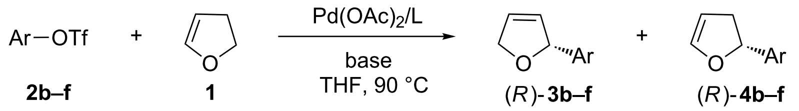
**Scheme 11:** For discussion on isomerization **3**→**4** imparted by Pd/**L4** complex (originally published in [64]).

similar electronic effect was previously observed in the asymmetric Heck arylation in the presence of diphosphine-oxazoline ferrocenyl ligands [56].

Next, the most efficient ligands **L4** and **L5** were tested in the asymmetric arylation of dihydrofuran **1** against various aryl triflates (Table 4). It was found that all reactions catalyzed by Pd/**L4** provided excellent enantioselectivities (98–99%) regardless of the nature of the aryl triflate (Table 4, entries 1–5). However, the reactions carried out in the presence of **L4**/Hünig's base combination proceeded much more sluggishly; as a result, the selectivity toward formation of **3** was slightly lower in these cases. Reactions performed in the presence of Pd/**L5** catalyst and proton sponge proceeded much faster, albeit providing somewhat lower ee's (Table 4, entries 6–10). In contrast to the Pd/**L4**-catalyzed reactions, enantioselectivities in this case varied slightly depending on the aryl triflate used, with the highest value obtained from 1-naphthyl triflate (96%, Table 4, entry 9) and the lowest from 2-naphthyl triflate (87%, Table 4, entry 10). Interestingly, the electronic nature of the aryl triflate had a pronounced effect on the reaction rate, which is best seen in the Pd/**L5** series of catalyzed reactions. Thus, electron-rich aryl triflates (Table 4, entries 6, 7, and 9) reacted much faster than the electron-poor analog **2d** (Table 4, entry 8). Furthermore, a remarkable difference between the reactivity of 1- and 2-naphthyl triflates was also observed, suggesting the reaction is also sensitive to sterics (Table 4, entries 9 and 10).

We also tested all new ligands **L1**–**L6** in the asymmetric Heck arylation of cyclopentene (Table 5). Initial experiments

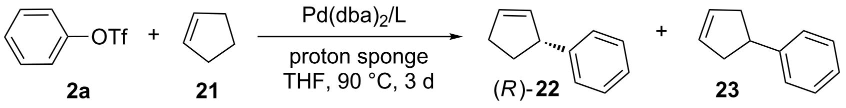
**Table 4:** Asymmetric arylation of dihydrofuran with aryl tiflates.



| Entry | Aryl | | Ligand/Base | Time, h | **3**:**4** | ee (**3**), % | Conv, %[a] |
|---|---|---|---|---|---|---|---|
| 1 | *p*-Me-$C_6H_4$ | **2b** | **L4**/Hünig's base | 48 | 16:1 | 99 | 96 |
| 2 | *p*-MeO-$C_6H_4$ | **2c** | **L4**/Hünig's base | 20 | 17:1 | 98 | 98 |
| 3 | *p*-$CF_3$-$C_6H_4$ | **2d** | **L4**/Hünig's base | 48 | >50:1 | 98 | 58 |
| 4 | 1-Nphth | **2e** | **L4**/Hünig's base | 48 | 18:1 | 98 | 70[b] |
| 5 | 2-Nphth | **2f** | **L4**/Hünig's base | 20 | >50:1 | 98 | 32[b] |
| 6 | *p*-Me-$C_6H_4$ | **2b** | **L5**/proton sponge | 6 | 39:1 | 95 | 93 |
| 7 | *p*-MeO-$C_6H_4$ | **2c** | **L5**/proton sponge | 6 | 35:1 | 92 | 99 |
| 8 | *p*-$CF_3$-$C_6H_4$ | **2d** | **L5**/proton sponge | 20 | 42:1 | 91 | 95 |
| 9 | 1-Nphth | **2e** | **L5**/proton sponge | 6 | 31:1 | 96 | 94[b] |
| 10 | 2-Nphth | **2f** | **L5**/proton sponge | 20 | 17:1 | 87 | 100[c] |

[a]Conversion by GC. [b]Formation of ca.10% of naphthalene was observed. [c]Formation of ca. 20% of naphthalene was observed.

**Table 5:** Evaluation of Ligands **L1**–**L6** in the intermolecular asymmetric Heck reaction of phenyl triflate (**2a**) with cyclopentene (**19**).



| Entry | Ligand | **22**:**23** | ee (**22**), % | Conv, %[a] | Yield, %[b] |
|---|---|---|---|---|---|
| 1 | **L1** | 12:1 | 81 | 99 | 85 |
| 2 | **L2** | 15:1 | 86 | 95 | 80 |
| 3 | **L3** | 13:1 | 82 | 15 | ND |
| 4 | **L4** | 27:1 | 92 | 32 | ND |
| 5 | **L5** | 44:1 | 89 | 96 | 80 |
| 6 | **L6** | 40:1 | 80 | 60 | ND |

[a]Conversion by GC. [b]Isolated yields, obtained by standard aqueous work-up of the reaction mixture, followed by fractionation.

conducted under the conditions optimized for arylation of dihydrofuran **1** provided no reaction with cyclopentene **21**. Additional optimization revealed that reasonable reaction rates can be achieved only in the presence of Pd(dba)$_2$ catalyst and proton sponge. It should be mentioned that employment of Pd$_2$(dba)$_3$·CHCl$_3$ catalyst in place of Pd(dba)$_2$ provided no reaction. Generally, the enantioselectivities obtained in this transformation (Table 5) were somewhat lower than those obtained in the arylation of dihydrofuran (Table 2 and Table 3) for all ligands tested except **L4**. Notably, similarly to the arylation of dihydrofuran (Table 2 and Table 3), the isomerization rates (**22**→**23**) in this transformation were significantly lower in the reactions carried out in the presence of ligands with the (*S*,*S*,*S*) absolute configuration (**L4**–**L6**, Table 5, entries 4–6), as compared to the ligands in the diastereomeric series (**L1**–**L3**, Table 5, entries 1–3).

# Conclusion

In conclusion, a series of novel PHOX ligands featuring a chiral cyclopropyl backbone have been synthesized and examined in the intermolecular asymmetric Heck arylation of cyclic olefins. By lowering degrees of freedom in the catalyst structure through the introduction of additional conformation constrains, we have created a model catalytic system with predictable, tuneable and easily adjustable properties. Structure–activity relationship studies allowed for identifying the key topological and stereochemical features of the ligands, responsible for achieving high enantioselectivity and for suppressing product isomerization. This has resulted in the development of efficient catalytic systems demonstrating excellent enantioselectivities in the asymmetric arylation of dihydrofuran with various aryl triflates. It was also shown that the product isomerization in the presence of these ligands has a different nature from that reported previously using chiral diphosphine ligands. Furthermore, a number of factors were shown to affect the isomerization rate including the absolute configuration of the ligand, its electronic properties, and the base employed.

# Supporting Information

## Supporting Information File 1

Detailed experimental procedures of chiral ligands **L2**, **L5**, and **L6**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-158-S1.pdf]

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# Synthesis of isoprenoid bisphosphonate ethers through C–P bond formations: Potential inhibitors of geranylgeranyl diphosphate synthase

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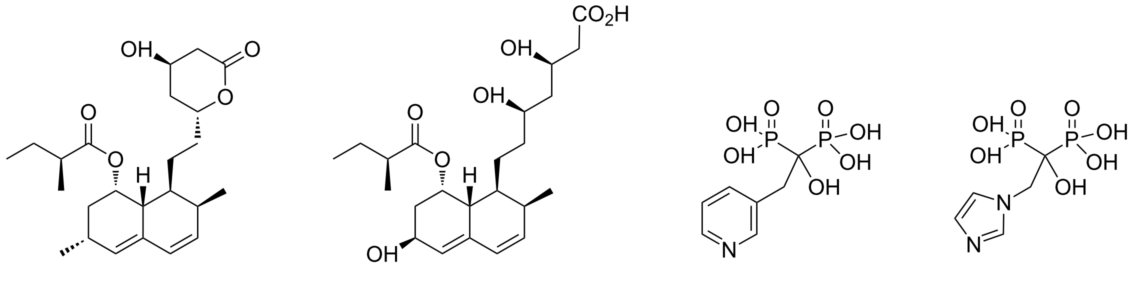
## Abstract

A set of bisphosphonate ethers has been prepared through sequential phosphonylation and alkylation of monophosphonate ethers. After formation of the corresponding phosphonic acid salts, these compounds were tested for their ability to inhibit the enzyme geranylgeranyl diphosphate synthase (GGDPS). Five of the new compounds show $IC_{50}$ values of less than 1 μM against GGDPS with little to no activity against the related enzyme farnesyl diphosphate synthase (FDPS). The most active compound displayed an $IC_{50}$ value of 82 nM when assayed with GGDPS, and no activity against FDPS even at a 10 μM concentration.

## Introduction

Several enzymes of the isoprenoid biosynthesis pathways are the targets of widely prescribed drugs. For example, hydroxymethylglutaryl CoA reductase (HMGCoA) is viewed as the first committed step of isoprenoid and steroid biosynthesis, and is the target of the statin class of cholesterol-lowering agents including lovastatin (**1**, Figure 1) and pravastatin (**2**) [1]. The downstream enzyme farnesyl diphosphate synthase (FDPS) is the target of the nitrogenous bisphosphonates including risedronate (**3**) and zoledronate (**4**), which are widely used for treatment of osteoporosis [2]. It can be argued that the success of these drugs is due at least in part to the central roles that isoprenoids play in mammalian metabolism, which suggests that other enzymes in these pathways also may have value as drug targets.

One of our interests in isoprenoid biosynthesis has been the enzyme geranylgeranyl diphosphate synthase (GGDPS), which mediates the reaction of the $C_{15}$ compound farnesyl diphos-



**1** (lovastatin) **2** (pravastatin) **3** (risedronate) **4** (zoledronate)

**Figure 1:** Inhibitors of isoprene biosynthesis.

phate (FPP) with the $C_5$ isopentenyl diphosphate to form the $C_{20}$ isoprenoid geranylgeranyl diphosphate (GGPP) (Figure 2) [3]. Geranylgeranylation is an important posttranslational modification, especially among proteins in the Ras superfamily of small GTPases that are involved in a variety of signaling pathways [4]. Based on the premise that inhibition of GGDPS should reduce cellular levels of GGPP and thus diminish protein geranylgeranylation, one might expect that inhibitors of this enzyme would interfere with essential cell signaling pathways and demonstrate antiproliferative activity.

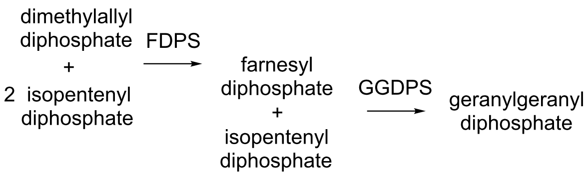
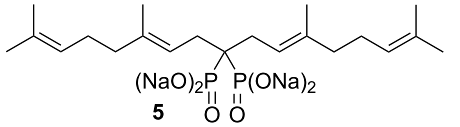
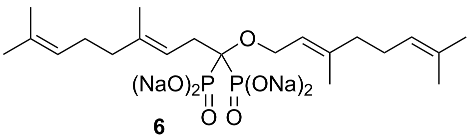


**Figure 2:** Biosynthesis of geranylgeranyl diphosphate.

Several years ago we reported the synthesis of digeranyl bisphosphonate (DGBP, **5**, Figure 3) [5], and determined that this compound was an inhibitor of GGDPS ($IC_{50}$ ~ 200 nM), competitive with FPP, and yet showed much less activity against FDPS ($IC_{50}$ > 10 μM) in enzyme assays [6]. Furthermore, despite the high degree of negative charge on DGBP at physiological pH, Western blot analyses of K562 cells (a human-derived, myeloid leukemia cell line) treated with this compound make clear that it penetrates the cell membrane at a concentration sufficient to impact GGPP levels. For example in the presence of micromolar DGBP, Rap1a which is normally found to be fully geranylgeranylated through posttranslational processing, instead is only partially modified [5]. Preparation of a prodrug form of DGBP does increase the impact of the drug by nearly an order of magnitude [7], but masking the negative charges of DGBP is not essential for observation of cellular activity. Following our reports on the activity of DGBP, a beautiful set of crystallographic analyses from the Oldfield group attributed the activity of this compound and a number of others in part to a V-like shape [8]. This shape allows one geranyl group to occupy the enzyme channel where FPP enters the active site of GGDPS, while at the same time the second isoprenoid chain can fit nicely in the groove where the product GGPP normally departs from the active site.



**5**



**6**

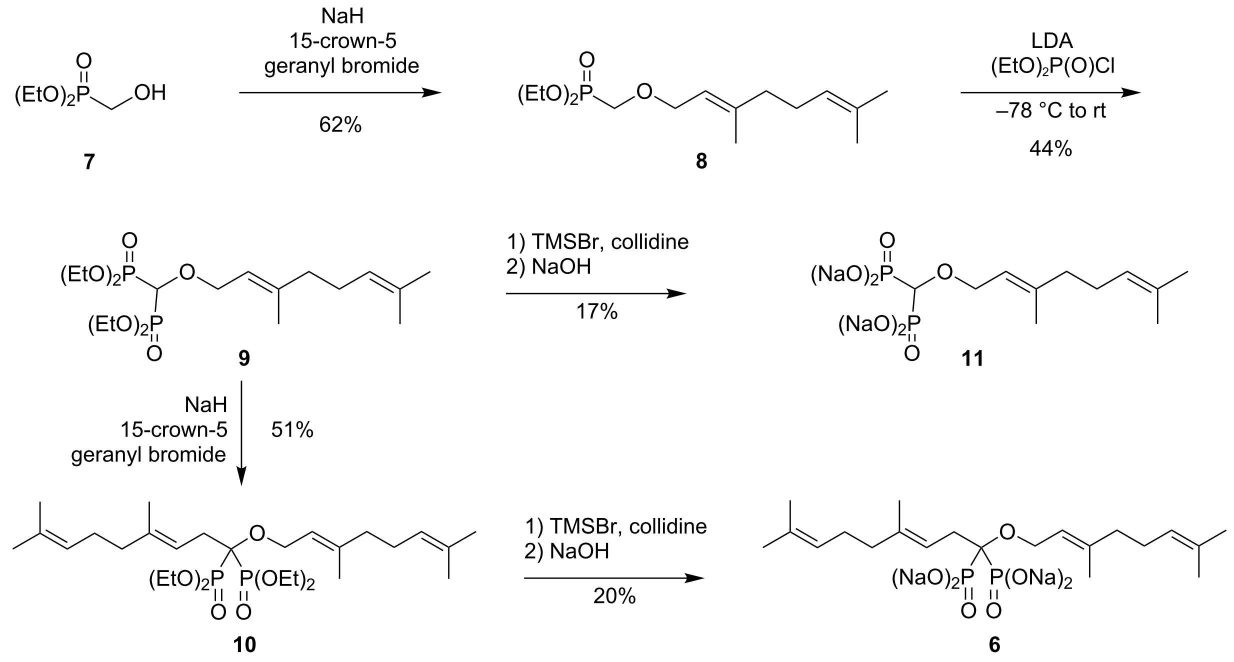
**Figure 3:** A known inhibitor of GGDPS (**5**) and a new analogue (**6**).

To continue efforts [9] to increase the potency of GGDPS inhibitors, we sought a new set of isoprenoid bisphosphonates as represented by structure **6** (Figure 3). This *O*,*C*-digeranyl geminal bisphosphonate was expected to preserve a V-like structure very similar to that of DGBP. However, the presence of an oxygen substituent on the geminal carbon should lower the $pK_a$ of bisphosphonate **6** relative to that of compound **5**, which might enhance its similarity to an isoprenoid diphosphate. In both monophosphonates [10] and bisphosphonates [11] introduction of an alpha hydroxy group has been reported to increase biological activity significantly. In bisphosphonates even a small change in $pK_{a3}$ may be important because it lies in a range close to physiological pH [12]. If an ether substituent on this template had a comparable impact, it could significantly increase the activity relative to DGBP itself [13]. Furthermore, one binding model suggests that the hydroxy group itself, so prominent in the clinically used bisphosphonates, contributes only modestly to binding with the bone surface [14], and therefore might be a site appropriate for further modification. Thus we decided to pursue compounds of the general structure **6**. We report here the synthesis of some isoprenoid bisphosphonate ethers in this family and our initial studies of their biological activity.

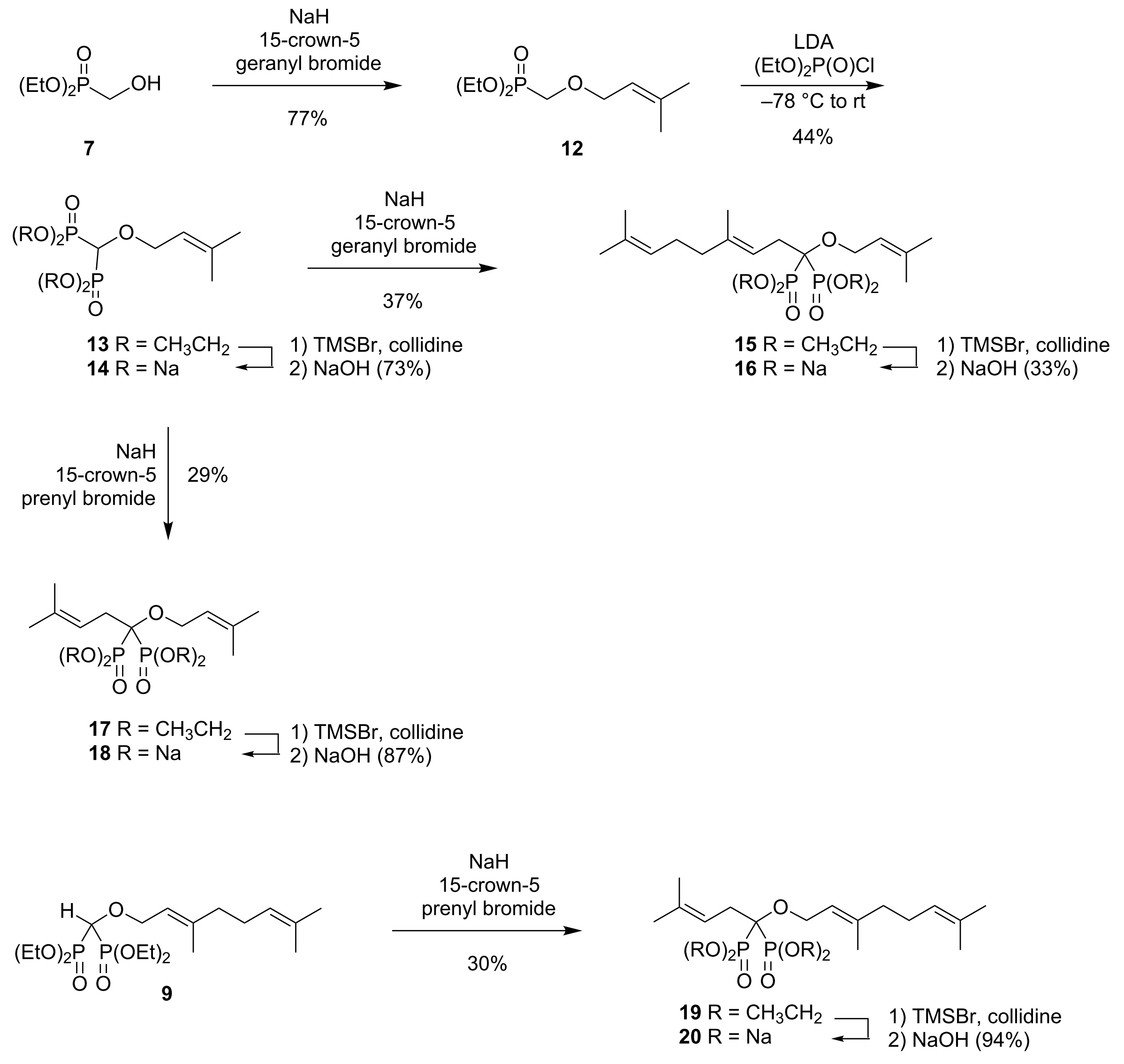
## Results and Discussion

Of the different routes one might consider to prepare geminal bisphosphonate ethers, some can be readily dismissed. For example, while several routes to hydroxybisphosphonates are known [15], any attempt to incorporate an ether linkage through the corresponding alkoxide after formation of the bisphosphonate would face the strong possibility of phosphonate–phosphate rearrangement [15-17]. However, diethyl hydroxymethylphosphonate (**7**, Scheme 1) is known to react with a base and geranyl bromide to afford the ether **8** in good yield [18]. With compound **8** in hand, formation of the second C–P bond occurred readily upon treatment with base and diethyl chlorophosphate [19-23] to give the bisphosphonate ether **9** in modest yield. Alkylation of ether **9** with geranyl bromide proceeded under conditions similar to those we have reported for the preparation of dialkyl bisphosphonate **5**, and gave the desired tetraethyl *O*,*C*-digeranylbisphosphonate **10**. Hydrolysis of the phosphonate esters proceeded under standard McKenna conditions [24], but only a limited amount of the product **6** was recovered after precipitation from acetone/water. A parallel hydrolysis of bisphosphonate **9** gave compound **11**, also in modest yield. Because the $^{31}$P NMR spectra of the reaction mixtures showed a single resonance in both cases, it is quite likely that the low yield results from low recovery of the bisphosphonate salts.

Compound **6** should preserve the V-shape that would allow one isoprenoid chain to nestle within the FPP site while the other occupies the GGPP site [8]. It would not be readily apparent however, if one site is occupied preferentially by the *O*-geranyl group, or whether this group is randomly distributed between the two possibilities. In an initial effort to distinguish between random binding and differential binding, we have prepared the two isomeric bisphosphonate salts **16** and **20** through variations on the strategy used to prepare the digeranyl compound **6**. As shown in Scheme 2, reaction of phosphonate **7** with base and prenyl bromide gave the known phosphonate **12** [25]. Treatment of this phosphonate with base and diethyl chlorophosphate gave the desired bisphosphonate ester **13**. This ester was converted to the corresponding salt under standard conditions to obtain compound **14**. Alternatively, reaction of ester **13** with base and geranyl bromide gave the tetraethyl ester **15** and hydrolysis in this case afforded the desired phosphonate **16**. In a similar manner, reaction of the bisphosphonate ester **13** with base and prenyl bromide gave the *O*,*C*-diprenyl product **17**, and standard hydrolysis gave the salt **18**. To prepare the isomeric *O*-geranyl-*C*-prenyl compounds, the geranyl ether **9** was treated with base and prenyl bromide under parallel reaction conditions to afford compound **19**. Standard hydrolysis of this ester then gave the desired phosphonate salt **20**.



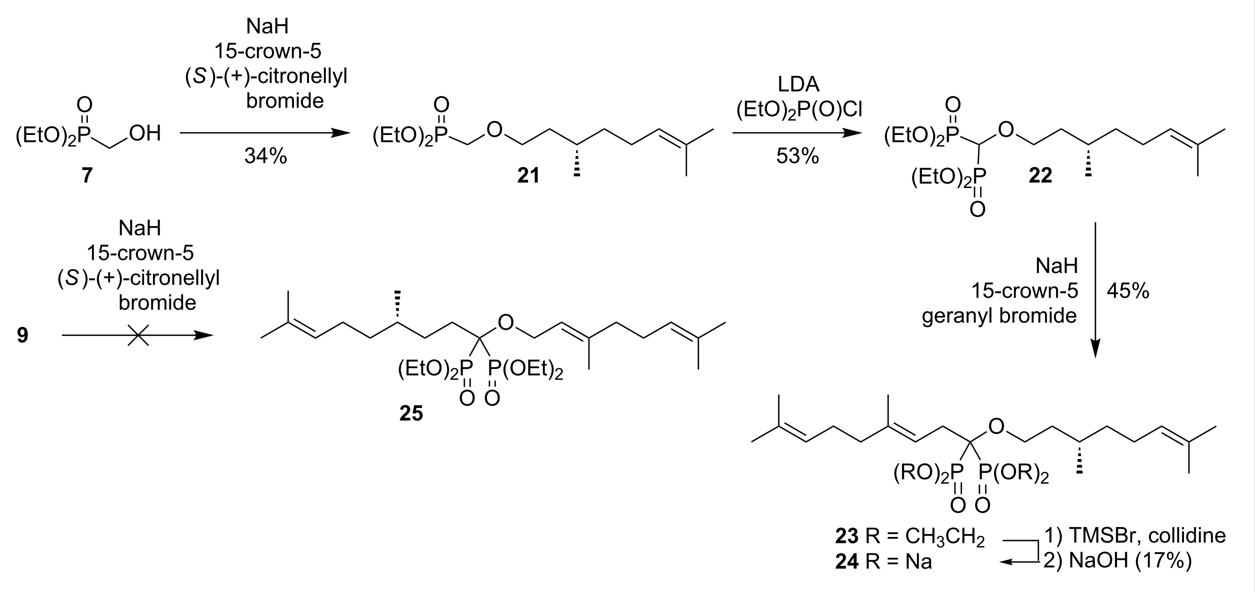
**Scheme 1:** Synthesis of bisphosphonate ethers **6** and **11**.



**Scheme 2:** Synthesis of prenyl/geranyl bisphosphonate isomers.

To gauge the generality of this approach to bisphosphonate ethers while still maintaining isoprenoid substructures, preparation of a citronellal series was examined. Alkylation of phosphonate **7** with (*S*)-(+)-citronellyl bromide occurred under the standard conditions, albeit in lower yield (Scheme 3). The resulting ether **21** was converted to the corresponding bisphosphonate **22** through formation of the anion and reaction with diethyl chlorophosphate. Alkylation of this bisphosphonate with geranyl bromide also proved feasible, and gave the expected tetraethyl ester **23**. Hydrolysis of compound **23** under standard conditions gave the desired salt **24**. In contrast, efforts to alkylate the *O*-geranyl bisphosphonate **9** with citronellyl bromide under parallel conditions went unrewarded, which might be attributed to the lower reactivity of this alkyl bromide vis-à-vis the allylic geranyl and prenyl bromides used above. Alternate strategies for preparation of compound **25** have not yet been explored, pending determination of the biological activity of the compounds in hand.

Preliminary evaluation of the biological activity of the dialkyl bisphosphonates was based on their ability to inhibit the enzymes GGDPS and FDPS [26]. The two prenyl bisphosphonate ethers, compounds **18** and **14**, showed little or no activity in these assays, as might be expected given their minimal isoprenoid chains [27]. However the compounds bearing longer alkyl chains were more interesting. As shown in Table 1, a range of activities was observed for these bisphosphonates. Under the specific conditions employed for the enzyme assays,



**Scheme 3:** Synthesis of citronellyl bisphosphonates.

**Table 1:** Activity of bisphosphonate ethers as inhibitors of GGDPS and FDPS.

| Compound | GGDPS $IC_{50}$ (nM) | FDPS $IC_{50}$ (nM) |
|---|---|---|
| **5** | 210 | >10,000 |
| **6** | 408 | >10,000 |
| **11** | 238 | >10,000 |
| **16** | 684 | 830 |
| **18** | 4,750 | 5260 |
| **20** | 274 | >10,000 |
| **24** | 82 | >10,000 |
| **4** (zoledronate) | ND | 18 |

compound **5** had an $IC_{50}$ of 210 nM, which is very comparable to the value initially observed [6]. The *O*,*C*-digeranyl compound **6** was similar to this value which was disappointing, but the *O*-geranyl compound **11** could be considered surprisingly potent given the limited activity previously reported for geranyl bisphosphonate (10 μM) [27]. The two prenyl–geranyl isomers, compounds **16** and **20** differed by a factor of ~2.5 with one roughly as potent and one ~3 fold less potent than the digeranyl compound **5**. Our hypothesis was that random placement of the two isoprenoid chains should result in nearly identical biological activity for these isomeric compounds, while if placement of the isoprenoid chains were ordered then the two isomers might well show different biological activity. The observed difference is intriguing and may support the concept of an ordered binding. However, the most interesting result was observed with the citronellyl derivative **24**. This compound displayed an $IC_{50}$ of 82 nM, which is ~2.6 fold more potent than the DGBP control (**5**). Furthermore, compound **24** displayed no activity in assays with FDPS, suggesting that its inhibition is highly selective.

## Conclusion

In conclusion, we have prepared a family of bisphosphonate ethers that incorporated terpenoid elements designed to enhance their ability to inhibit the enzyme GGDPS. The increased potency observed with the citronellyl ether **24** versus compounds prepared earlier, as well as the difference in activity between the two prenyl–geranyl isomers, encourage a more extensive investigation of the biological activity of these compounds [28]. Such studies are ongoing and will be reported in due course.

## Supporting Information

### Supporting Information File 1

Experimental procedures, characterization data, and $^{1}H$ and $^{13}C$ NMR spectra are provided for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-171-S1.pdf]

## Acknowledgements

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   An application for a patent on compounds of this general structure has been filed by the University of Iowa Research Foundation and is currently pending.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

# Application of cyclic phosphonamide reagents in the total synthesis of natural products and biologically active molecules

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Review

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## Abstract

A review of the synthesis of natural products and bioactive compounds adopting phosphonamide anion technology is presented highlighting the utility of phosphonamide reagents in stereocontrolled bond-forming reactions. Methodologies utilizing phosphonamide anions in asymmetric alkylations, Michael additions, olefinations, and cyclopropanations will be summarized, as well as an overview of the synthesis of the employed phosphonamide reagents.

## Introduction

Chiral non-racemic and achiral cyclic phosphonamide reagents **1**–**7** (Figure 1) have been employed in organic synthesis primarily as stabilized anionic nucleophiles in addition reactions to electrophilic substrates with good to excellent stereocontrol. The products obtained from these reactions were used as key building blocks in the total synthesis of a variety of structurally highly diverse and complex natural products and also of biologically active compounds.

The phosphonamide anions are derived from a small number of common motifs as shown in Figure 1. Diazaphospholidine **2** was introduced by Hanessian and co-workers, and represents the most commonly used phosphonamide in organic synthetic

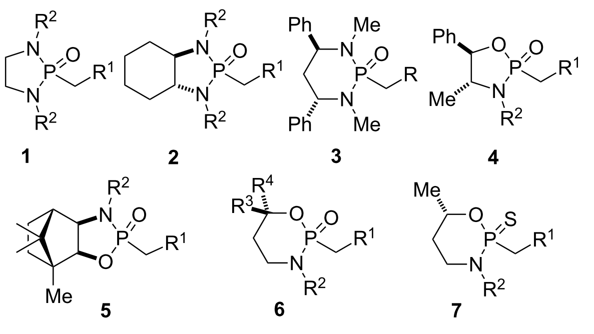


**Figure 1:** Examples of phosphonamide reagents used in stereoselective synthesis.

transformations [1]. This chiral phosphonamide typically yields reaction products with excellent stereocontrol, which are easily isolated as diastereometrically pure or highly enriched compounds. Many are crystalline solids that can be purified further by recrystallization. Diazaphosphorinane **3** and oxazaphosphorinanes **6** and **7** have been extensively studied by Denmark and co-workers [2-4]. Oxazaphospholidine **4** was independently developed by Hua [5,6], Steglich [7] and their respective co-workers. Camphor oxazaphospholidine **5** was reported by Sisti and co-workers [8,9].

This review focuses on the application of phosphonamide reagents in the total synthesis of natural products and biologically active compounds. An overview of the molecules synthesized by phosphonamide technology is shown in Figure 2. Each molecule shown will be discussed in detail later in this review. First, relevant methodologies utilizing phosphonamides will be discussed, followed by an overview of synthetic routes for the preparation of phosphonamide reagents.

# Review

## Phosphonamides in stereoselective synthesis

For the purpose of this review, only phosphonamide methodologies with applications in the synthesis of natural products or bioactive molecules will be discussed [10]. Similar technologies to the ones discussed here without such applications and other uses of chiral phosphonamide reagents in asymmetric synthesis such as Denmark's carbanion-accelerated Claisen rearrangements [11,12] have been reviewed elsewhere [13,14]. These methodologies will be mentioned where appropriate but not discussed in detail.

## Olefination

Monocyclic phosphonamide reagents of type **1** bearing a *N*,*N*'-dialkylethane-1,2-diamine backbone were first reported as olefination reagents by Corey and Cane [15] and later by Savignac [16,17], and Hanessian [18] and their co-workers. Deprotonation of phosphonamides of type **1** affords weakly basic anions

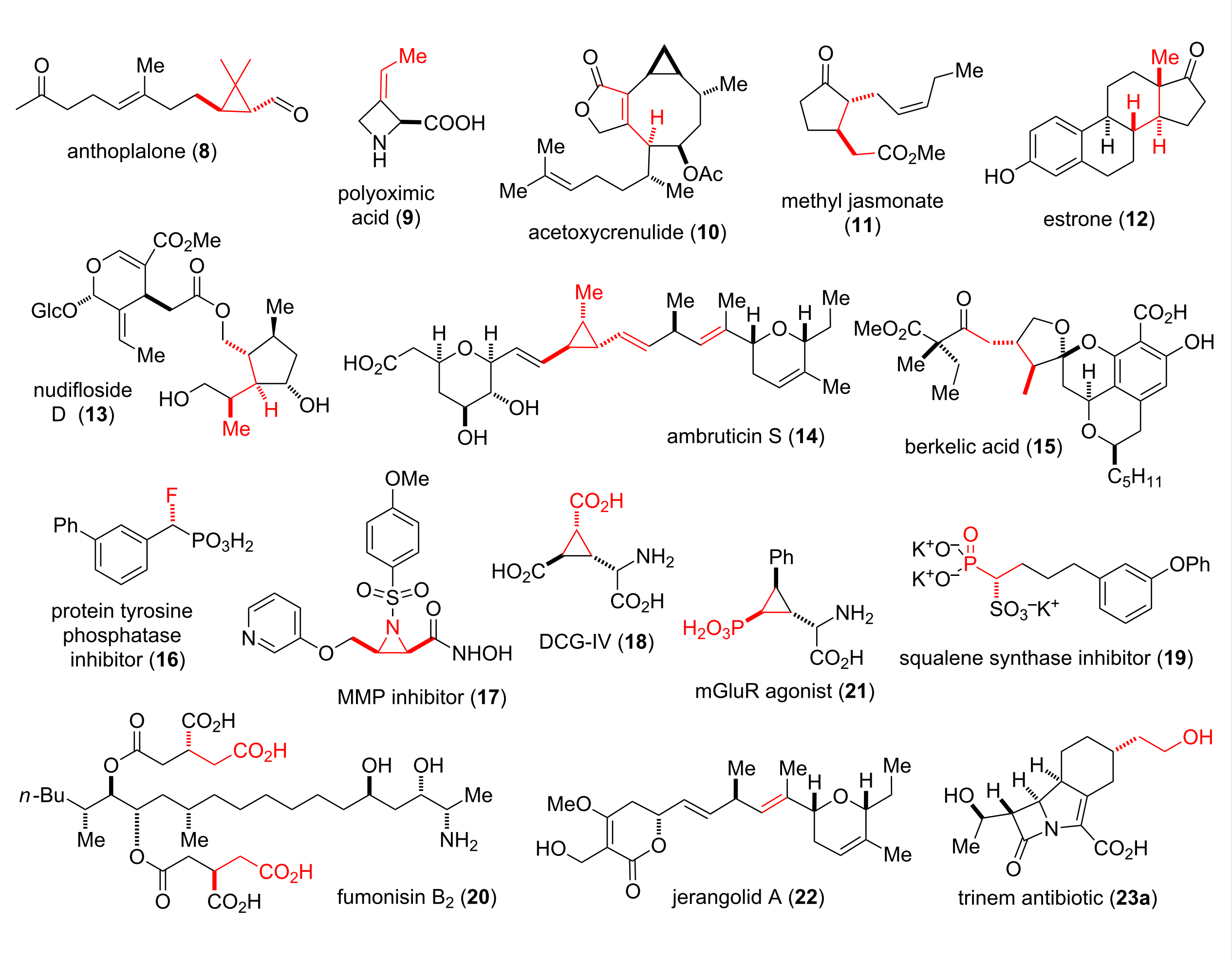
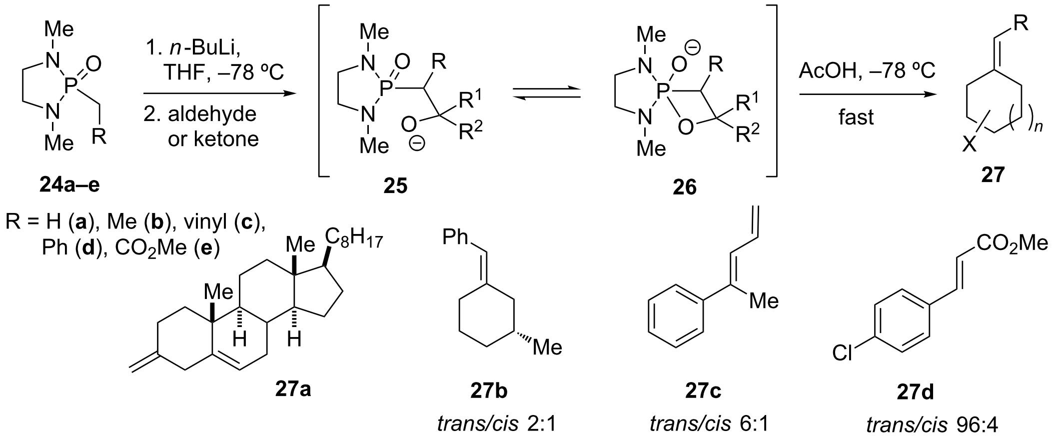


**Figure 2:** Natural products and bioactive molecules synthesized using phosphonamide-based chemistry (atoms, bonds and stereocenters formed by phosphonamide reagents are highlighted in red).

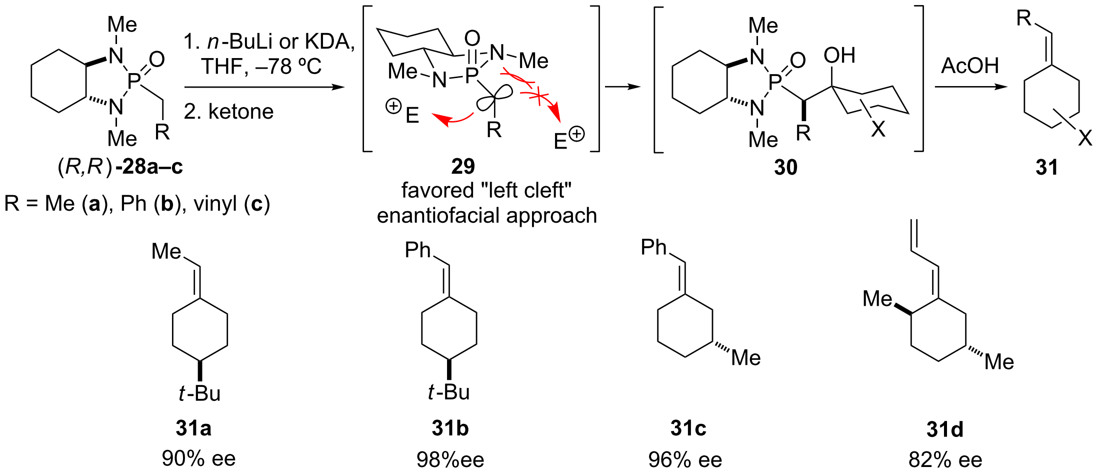
which are excellent reagents for the transformation of aldehydes and ketones into the corresponding alkenes **27** via intermediates **25** and **26** (Scheme 1) [18]. Contrary to their acyclic *N*,*N*-diethyl phosphonamides, which require harsher conditions to undergo fragmentation [19], cyclic oxaphosphetane oxide **26** releases the corresponding olefin **27** upon treatment with cold acetic acid [18]. Moreover, the only weakly basic nature of the "soft" phosphonamide anion favors the attack on the carbonyl group over enolization. Thus, treatment of Δ5-cholestenone with **24a** yielded the unconjugated olefin **27a** in addition to recovered unreacted enone, whereas phosphorus ylides would form Δ4-cholestenone via enolization and double bond conjugation [20].

Other monocyclic phosphonamides with application in olefination reactions are those derived from 1-(*tert*-butylamino)-2-methylpropan-2-ol. Denmark and Amburgey used this type of phosphonamides in a four-step protocol for the highly stereoselective synthesis of trisubstituted alkenes [21].

The application of cyclic phosphonamides was further extended toward asymmetric olefination reactions by Hanessian and co-workers, using a chiral, non-racemic diamine to generate the corresponding olefination reagents [1,22,23]. To this end the $C_2$-symmetric phosphonamide (*R*,*R*)-**28** derived from *trans*-(*R*,*R*)-*N*,*N'*-dimethyl-1,2-diaminocyclohexane [14] was conceived of as a chiral version of *N*,*N'*-dialkylethane-1,2-diamine phosphonamide **24** (Scheme 1 and Scheme 2). The reaction of anions **29** with ketones leads to the corresponding β-hydroxy phosphonamide intermediates **30**, which undergo elimination of the intermediate oxaphosphetanes to give chiral olefins **31** with moderate to high enantioselectivities. The attack



**Scheme 1:** Olefination with cyclic phosphonamide anions, mechanistic rationale, and selected examples **27a–d** [18].



**Scheme 2:** Asymmetric olefination with chiral phosphonamide anions and selected examples **31a–d** [1,22].

of electrophiles E is favored from the "left cleft" of the anion **29** in the (*R*,*R*)-isomer due to steric and stereoelectronic effects. Intermediates such as **30** can be isolated and purified as crystalline solids suitable for X-ray analysis if water is used for quenching instead of acetic acid.

Olefinations based on phosphonamides were employed in the construction of di- and trisubstituted double bonds in the total synthesis of polyoximic acid [24-26], jerangolid A [27], and ambruticin S [28], as discussed later in this review.

## Alkylations and aminations

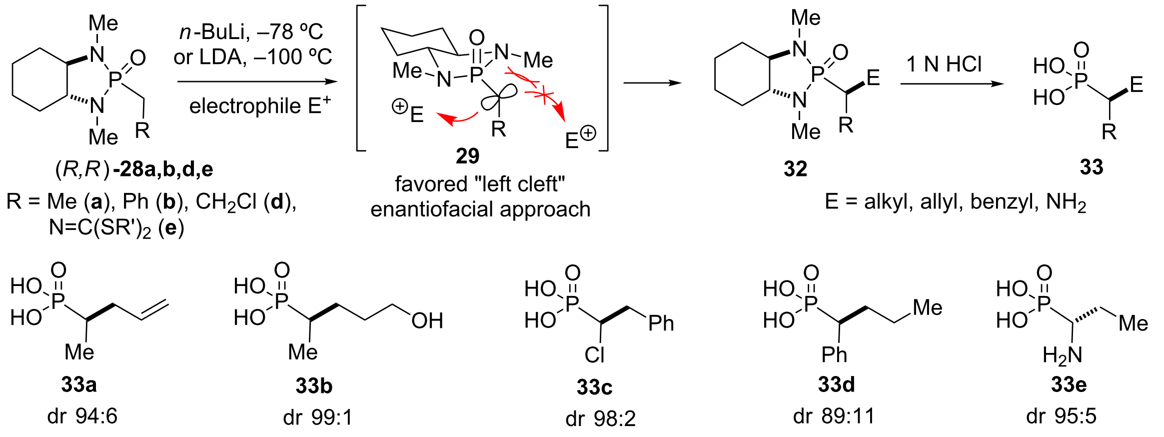
Treatment of α-phosphoryl carbanions with alkyl halides gives stereoselective access to a variety of α-substituted alkylphosphonic acids (Scheme 3). The attack on the alkyl halide occurs from the "left cleft" side of the anion **29** in the (*R*,*R*)-isomer. Thus, α-substituted phosphonamides **32** can be obtained in good to excellent diastereoselectivity and further hydrolyzed to the corresponding enantiomerically pure α-substituted phosphonic acids **33** [22,29,30]. Other asymmetric alkylation methodologies using chiral phosphonamides were reported by the groups of Denmark [3,4] and Steglich [7].

Remarkably, the alkylation of α-dithioalkylimino phosphonamide **28e** provided a diastereomer of **32** with the opposite configuration of the newly formed stereocenter. This inversion in asymmetric induction relative to non-heteroatom substituted phosphonamides such as **28a** is presumably a result of a chelated intermediate that exposes the opposite face of the anion to the electrophile compared to the conventionally accepted model [31]. The use of other electrophiles for the stereoselective formation of C–N bonds has also been reported. Thus, α-amino-α-alkyl phosphonic acids [32-34] could be obtained through amination and azidation of phosphonamide anions, respectively, and subsequent conversion of the primary adducts [35]. The enantioselective synthesis of α-phosphonosulfonic acids as squalene inhibitors, as discussed later in this review, was achieved using similar reactions – asymmetric alkylation of an α-sulfo phosphonamide and asymmetric α-sulfuration of an α-alkyl phosphonamide, respectively [36].

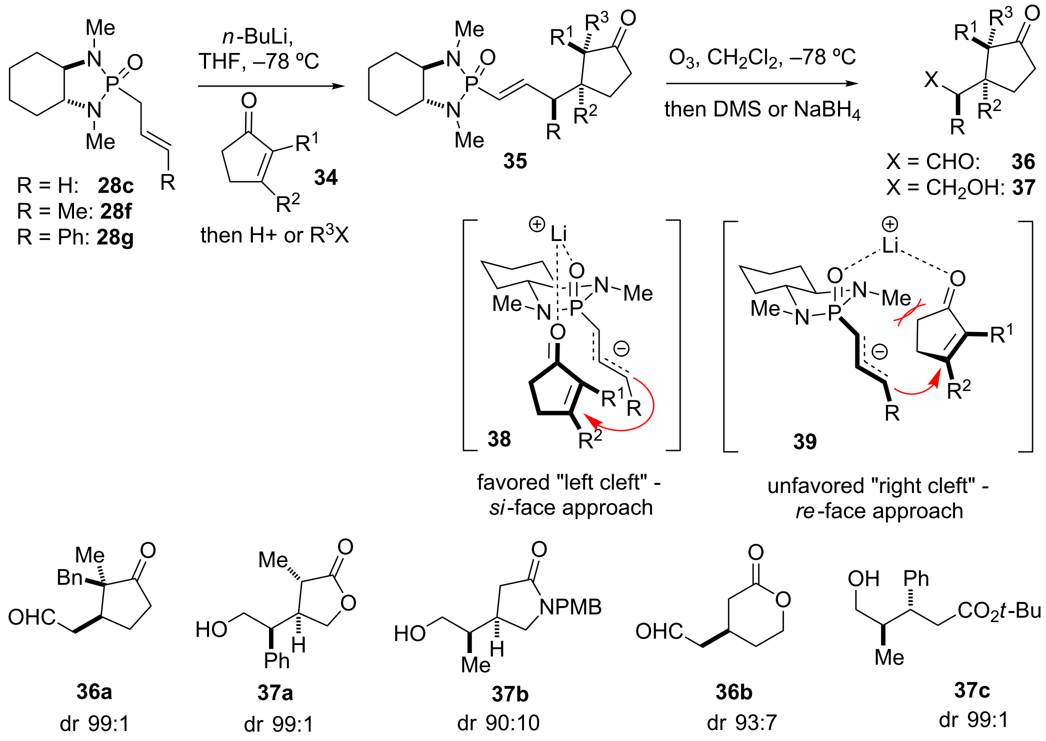
## Michael reactions

The application of chiral, cyclic phosphonamides such as **28c** in asymmetric Michael-type reactions has proven to be a powerful tool in natural product synthesis to generate up to three contiguous stereogenic centers in a single step with a high level of stereocontrol (Scheme 4) [37-40]. Thus, vicinal and quaternary carbon centers can be obtained in high diasteromeric purity by conjugate additions of allyl, crotyl, and cinnamyl-derived anions to Michael acceptors such as enones, lactones, lactams, and α,β-unsaturated esters followed by optional alkylation to give adducts **35**. The stereoselectivity of the reaction can be explained by lithium-coordinated intermediate **38**, in which chelated Michael acceptors are best accommodated within the "left-cleft" of the (*R*,*R*)-reagents **28c** and **28f**,**g**. The resulting vinyl phosphonamide product bearing the chiral auxiliary can be cleaved by ozonolysis to the corresponding aldehydes **36** and the latter reduced to alcohols **37**, respectively, as shown in Scheme 4. Many highly functionalized, vicinally substituted compounds could be prepared by this method in good to excellent enantiopurity [37-40].

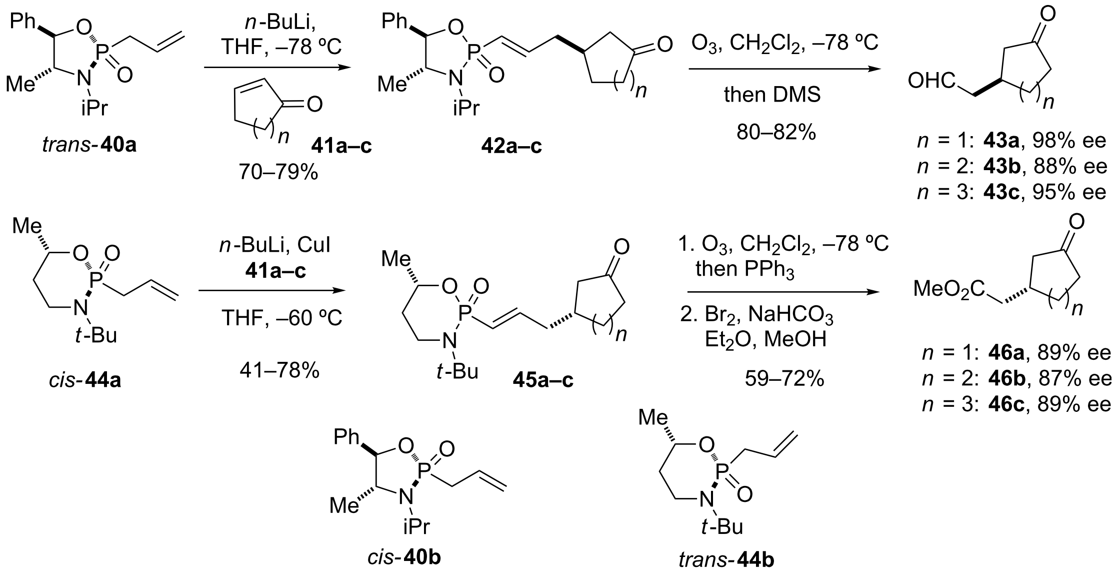
Asymmetric conjugate additions using *P*-chiral phosphonamides were reported by Denmark [2-4] and Hua [5,6], with remarkable differences in selectivity depending on the configuration of the *P*-stereogenic center (Scheme 5). Thus, the addition of the Li-anion of *trans*-**40a** to cyclic enones **41** proceeded with a high level of stereocontrol, providing adducts **42** with up



**Scheme 3:** Synthesis of α-substituted phosphonic acids **33a–e** by asymmetric alkylation of chiral phosphonamide anions, mechanistic rationale, and selected examples after hydrolysis. Diastereomeric ratios (dr) refer to the corresponding phosphonamide adducts **32** before hydrolysis [22,23].



**Scheme 4:** Asymmetric conjugate additions of $C_2$-symmetric chiral phosphonamide anions to cyclic enones, lactones, lactams, and α,β-unsaturated esters with optional enolate alkylations; mechanistic rationale, and selected examples **36** and **37** after cleavage of the auxiliary. Diastereomeric ratios (dr) refer to the corresponding phosphonamide adducts **35** before ozonolysis–reduction [37-40].



**Scheme 5:** Asymmetric conjugate additions of *P*-chiral phosphonamide anions generated from **40a** and **44a** to cyclic enones, and further derivatization of the adducts [2-6].

to 98% ee. *Cis* and *trans* refer to the orientation of the *P*-alkyl group relative to the *N*-alkyl group, in agreement with Denmark's naming of oxazaphosphorinanes [2-4]. Thus, *trans* describes a compound with a *S*-configurated phosphorus center, whereas *cis* confers to a *R*-configuration. Degradation of the adducts by ozonolysis yielded oxocycloalkane-3-carboxaldehydes **43**, which are useful synthetic intermediates. Diastereomer *cis*-**40b** however gave only poor diastereofacial selection, providing the corresponding 1,4-addition adducts in 28–64% ee [5]. In a similar fashion, Denmark's oxazaphosphorinane *cis*-**44a** yielded keto esters **46a–c** in high optical purities via conjugate addition to enones **41** followed by ozonolysis and oxidative esterification. Using diastereomer *trans*-**44b** on the other hand provided ketoesters **46a–c** with only 10–15% ee [2].

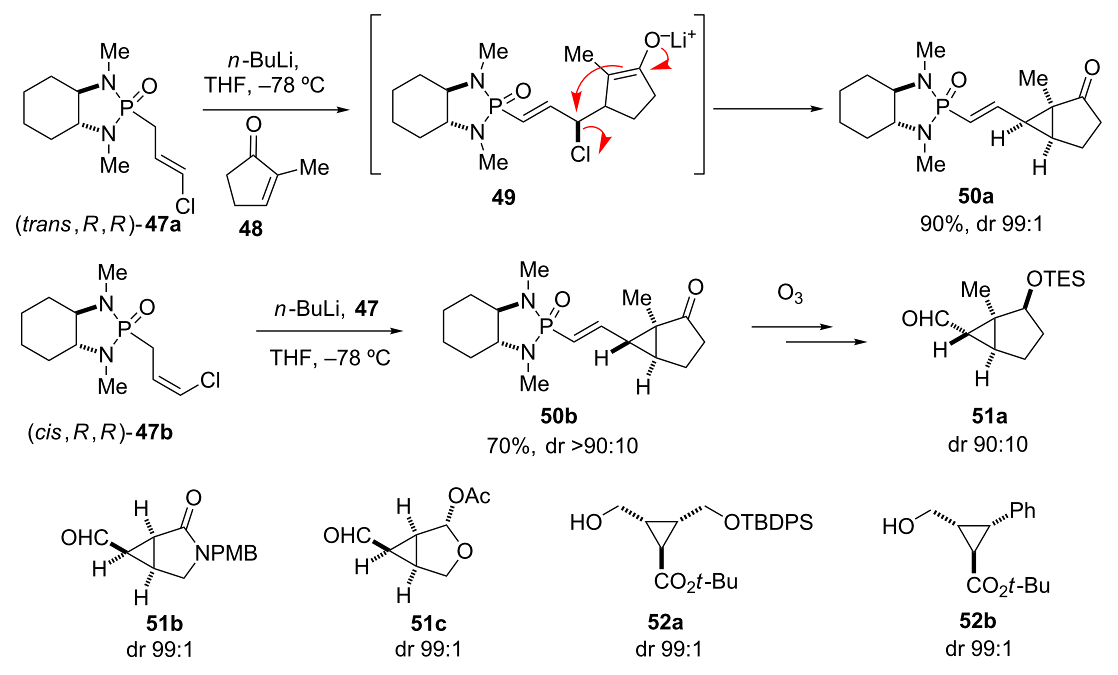
Asymmetric Michael additions using phosphonamides **28c**,**f**, or analogs of **28** and **40**, respectively, were applied in the total synthesis of acetoxycrenulide (**10**) [41,42], berkelic acid (**15**) [43], estrone (**12**) [44], fumonisin $B_2$ (**20**) [45-47], methyl jasmonate (**11**) [48], and nudifloside A and D (**13**) [49], as discussed later in this review. Studies for the synthesis of the polyphenolic natural products tatanans A–C also explored the use of phosphonamide technology [50]. The discussion of the latter natural products is not included in this review, as phosphonamide technology was only used for limited exploratory studies.

## Cyclopropanation and aziridination

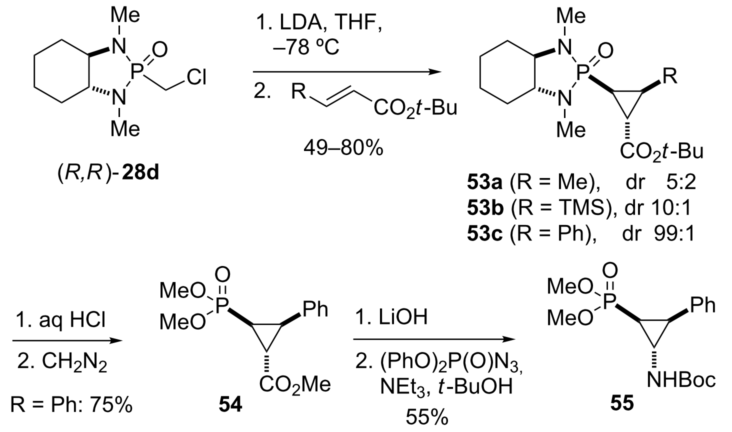
The cyclopropanation of α,β-unsaturated esters and lactones using chiral phosphonamide reagents is a special case of the conjugate addition–enolate alkylation sequence. The application of chloroallyl phosphonamides such as (*trans*,*R*,*R*)-**47a** in the conjugate addition to enones provides the corresponding fused *endo*,*endo*-cyclopropane **50a** in high diastereomeric excess [51]. The transformation proceeds via the intermediate Michael adduct **49**, which eliminates chloride after stereocontrolled attack of the enolate to afford cyclopropane **50a**. Starting with (*cis*,*R*,*R*)-**47b**, the isomeric *exo*,*endo* product **50b** is obtained as major isomer. The cyclopropanation reaction tolerates a wide range of Michael acceptor subtrates such as enones, lactones, lactams, and acyclic α,β-unsaturated esters. The obtained products can easily be cleaved to the corresponding aldehydes **51** by ozonolysis, reduced further to alcohols **52**, and constitute versatile cyclopropane chirons (Scheme 6) [51-55].

The cyclopropanation with chloroallyl phosphonamide **47a** was used to construct the cyclopropane fragments of anthoplalone (**8**) [56], ambruticin S (**14**) [28], and mGluR agonist DCG-IV (**18**) [57], as discussed later in this review. Studies for the synthesis of ottelione A and B [58] also employed this cyclopropanation methodology using a mixture of **47a** and **47b**. The discussion of the latter natural products is not included in this review, as phosphonamide technology was only used for limited exploratory studies.

Replacing chloroallyl phosphonamides **47** with chloromethyl phosphonamide **28d** in the addition to α,β-unsaturated esters also gives cyclopropane products, which can be converted to cyclopropylphosphonic acids **54** and aminocyclopropylphosphonic acids **55** (Scheme 7) [59]. The synthesis of an mGluR



**Scheme 6:** Asymmetric cyclopropanation with chiral chloroallyl phosphonamide **47**, mechanistic rationale, and selected examples **51** and **52** after cleavage of the auxiliary and further derivatization. Diastereomeric ratios (dr) refer to the corresponding phosphonamide adducts **50** before ozonolysis–reduction [51].



**Scheme 7:** Asymmetric cyclopropanation with chiral chloromethyl phosphonamide **28d** [59].

agonist was achieved using chloromethyl phosphonamide **28d** [60,61], as discussed later in this review.

Replacing Michael acceptors with oximes in the reaction with chloroallyl phosphonamide **47a** leads to the stereoselective formation of *cis*-aziridines **57** (Scheme 8) [62]. Thus, addition of the anion of phosphonamide **47a** to *tert*-butyl glyoxylate *O*-protected oximes affords the corresponding aziridine adducts **57** in excellent diastereoselectivity in a Darzens-type reaction via intermediate **56**. This aziridination methodology was then used in the synthesis of MMP-inhibitors [63], as discussed later in this review. Aziridines are also obtained as primary products in the addition of chloromethyl phosphonamide **28d** to imines. The initial attack leads to a α-chloro-β-amino phosphonamide adduct as intermediate, which then undergoes intramolecular cyclization to form the aziridine ring after elimination of chloride. When *N*-substituted aromatic imines are used, the corresponding aziridines can be reduced at the benzylic carbon to give α-aminophosphonic acids [64].

## Synthesis of phosphonamides

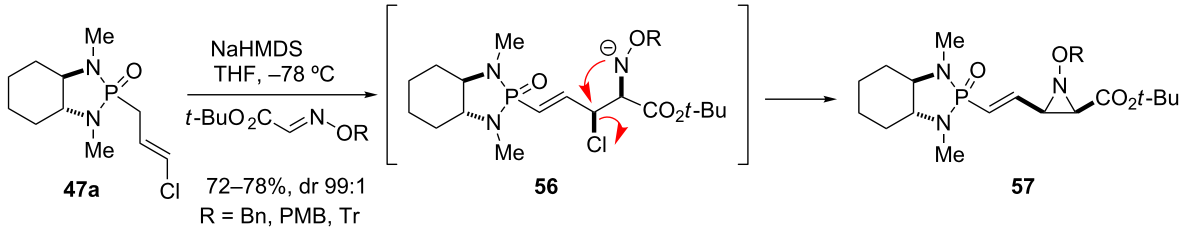
There are four major methods for the synthesis of phosphonamides: (A) Arbuzov reaction, (B) condensation of diamines with phosphonic acid dichlorides, (C) nucleophilic displacement, and (D) alkylation of 2-oxo-1,3,2-diazaphospholidine (Scheme 9). All of these methods were employed to prepare the phosphonamide reagents used in the synthesis of the natural products and bioactive compounds discussed in this review.

### Phosphonamides by Arbuzov reaction

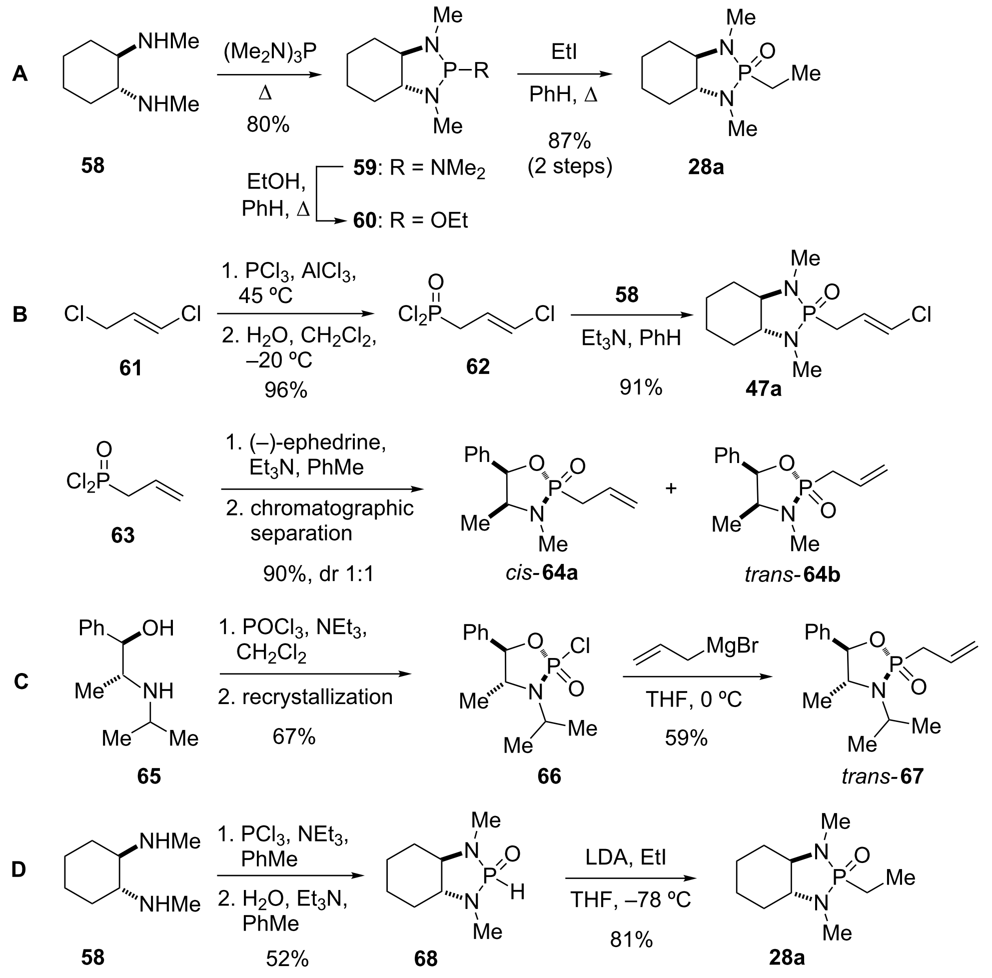
An example for the application of the Arbuzov reaction is the synthesis of phosphonamide (*R,R*)-**28a**. Thus, heating of (*R,R*)-*N,N'*-dimethyl-1,2-diaminocyclohexane (**58**) with hexamethylphosphorus triamide gave the distillable phospholane **59**, which was further converted with ethanol into **60**. Treatment with ethyl iodide in an Arbuzov reaction provided the desired ethyl phosphonamide **28a** (Scheme 9A) [1,30]. Cyclic phosphonamides derived from $C_2$-symmetric diamines such as **28a** do not have a stereogenic P-atom and therefore exist as a single pair of enantiomers. An example for the synthesis of a complex phosphonamide by the Arbuzov reaction can be found in the total synthesis of estrone (**12**) [44], as discussed later in this review.

### Phosphonamides by condensation of diamines with phosphonic acid dichlorides

The most commonly applied method for the synthesis of simple phosphonamides is the condensation of phosphonic acid dichlorides with a diamine. Thus, treatment of acid dichloride **62** with



**Scheme 8:** Stereoselective synthesis of *cis*-aziridines **57** from chiral chloroallyl phosphonamide **47a** [62].



**Scheme 9:** Synthesis of phosphonamides by (A) Arbuzov reaction, (B) condensation of diamines with phosphonic acid dichlorides, (C) nucleophilic displacement, (D) alkylation of phosphorus acid diamides [1,5,6,28,30,51,69].

*(R,R)-N,N'*-dimethyl-1,2-diaminocyclohexane (**58**) afforded cyclopropanation reagent **47a** [28,51]. The required phosphonic acid dichlorides can be obtained either from chlorination of phosphonic acids [65,66] or from treatment of an allyl chloride such as **61** with phosphorus trichloride followed by hydrolysis to give **62** [15,67]. Reactions of unsymmetrical amines or aminoalcohols such as ephedrine with phosphonic acid dichlorides result in the generation of a stereogenic center at the P-atom and thus to diastereomeric phosphonamides *cis*-**64a** and *trans*-**64b**, which typically can be separated by chromatography [5].

Cyclopropanation reagent **47a** was used in the total synthesis of anthoplalone (**8**) [56] and ambruticin S (**14**) [28], whereas an unsymmetrical phosphonamide of type **64** was used in the synthesis of PTP inhibitors [68], and methyl jasmonate [48], as discussed later in this review.

## Nucleophilic displacement

The stereoselective synthesis of unsymmetrical phosphonamides **67** by nucleophilic displacement was reported by Hua and co-workers [6]. Treatment of aminoalcohol **65** with phosphoryl chloride provided **66** as a mixture of diastereomers (dr 93:7), from which pure **66** was obtained by recrystallization. Chloride displacement at phosphorus with allylmagnesium bromide proceeded with retention of configuration to give allyl phosphonamide **67**. A similar displacement reaction was used to generate a phosphonamide reagent in the synthesis of squalene synthase inhibitors [36] and is discussed later in this review.

## Phosphonamides by alkylation of phosphorus acid diamides

Spilling and co-workers reported the preparation of alkyl phosphonamides through alkylation of bicyclic phosphite anions [69-71]. Thus, condensation of diamine **58** with phosphorus trichloride followed by hydrolysis of the formed 2-chloro-1,3,2-diazaphospholidine with one equivalent of water gave phosphorus acid diamide **68**. The latter could be deprotonated with LDA at low temperature and alkylated to give phosphonamide **28a**. Spilling's alkylation methodology was used in the total synthesis of jerangolid A (**22**) [27] and ambruticin S (**14**) [28].

## Application in total synthesis

### Polyoximic acid (1993)

Polyoximic acid (**9**) is a unique amino acid that occurs only as a component of polyoxins A, F, H, and K, which exhibit antibiotic properties [72]. Originally, the stereochemistry of the exocyclic double bond of polyoximic acid was incorrectly assigned as *E* based on a low resolution nOe experiment (Figure 3). The total synthesis of polyoximic acid (**9**) by Hanessian and co-workers led to a reassignment of its structure and that of the parent molecules, such as polyoxin A (**69**) [24-26].

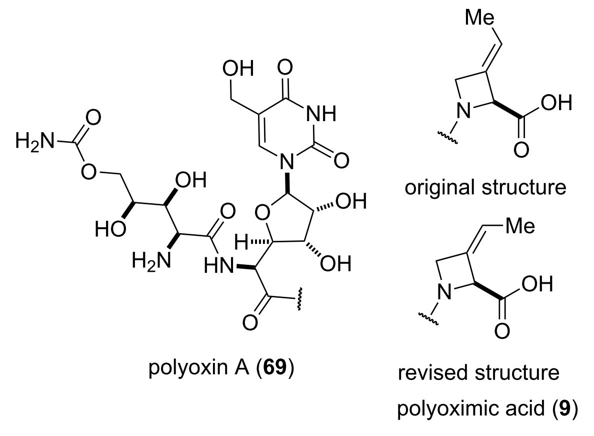
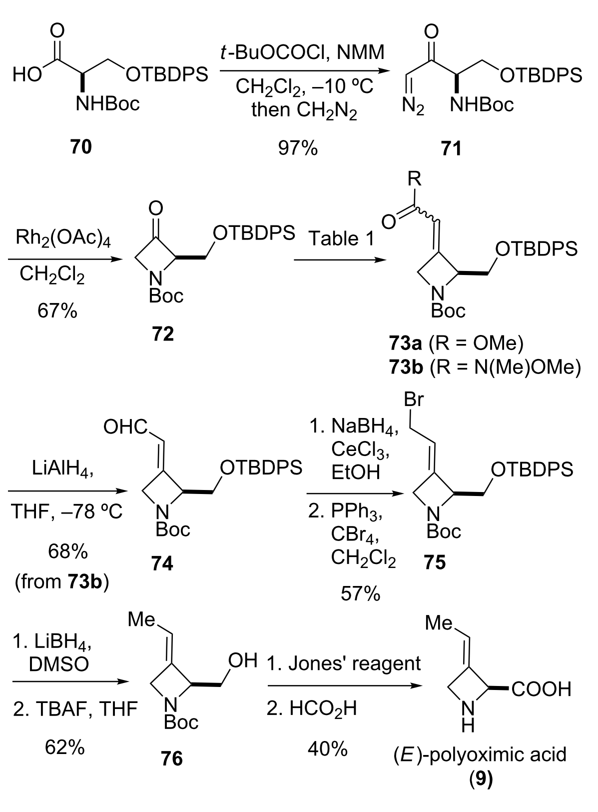


**Figure 3:** Original and revised structure of polyoxin A (**69**) [24-26].

The synthesis of the *E*-isomer of polyoximic acid started from protected D-serine **70**, which was converted into diazoketone **71** by reacting a mixed anhydride with diazomethane (Scheme 10). Azetidinone **72** was then formed through a rhodium-catalyzed intramolecular carbenoid insertion into the N–H bond as the first pivotal step of the synthesis. The next key step was to introduce the exocyclic double bond with control of the stereochemistry of the double bond. For that purpose, a variety of 'typical' Wittig and Horner–Wadsworth–Emmons reagents were screened. In addition, cyclic phosphonamides were utilized as olefination reagents (Table 1).

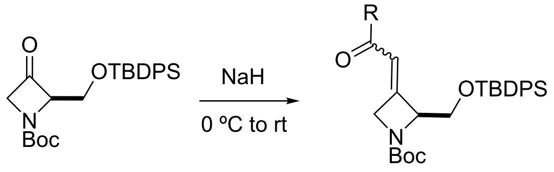


**Scheme 10:** Synthesis of (*E*)-polyoximic acid (**9**) [24-26].

Employing phosphonamides **24e** and **77** in the olefination of **72** favored the formation of the desired *E*-isomer of **73a**, however the mixture of isomers was inseparable by normal chromatographic methods. The chiral backbone of **77** had a beneficial effect on the stereoselectivity of the olefination, with an improved *E*/*Z* ratio of 91:9 compared to the achiral analogue **24e** (Table 1, entries 1 and 2). Employing phosphonate-Weinreb amide **78** and phosphonamide-Weinreb amide **79** not only afforded good *E*/*Z* ratios of 87:13 to 88:12 of **73b** but also provided a product that could now be separated by column chromatography (Table 1, entries 3 and 4). Reduction of amide *E*-**73b** by $LiAlH_4$ to aldehyde **74** and further reduction under Luche conditions delivered an allylic alcohol, which was then converted into bromide **75**. Debromination and cleavage of the TBDPS protecting group gave protected amino-alcohol **76**. Finally, Jones oxidation and removal of the *N*-Boc protecting group produced crystalline (*E*)-polyoximic acid (*E*-**9**), whose structure was unambiguously confirmed by X-ray analysis. A comparison of the NMR spectrum of *E*-**9** with an authentic sample of natural polyoximic acid led to the conclusion that the natural product contains a *Z*-double bond, contrary to the original assignment (Figure 3).

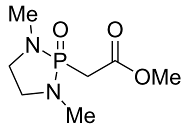
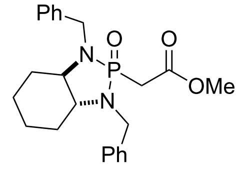
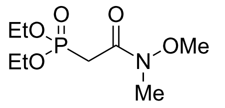
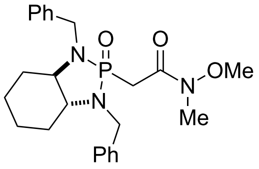
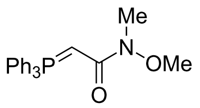
The synthesis of *Z*-polyoximic acid (*Z*-**9**) was eventually achieved through a similar sequence as shown in Scheme 10. Replacing phosphonamide **79** with Wittig-reagent **80** as olefinating reagent gave a separable *E*/*Z* mixture in a ratio of 1:9 in favor of the desired *Z*-isomer of **73b** (Table 1, entry 5). The

**Table 1:** Horner–Wadsworth–Emmons olefination of ketone **72** [26].



**72**

**73a** (R = OMe)
**73b** (R = N(Me)OMe)

| Entry | Reagent | Solvent | Product | Yield (%) | *E*/*Z* |
|---|---|---|---|---|---|
| 1 |  **24e** | THF | **73a** | 71 | 80:20 |
| 2 |  **77** | THF | **73a** | 62 | 91:9 |
| 3 |  **78** | DME | **73b** | 61 | 87:13 |
| 4 |  **79** | THF | **73b** | 83 | 88:12 |
| 5[a] |  **80** | MeOH | **73b** | 73 | 10:90 |

[a]Without NaH, at −78 °C.

latter was then transformed into *Z*-**9** in an analogous fashion as described for the *E*-isomer. Comparison of the spectroscopic and physical data of synthetic *Z*-**9** with the amino acid derived from the natural product confirmed the revised structure of the latter [24-26,73].

## Acetoxycrenulide (1995)

The marine toxin acetoxycrenulide (**10**) was isolated independently from small brown seaweed of the family *Dictyotaceae* and from the sea hare [74,75]. Paquette and co-workers reported the first and only total synthesis of this diterpene (Figure 4) [41,42]. The cyclooctanoid core of the target was envisioned to be formed by a Claisen rearrangement of intermediate **81**. The latter and most of its stereocenters would originate from lactone **82**, which in turn is the product of a conjugate addition of chiral allyl phosphonamide reagent **28c** to butenolide **83** prepared from (*R*)-citronellol. The correct installation of the stereocenters of **82** was crucial to the success of the synthesis, as they would form a template for the stereocontrolled incorporation of the remaining stereocenters.

The construction of butenolide **83** started from (*R*)-citronellol (**84**), which could in principle, deliver the entire alkenyl side chain of acetoxycrenulide (**10**) (Scheme 11). However, the

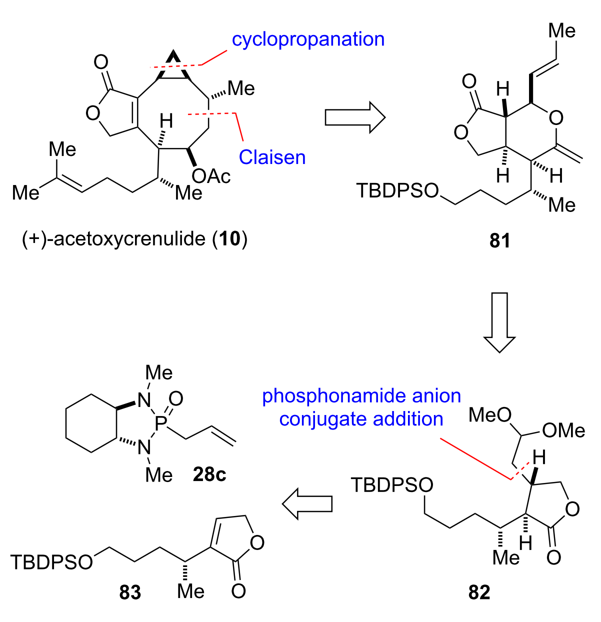


**Figure 4:** Key assembly strategy of acetoxycrenulide (**10**) [41,42].

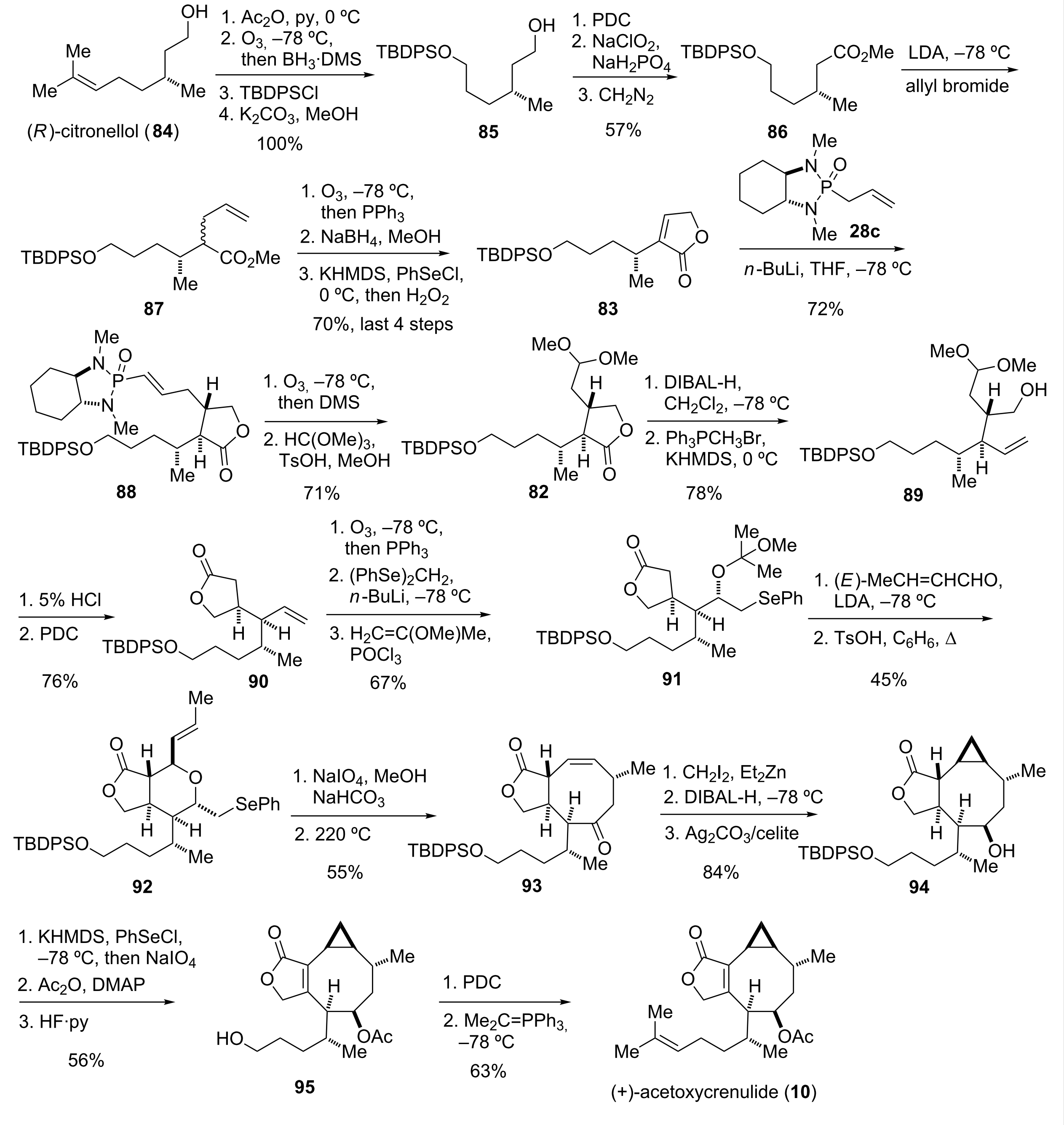
double bond needed to be transformed into a TBDPS ether as it would not survive the late-stage cyclopropanation (Figure 4). Thus, protection of the primary alcohol as acetate, ozonolysis with reductive work-up, treatment with TBDPSCl and ensuing hydrolytic removal of the acetate yielded mono-protected diol **85**. Conversion into methyl ester **86** by a three-step procedure and subsequent alkylation with allyl bromide gave alkene **87**. Ozonolysis with reductive work-up was followed by spontaneous cyclization to the corresponding γ-lactone, which was then transformed into **83** by means of α-selenenylation, oxidation, and elimination (Scheme 11).

With butenolide **83** in hand the stage was set for one of the key steps of the synthesis. Addition of the anion of phosphonamide **28c** to **83** proceeded with a high level of facial and *cis*/*trans*-selectivity to afford adduct **88** as a single diastereomer with the correct stereochemistry. Removal of the chiral auxiliary by ozonolysis, protection of the resulting aldehyde, reduction of the lactone ring to the lactol, and treatment with methylenetriphenylphosphorane delivered **89**. Mild acidic hydrolysis of the acetal followed by oxidation then yielded **90** with the γ-lactone unit that constitutes ring A of acetoxycrenulide. Cleavage of the double bond by ozonolysis and addition of (phenylseleno)methyllithium followed by protection of the formed hydroxy group provided **91** as a single diastereomer. Condensation of **91** with (*E*)-crotonaldehyde and heating of the obtained aldol adduct with catalytic amount of acid formed tetrahydropyran **92** as key intermediate of the synthesis. Oxidation of **92** and heating to 220 °C resulted in a concurrent selenoxide elimination and Claisen rearrangement to give **93** via intermediate **81**. Face-selective Simmons–Smith cyclopropanation, reduction of both carbonyl groups, and chemoselective oxidation of the formed lactol with Fetizon’s reagent afforded **94**. The final steps of the synthesis involved conversion to the corresponding α,β-unsaturated lactone **95** and modification of the side chain to re-build the original double bond to eventually give (+)-acetoxycrenulide (**10**) [41,42].

## Squalene synthase inhibitor (1996)

Inhibitors of squalene synthase have sparked interest as selective cholesterol lowering agents [76,77]. The enzyme is involved in the first committed step in the cholesterol synthesis and catalyses the conversion of two molecules of farnesyl diphosphate into squalene, which is later converted exclusively into various sterols, such as cholesterol, by a multi-step pathway [78]. The α-phosphono sulfonate **19** was found to be a potent inhibitor of squalene synthase, however, only the racemic version was originally tested. Biller and co-workers designed an enantioselective synthesis of **19** based on an asymmetric sulfuration (route A) or asymmetric alkylation (route B) of a chiral phosphorus carbanion (Scheme 12) [36]. Deprotonation of (*R*,*R*)-**28a** and alkylation with 3-(3’-phenoxyphenyl)-propyl iodide (**96**) gave **97**. Sulfuration of the Li anion of **97** with tetramethylthiuram disulfide provided the adduct as a 3:1 mixture of diastereomers, with **98** as the major isomer. The low diastereoselectivity observed for the sulfuration as compared to that reported for the alkylation of phosphonamides similar to **97** was explained with a longer C–S bond in the transition state and the steric hindrance sensed by a thiuram relative to an alkyl halide. Further support for this theory comes from a control experiment, in which **97** was alkylated under the same conditions with benzyl bromide, leading to a 10:1 mixture of diastereomers. The pure diastereomer **98** was then hydrolyzed with mild acid to remove the chiral auxiliary and oxidized to diacid **99**. Converison into its potassium salt yielded squalene synthase inhibitor (*S*)-**19**. In a similar sequence, the minor diastereomer from the sulfuration, 1-*epi* **98**, was converted into the opposite enantiomer (*R*)-**19** (Scheme 12A).

Reversing the steps for the introduction of the alkyl chain and the sulfonate moiety with the aim to achieve better selectivity led to route B (Scheme 12B). Thus, treatment of **100**, obtained from (*R*,*R*)-*N*,*N*’-dimethyl-1,2-diaminocyclohexane and phosphoryl chloride, with the anion generated from ethyl methanesulfonate followed by cleavage of the ethyl sulfonate gave tetrabutylammonium salt **101**. Deprotonation of **101** followed by reaction of the dianion with 3-(3’-phenoxyphenyl)propyl iodide (**96**) provided adduct **102** with excellent selectivity (dr >20:1). Removal of the chiral auxiliary and purification by cation exchange finally afforded (*S*)-**19**.

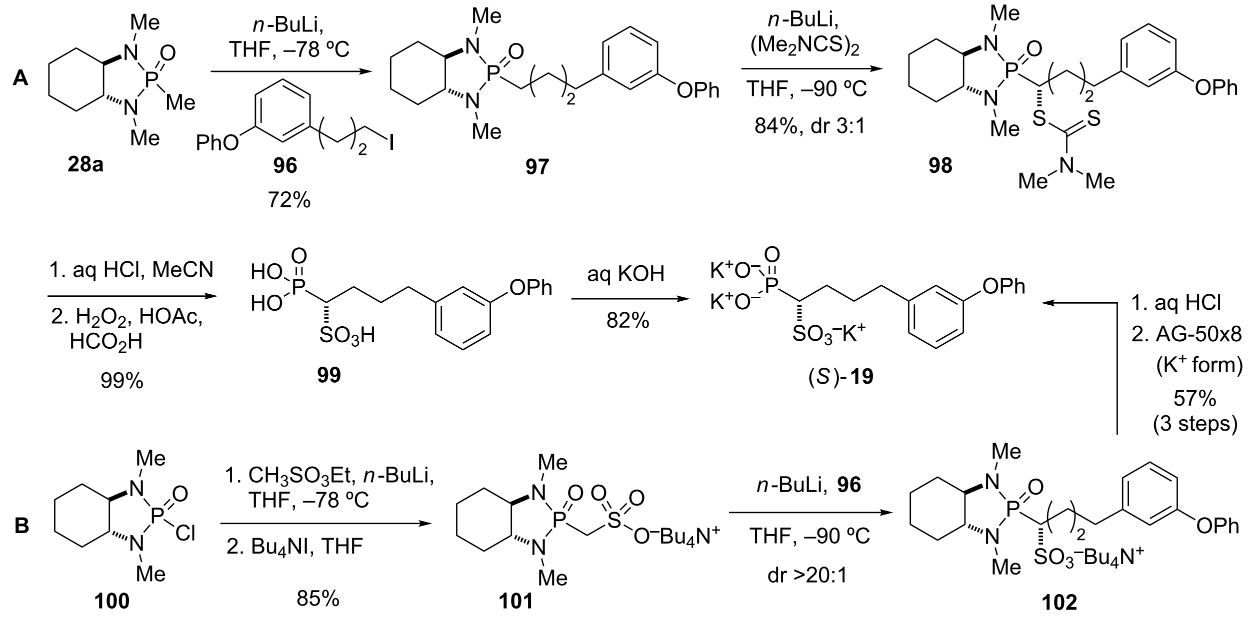


**Scheme 11:** Total synthesis of (+)-acetoxycrenulide (**10**) [41,42].

Both enantiomers of **19** were tested in *in vitro* assays for their ability to inhibit squalene synthase. Enantiomer (*S*)-**19** was found to be 16-fold more potent than the (*R*)-enantiomer, with $IC_{50}$ values of 68 and 1120 nM, respectively [36].

## Fumonisin $B_2$ (1997)

Fumonisin $B_2$ (**20**) belongs to the family of fumonisin mycotoxins produced by fungi of the genus *Fusarium*, a common grain mold. It is a close structural analogue of fumonisin $B_1$, the most prevalent member of the family of fumonisins [79,80]. Fumonisin $B_1$, $B_2$ and other fumonisins frequently contaminate maize and other crops [81-83]. Kishi and co-workers adopted a convergent approach to fumonisin $B_2$, with the molecule being cleaved into three main fragments **103–105** [45,46]. The connection of **103** and **104** under formation of the fumonisin backbone would employ a Wittig reaction, followed by attach-



**Scheme 12:** Synthesis squalene synthase inhibitor **19** by asymmetric sulfuration (A) and asymmetric alkylation (B) of a phosphonamide anion [36].

ment of two molecules of tricarballylic acid (**105**). The latter fragment would be accessed by conjugate addition of the anion of phosphonamide **28c** to *tert*-butyl sorbate (**106**) to give intermediate **107** followed by oxidative cleavage of the chiral auxiliary (Figure 5 and Scheme 13).

The preparation of **107** was performed as previously reported with minor modifications (Scheme 13) [37]. Thus, addition of the Li anion of **28c** to *tert*-butyl sorbate (**106**) afforded adduct **107** with excellent diastereoselectivity. Cleavage of both double bonds by ozonolysis followed by oxidative work-up with Jones' reagent provided a monoprotected tricarballylic acid intermediate. Conversion of the free carboxylic acid moieties into their benzyl esters followed by cleavage of the *tert*-butyl ester gave **108**. This fragment was then coupled with diol **109** to afford the fully protected fumonisin $B_2$ precursor **110**. Final hydrogenation and hydrogenolysis of all eight benzyl protecting groups was accomplished using Pearlman's catalyst under mild acidic conditions to give fumonisin $B_2$ (**20**) [45-47,84].

## Tricylic β-lactams (1997)

β-Lactam antibiotics are the most prescribed and successful class of antibiotics developed and used in clinical practice. This broad class of antibiotics shares a highly reactive four-membered β-lactam ring and includes penicillin derivatives, cephalosporins, monobactams, carbapenems, and other related compounds [85-87]. Approved drugs such as imipenem (**111**) and meropenem (**112**) (Figure 6) belong to the subclass of carbapenems, which are powerful antibiotics with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and are often used as antibiotics for many hard-to-treat bacterial infections, such as *Escherichia coli* and *Klebsiella pneumoniae* [88,89]. Resistance of bacterial strains to antibi-

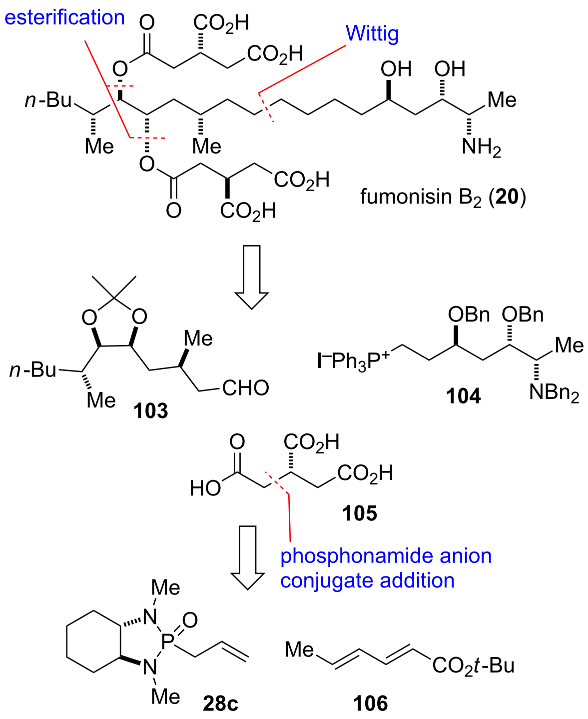
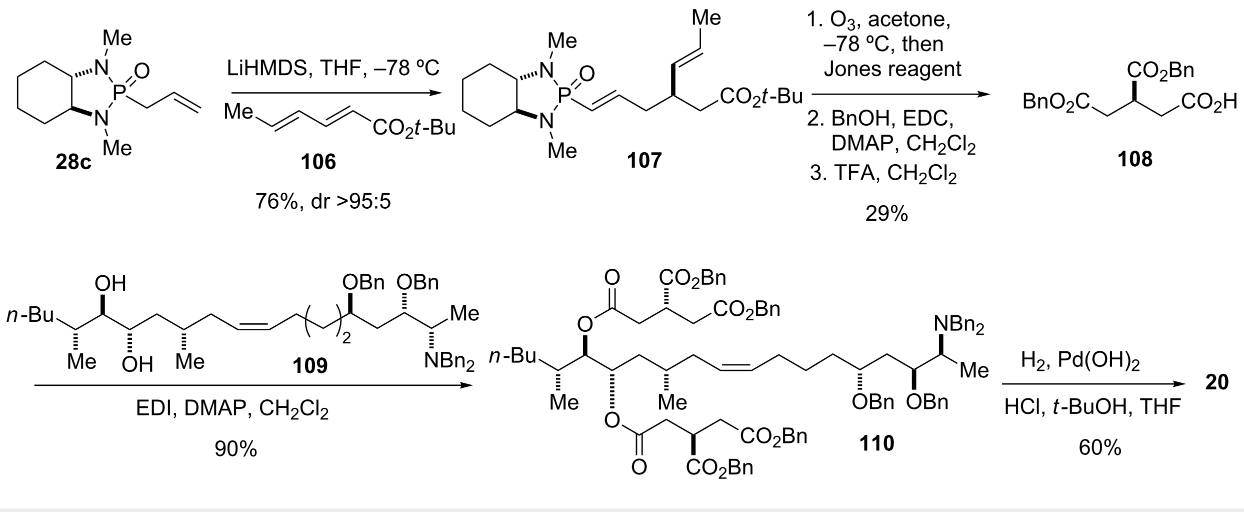


**Figure 5:** Key assembly strategy of fumonisin $B_2$ (**20**) and its tricarballylic acid fragment **105** [45,46].



**Scheme 13:** Final steps of the total synthesis of fumonisin $B_2$ (**20**) [45,46].

otics has dictated the need for continuous development of existing and discovery of new antibiotics ever since the introduction of the first antibacterial agents in the first half of the 20th century. In recent years, this trend has become a serious threat for public health with the emergence of carbapenem-resistant enterobacteriaceae such as *Klebsiella pneumoniae* [90,91].

In the 1990's, scientists at GlaxoWellcome developed sanfetrinem (**113**), a member of a novel class of tricyclic β-lactam antibiotics known as trinems [92,93]. Eventually the development of sanfetrinem was stopped in 2009 after phase II clinical trials [86], but the compound inspired others to study its structural variants. Hanessian and co-workers reported on the synthesis of analogs of sanfetrinem (**113**) [94-96], including the 5α-hydroxyethyltrinems **23a**,**b** (Figure 6) [97], as well as a total synthesis of sanfetrinem (**113**) [96].

The installation of the two-carbon side chain of **23** was achieved through a stereoselective conjugate addition of a phosphonamide allyl anion to an advanced intermediate (Scheme 14). The latter was constructed in four steps starting from cyclohexenone (**41b**). Thus, addition of the Li salt of **41b** to allyl diethylphosphonoformate (**114**) afforded β-ketoester **115**, which in turn was condensed with commercially available azetidinone **116** to give **117** as a mixture of diastereomers. Protection of the nitrogen with TBS triflate followed by deprotection of the allyl carboxylate with formic acid under palladium catalysis and subsequent decarboxylation yielded enone **118** as a single diastereomer.

Addition of the Li anion of phosphonamide **24c** to enone **118** afforded adduct **119** as a single isomer, with the attack occurring to the less hindered face of the enone. Further elaboration of the side chain was achieved by ozonolysis to give an aldehyde, selective reduction of the latter with 9-BBN, and protection of the obtained primary alcohol as its TBS ether. *N*-Deprotection to give **120** was followed by acylation with benzyloxalyl chloride and treatment with triethylphosphite at elevated temperature to yield tricyclic intermediate **121**. Cleavage of the TBS ethers and hydrogenolysis of the benzyl ester in presence of amidine **122** yielded trinem **23a** as its amidinium salt **123**.

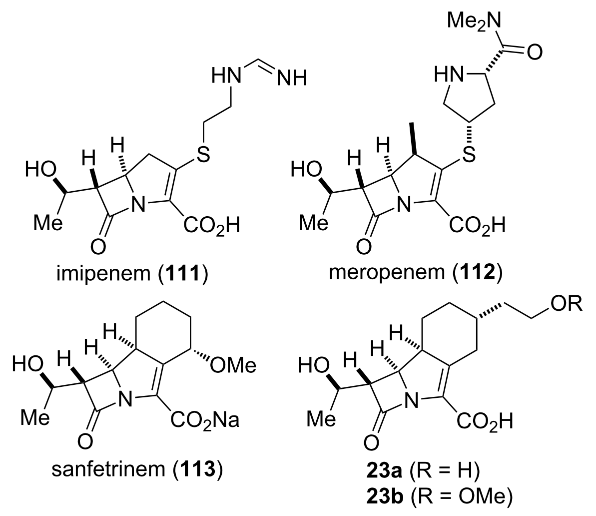
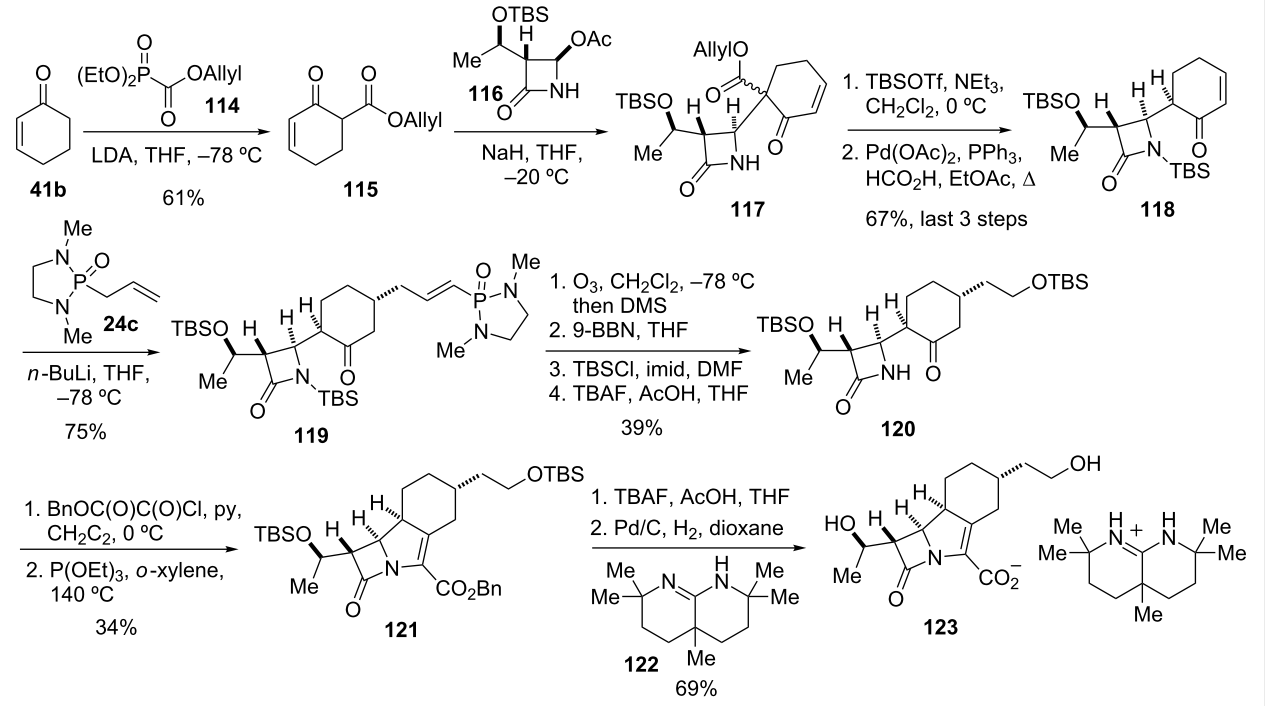


**Figure 6:** Selected examples of two subclasses of β-lactam antibiotics – carbapenems (**111** and **112**) and trinems (**113** and **23**).

Trinem **123** exhibited antibacterial activity against a variety of strains, with MIC's of 1.0 µg/mL against *Staphylococcus aureus* 853E and 0.1 µg/mL against *Streptococcus pneumoniae* 3512. The antibacterial activity of **123** was considerably weaker



**Scheme 14:** Synthesis of tricyclic β-lactam antibiotic **123** [97].

compared to imipenem (**111**) and sanfetrinem (**113**), which showed MIC's of 0.06 and 0.2 µg/mL, respectively, against *S. aureus* and 0.01 µg/mL against *S. pneumoniae*. The lack of potency of **123** was attributed in part to the missing α-orientated 4-alkoxy substituent present in sanfetrinem (**113**), which may act as a potential leaving group and appears to be crucial for activity [97].

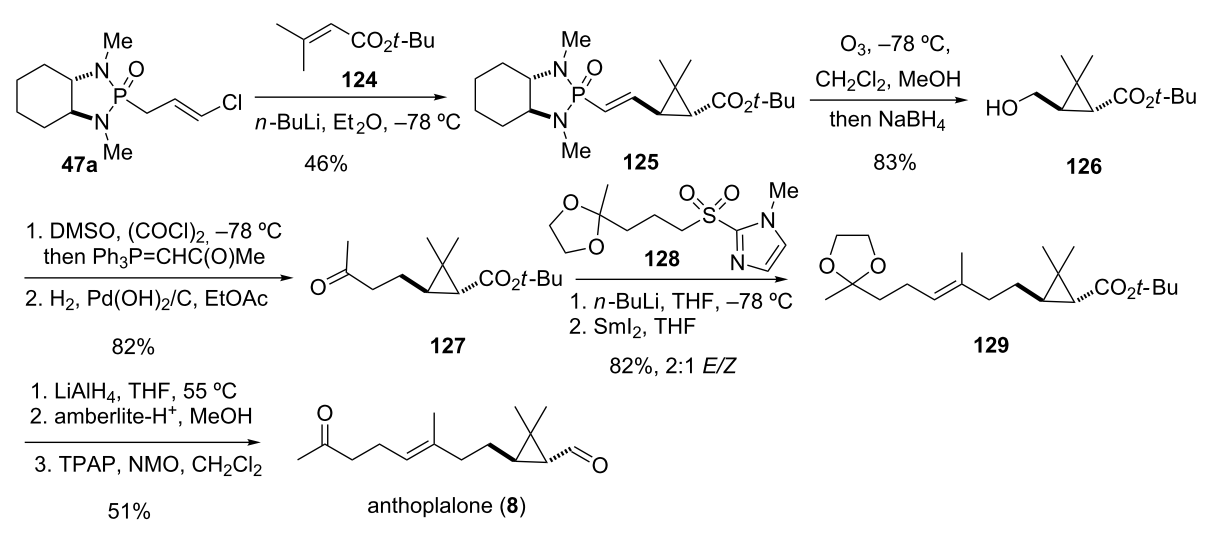
## Anthoplalone (1999)

Isolated from the Okinawan actinian *Anthopleura pacifica,* anthoplalone (**8**) is a secosesquiterpene with a tetrasubstituted *trans*-cyclopropane subunit. The compound shows modest cytotoxic activity against murine melanoma cells [98,99]. The first enantioselective total synthesis of anthoplalone was achieved by Hanessian and co-workers and utilized their chloroallyl phosphonamide anion cyclopropanation methodology [56]. Thus, deprotonation of **47a** with butyllithium at low temperature and addition to *tert*-butyl 3,3-dimethylacrylate (**124**) provided adduct **125** as a single diastereomer (Scheme 15). Removal of the chiral auxiliary by ozonolysis and subsequent reduction afforded alcohol **126**. Chain extension was accomplished through a one-pot Swern oxidation/Wittig olefination protocol followed by hydrogenation to give ketone **127**. For further extension of the carbon chain and installation of the trisubstituted double bond, a modified Julia olefination with imidazole sulfone **128** was employed [100-102]. Thus, reaction of ketone **127** with the lithium anion of sulfone **128** and treatment of the obtained β-hydroxysulfone with $SmI_2$ led to olefin **129** as a 2:1 mixture of *E/Z*-isomers. After reduction of the *tert*-butyl ester to the primary alcohol, the *E/Z*-isomers could be separated chromatographically. Cleavage of the ketal under acidic conditions to reveal the ketone moiety and final oxidation of the primary alcohol with tetrapropylammonium perruthenate (TPAP) completed the first enantioselective total synthesis of anthoplalone (**8**) and confirmed the absolute configuration of the natural product [56,103,104].

## PTP inhibitors (2000)

Protein tyrosine phosphatases (PTPs) are part of a superfamily of enzymes that catalyze protein tyrosine dephosphorylation. They are key regulators in various, crucial kinase-dependent signal transduction pathways and act to counterbalance the kinases. In particular, PTP1B has attracted considerable attention for its role in the complex insulin-signaling pathway. It has been shown that overexpression of PTP1B contributes to diabetes and obesity [105,106]. Therefore, inhibititors of PTP1B may have potential as treatment for type-2 diabetes [107-110].

Hydrolytically-stable phosphotyrosyl mimetics have been developed as PTP1B inhibitors, including molecules such as **131** containing an α,α-difluoromethylenephosphonic (DFMP) moiety (Figure 7). In particular, peptides bearing a phosphonodifluoromethylphenylalanine ($F_2Pmp$) group such as **130** have



**Scheme 15:** Total synthesis of (−)-anthoplalone (**8**) [56].

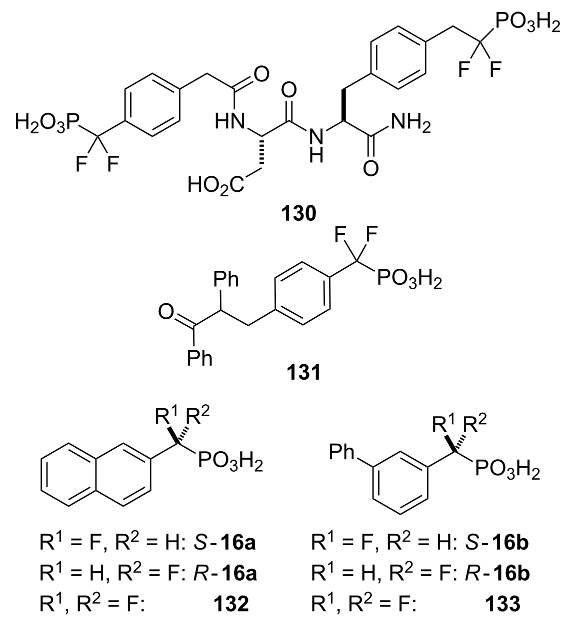


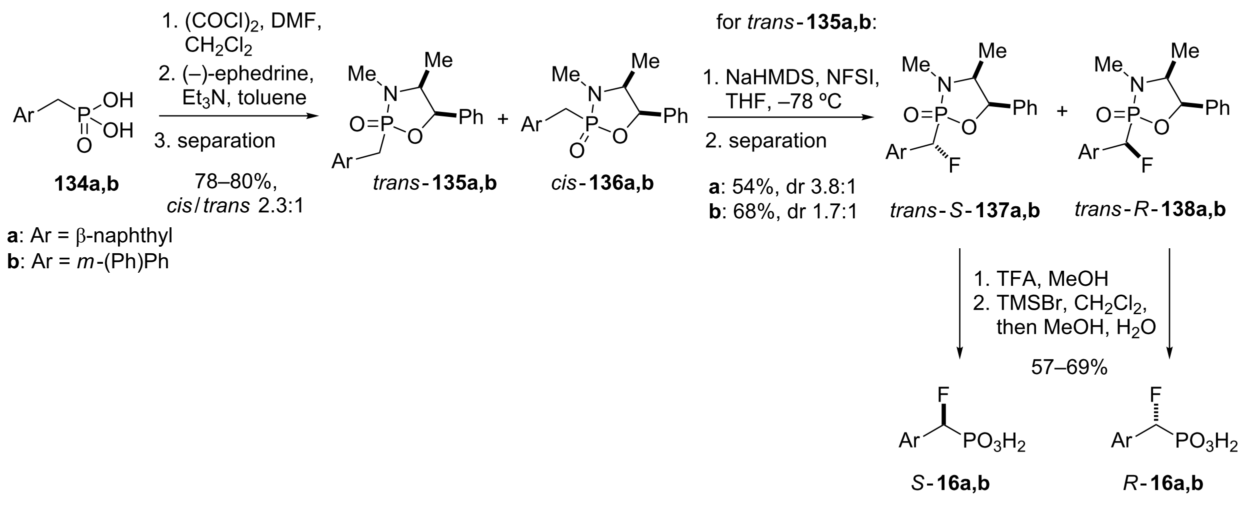
**Figure 7:** Protein tyrosine phosphatase (PTP) inhibitors **130**, **131** and model compounds **16**, **132** and **133** [68].

been shown to be among the most potent inhibitors with nanomolar potency against PTP1B [110,111].

Taylor and co-workers were interested to study α-monofluoroalkylphosphonic acids as PTP1B inhibitors in comparison to their difluoro analogues and compounds **16a,b** and **132**,**133** were chosen as model PTP1B inhibitors [68]. The enantiopure α-monofluoroalkylphosphonic acids were synthesized by diastereoselective fluorination of phosphonamides bearing (−)-ephedrine as chiral auxiliary, originally introduced by Sting and Steglich for the synthesis of aminoalkylphosphonic acids [7] (Scheme 16). Thus, condensation of the phosphonic acid dichloride obtained from **134a,b** with ephedrine yielded a separable mixture of diastereomeric phosphonamides, *trans*-**135a,b** and *cis*-**136a,b**. The fluorination with *N*-fluorobenzenesulfonimide (NFSI) of either *trans*-**135a** or *cis*-**136a** was found to be strongly dependant on the base used to generate the phosphonamidate anion. The best diastereomeric ratio of 3.8:1 (58% de) in favor of *trans*-*S*-**137a** was observed with NaHMDS as base in the reaction of *trans*-**135a**. The *cis*-isomer **136a** gave a similar result with NaHMDS, whereas the fluorination of *m*-(phenyl)benzyl phosphonamides **135b** and **136b** proved to be less selective. Although the diastereoselectivity was modest at best, the fluorinated products *trans*-*S*-**137a,b** and *trans*-*R*-**138a,b** could be readily separated by chromatography. Higher selectivities of up to 70% de were achieved in the fluorination step when *trans*-(*R*,*R*)-*N*,*N*'-dimethyl-1,2-diaminocyclohexane (**58**) was employed as chiral auxiliary, however, the diastereomeric products were not separable by chromatographic means.

Cleavage of the ephedrine auxiliary was accomplished by a three-step protocol. Treatment of **137a,b** and **138a,b** with trifluoroacetic acid in methanol followed by reaction with TMSBr and subsequent hydrolysis of the TMS ester gave the free acids (*S*)-**16a,b** and (*R*)-**16a,b**, respectively as pure enantiomers.

Compounds **16a,b**, **132** and **133** were found to be inhibitors of PTP1B. The monofluoro (*R*)-enantiomers *R*-**16a** ($IC_{50}$ 675 μM) and *R*-**16b** (315 μM) were about 10-fold more potent than the corresponding (*S*)-enantiomers ($IC_{50}$ 7500 μM and 3500 μM for *S*-**16a** and *S*-**16b**, respectively), but 10-fold less potent than the difluoro analogues **132** and **133** ($IC_{50}$ 71 μM and 33 μM,



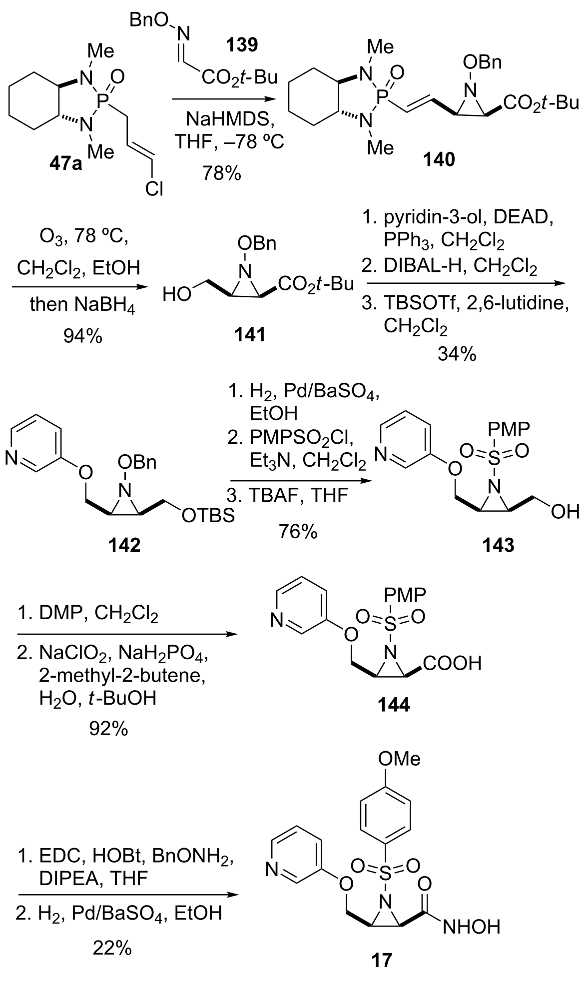
**Scheme 16:** Synthesis of model PTP inhibitors **16a,b** [68].

respectively). The inhibition studies indicated that the pro-*S* fluorine in difluoro inhibitors **132** and **133** is essential for good inhibition, although the pro-*R* fluorine contributes significantly more towards PTP1B affinity [68].

## MMP inhibitors (2001)

The matrix metalloproteinases (MMPs) are a family of structurally-related, zinc-containing enzymes that play a critical role in the degradation and remodelling of extracellular matrix. Over expression of MMPs has been associated with various physiological and pathological processes such as morphogenesis, angiogenesis, tissue repair, cirrhosis, arthritis, and metastasis, thus raising the possibility that inhibitors of these enzymes may possess therapeutic potential [112,113].

As part of studies on conformationally constrained MMP inhibitors by Hanessian and co-workers, *trans*- and *cis*-aziridines scaffolds were used as peptidomimetics to construct a series of hydroxamic acids analogs such as **17** (Scheme 17) [63]. While the *trans*-aziridines were prepared by conjugate addition of *O*-benzylhydroxylamine to α,β-unsaturated amides bearing a chiral oxazolidinone auxiliary, facile access to the *cis*-aziridine series was possible by using chiral chloroallyl phosphonamide **47a**. Thus, the addition of the anion of **47a** to *tert*-butylglyoxylate *O*-benzylamine (**139**) led to aziridine **140** as a single diastereomer. Ozonolysis followed by reductive work-up provided alcohol **141.** Coupling under Mitsunobu conditions with an appropriate alcohol, e.g., 3-hydroxypyridine, reduction of the *tert*-butyl ester with DIBAL-H, and treatment with TBS triflate gave silyl ether **142**. Hydrogenolysis of **142** using Pd/BaSO$_4$ produced the free aziridine, which was then converted to the corresponding sulfonamide with *para*-methoxyphenyl (PMP)



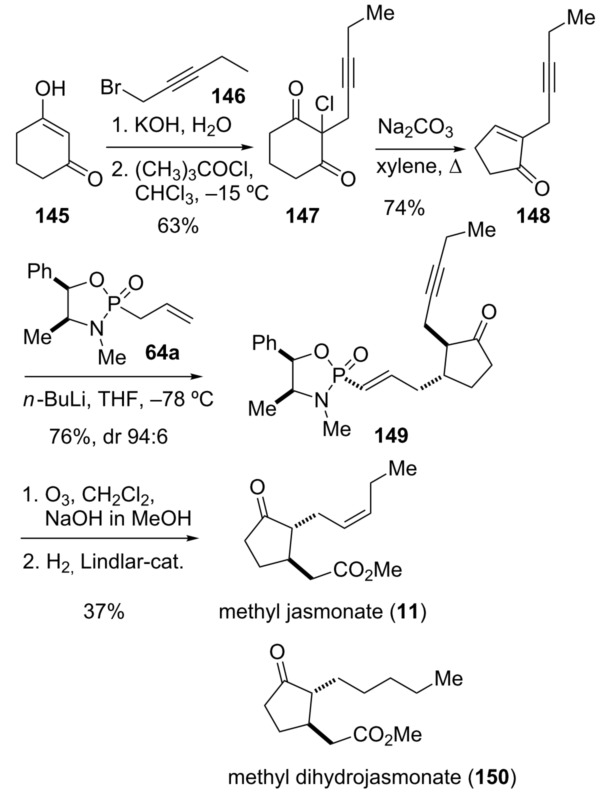
**Scheme 17:** Synthesis of aziridine hydroxamic acid **17** as MMP inhibitor [63].

sulfonyl chloride. Cleavage of the silyl ether moiety with TBAF gave primary alcohol **143**, which was oxidized to the corresponding acid **144** by a two-step protocol consisting of treatment with Dess–Martin periodinane followed by Pinnick oxidation. Hydroxamic acid **17** was then obtained by coupling with *O*-benzylhydroxylamine followed by hydrogenolysis.

The *cis*-aziridine hydroxamic acid **17** showed good inhibitory activity against several matrix metalloproteinases, in particular MMP-3 and MMP-9, with $IC_{50}$'s of 164 nM and 83 nM, respectively [63].

### Methyl jasmonates and dihydrojasmonates (2001)

The jasmonates, which comprise of methyl jasmonate (**11**) and the corresponding jasmonic acid, are important cellular regulators in plants. They participate in various developmental processes and defence mechanisms against biotic and abiotic stresses [114]. Originally isolated from *Jasminum grandiflorum*, the plant scent methyl jasmonate has found to be distributed ubiquitously in the plant kingdom. The unnatural analogue methyl dihydrojasmonate (**150**) possesses important olfactory properties and has become a major aroma chemical with a wide range of uses, mainly in fragrances (Scheme 18).



**Scheme 18:** Synthesis of methyl jasmonate (**11**) [48].

Hailes and co-workers were interested in developing a short synthetic route to both enantiomers of methyl jasmonate and methyl dihydrojasmonate, respectively [48]. To this end, they investigated the conjugate addition of chiral 2-propenylphosphonamides such as **64a**, derived from (1*R*,2*S*)-ephedrine, to α-substituted cyclopentenones. The required precursor for the synthesis of methyl jasmonate (**11**), 2-(2-pentynyl)-2-cyclopentene-1-one (**148**) was prepared by a known sequence [115] starting from 1,3-cyclohexanedione (**145**) (Scheme 18). Addition to 1-bromo-2-pentyne (**146**) followed by chlorination gave chlorodiketone **147**. The latter was then treated with sodium carbonate in boiling xylene to afford cyclopentenone **148**, presumably via decarbonylation of a cyclopropanone intermediate. Addition of the lithium anion of chiral phosphonamide **64a** at low temperature produced adduct **149** in good yield and diastereoselectivity. Cleavage of the phosphonamide auxiliary from **149** was achieved by ozonolysis in the presence of sodium hydroxide and methanol to give the corresponding methyl ester. The final reduction of the alkyne was carried out using the Lindlar catalyst to yield methyl jasmonate (**11**). Methyl dihydrojasmonate (**150**) was also synthesized using phosphonamide reagent **64a**, while replacing **148** with commercially available 2-pentyl-2-cyclopenten-1-one [48].

### Nudiflosides A and D (2006)

Extracts from *Jasminum nudiflorum* have been used as folk medicine in China for the treatment of inflammation and traumatic bleeding. The leaves and stems of this plant contain oleoside-type secoiridoid glucosides with structurally interesting tetrasubstituted cyclopentanoid monoterpene units [116]. Two representative examples of these glycosides are nudifloside A (**151**) and D (**13**), which share a common subunit (Figure 8) [116-118]. The first total synthesis of nudiflosides A and D was achieved by Hanessian and co-workers, which aimed at

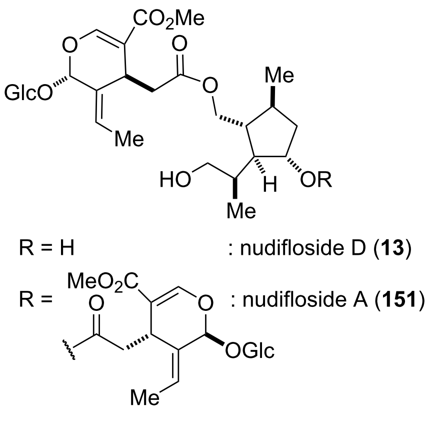


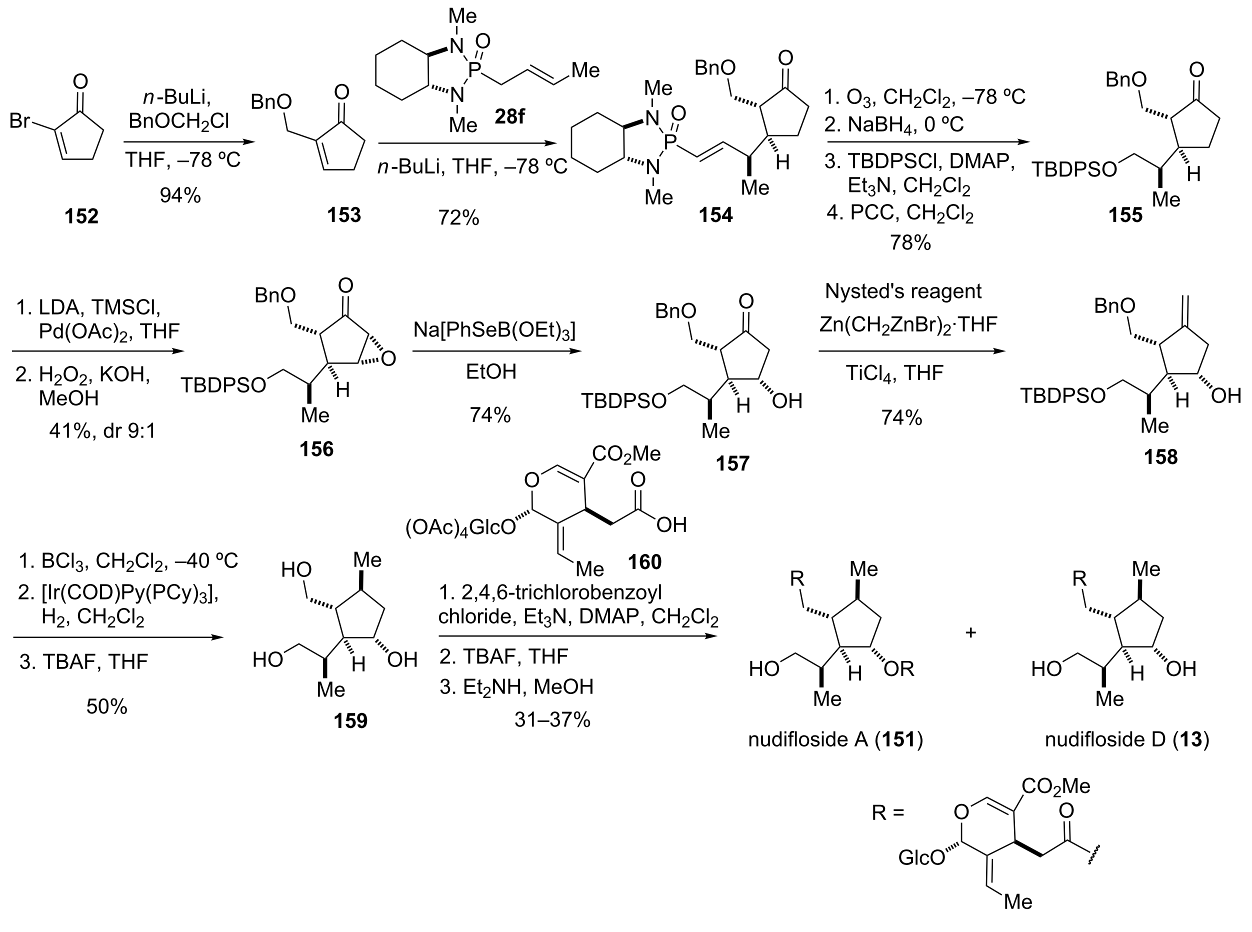
**Figure 8:** Structures of nudiflosides A (**137**) and D (**13**) [49].

confirming their proposed structural and stereochemical assignment (Scheme 19) [49].

The correct installation of the stereocenters of the cyclopentane subunit **159** was dependent on the stereocontrolled Michael addition of the anion generated from crotyl phosphonamide **28f**, which set three contiguous stereocenters in one step. Thus, addition of the Li anion of **28f** to cyclopentenone **153** gave adduct **154** as a single diastereomer on a gram scale. Cleavage of the chiral auxiliary through ozonolysis followed by protection of the side chain as TBDPS ether afforded cyclopentanone **155**. Saegusa–Ito oxidation followed by epoxidation of the formed enone gave **156** as the major isomer (dr 9:1). Regioselective reductive opening of the epoxide with $Na[PhSeB(OEt)_3]$ produced hydroxy ketone **157**, which was then converted into the *exo*-methylene analogue **158** with Nysted's reagent. Cleavage of the benzyl ether and stereocontrolled reduction of the olefin in the presence of Crabtree's catalyst afforded a single isomer, presumably due to a directing effect of the adjacent hydroxy group. Final removal of the TBDPS protecting group gave cyclopentane triol **159**, which was esterified with varying equivalents of oleoside monomethyl ester peracetate **160** under Yamaguchi conditions [119,120] to give nudiflosides A (**151**) and D (**13**), respectively, thereby completing the synthesis and confirming the proposed stereochemistry [49].

## Glutamate metabotropic receptor agonists (2000, 2007)

The metabotropic glutamate receptors (mGluRs) are members of the vast family of G-protein coupled receptors which are expressed throughout the central nervous system. They consist of at least eight sub-types, which are divided into three groups I–III. Through binding of glutamate **161** (Figure 9), the most abundant excitatory neurotransmitter in the mammalian central nervous system, the mGluRs are activiated and participate in the regulation of synaptic transmission and neuronal excitability through a metabotropic process. There is ongoing interest in mGluRs as drug targets, and the therapeutic potential of mGluR



**Scheme 19:** Total synthesis of the pentasubstituted cyclopentane core **159** of nudiflosides A (**151**) and D (**13**) and conversion to the natural products [49].

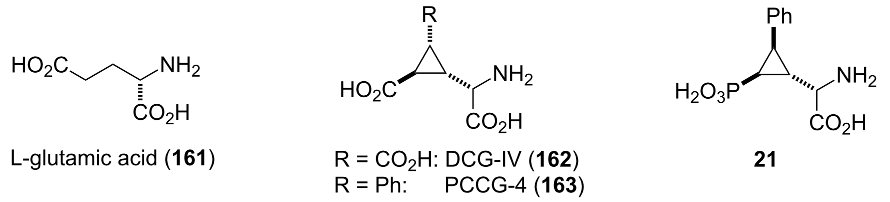
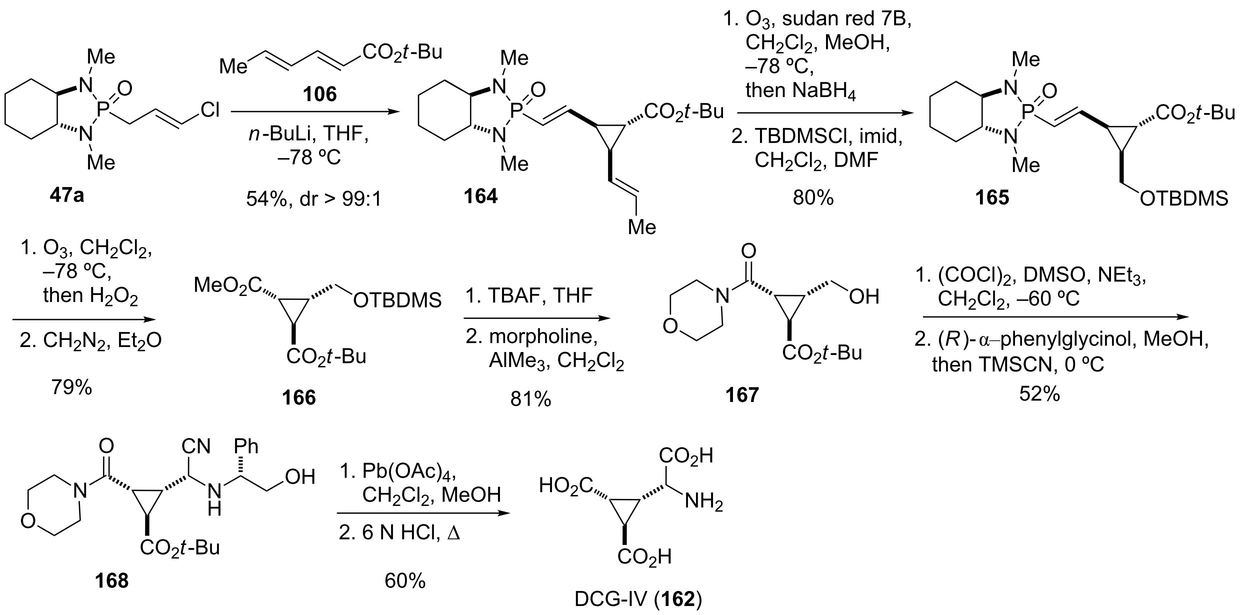


**Figure 9:** L-glutamic acid (**161**) and constrained analogues [57,124].

ligands for the treatment of CNS disorders and ailments such as Alzheimer's and Parkinson's disease, depression, anxiety, and schizophrenia is being validated [121,122].

The discovery of group II mGluR agonist DCG-IV (**162**) (Figure 9) as a potent anticonvulsant and neuroprotective agent [123] had sparked interest in more efficient routes for its synthesis. Pellicciari and Marinozzi developed an asymmetric synthesis of DCG-IV (**162**) based on Hanessian's cyclopropanation protocol (Scheme 20) [57]. Thus, addition of the Li anion generated from **47a** to *tert*-butyl sorbate (**106**) afforded the cyclopropane **164** as a single diastereomer. Selective ozonolysis of the propenyl side chain followed by reductive work-up and subsequent conversion of the formed primary alcohol into the corresponding TBDMS ether provided intermediate **165**. Removal of the chiral auxiliary and generation of the second carboxy moiety was then achieved by ozonolysis of **165** and ensuing esterification with diazomethane to give diacid ester **166**. Treatment of the latter with TBAF cleaved the TBDMS ether and gave a lactone intermediate, which was then opened by morpholine to afford amide **167**. The primary alcohol was then oxidized to the aldehyde under Swern conditions and submitted to a diastereoselective Strecker synthesis to install the amino acid moiety. Thus, condensation of the aldehyde with (*R*)-α-phenylglycinol followed by addition of trimethylsilylcyanide to the formed Schiff-base provided aminonitrile **168** as the major diastereomer (dr 95:5). Oxidative cleavage of the phenylglycinol moiety with $Pb(OAc)_4$ liberated the amino-functionality and hydrolysis of the amide and nitrile under acidic conditions finally gave DCG-IV (**162**) [57].

Pellicciari and co-workers also reported on the synthesis of other constrained bioisosteres of L-glutamic acid, such as PCCG-4 (**163**) (Figure 9) [124]. To this end, phosphonocyclopropylamino acid **21** was designed as an analogue to **163** by replacing a carboxylic acid with a phosphonic acid moiety [60,61]. The stereoselective synthesis of **21** relied on another cyclopropanation protocol developed by Hanessian and



**Scheme 20:** Stereoselective synthesis of DCG-IV (**162**) [57].

co-workers [59]. Thus, conjugate addition of the anion of **28d** to (*E*)-*tert*-butyl cinnamate (**169**) proceeded with excellent stereocontrol, and adduct **170** was isolated as a single diastereomer (Scheme 21).

Conversion of *tert*-butyl ester **170** into aldehyde **171** by a two-step protocol was followed by condensation with (*R*)-α-phenylglycinol and treatment of the formed Schiff base with trimethylsilylcyanide to afford α-aminonitrile **172** as major isomer (dr > 4:1). Oxidative cleavage with $Pb(OAc)_4$ liberated the amino functionality and hydrolysis of both the phosphonamide and nitrile groups under acidic conditions finally provided phosphonocyclopropylamino acid **21**. This compound showed to be a group III mGluRs selective ligand with moderate potency as mGluR4 and mGluR6 agonist ($EC_{50}$ 59 µM and 51 µM, respectively) [60,61,124].

## Berkelic acid (2009)

Berkelic acid (**15**) (Figure 10) is a spiroketal isolated from a fungus of the *Penicillium* species that grows in an unusual and harsh environment, Berkeley Pit Lake, an abandoned open-pit copper mine filled with acidic, metal-contaminated water [125]. The natural product shows moderate activity against MMP-3 and caspase-1, and high, selective activity toward ovarian cancer cell line OVCAR-3 with a $GI_{50}$ of 91 nM. Both the relative configuration of the side chain as well as the absolute stereochemistry of the molecule was originally not assigned. The interesting biological profile in combination with the unknown stereochemical assignments made berkelic acid an attractive target for total synthesis, with the first one completed by Snider and co-workers [43].

The tetracyclic core of berkelic acid (**15**) was thought to be assembled through an oxa-Pictet–Spengler reaction from 2,6-dihydroxybenzoic acid **173** and ketal aldehyde **174** as key building blocks (Figure 10). The 2,6-dihydroxybenzoic acid **173** is accessible by opening of epoxide **175** as chiron with a suitable nucleophile. The ketal aldehyde **174** would be derived from butenolide **176** through a conjugate addition sequence employing phosphonamide **28c**, thereby setting two of the three stereocenters of the five-membered ring in a single step.

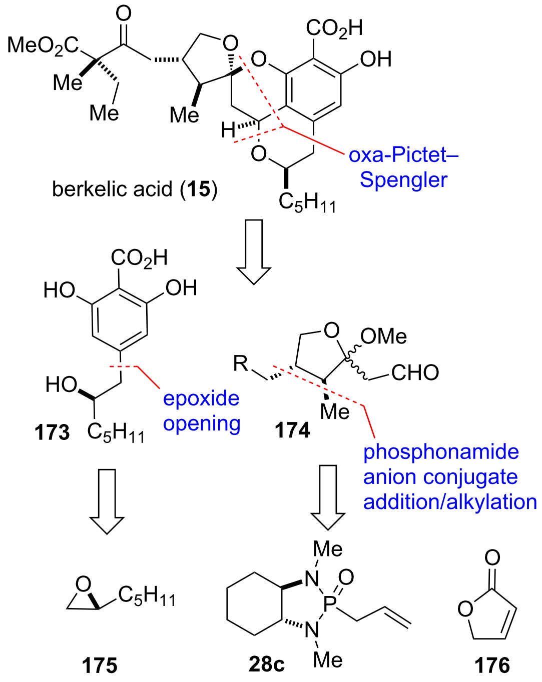
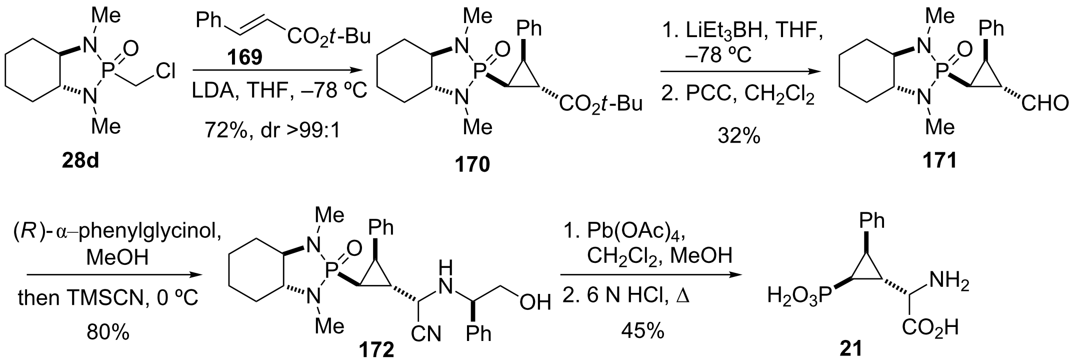
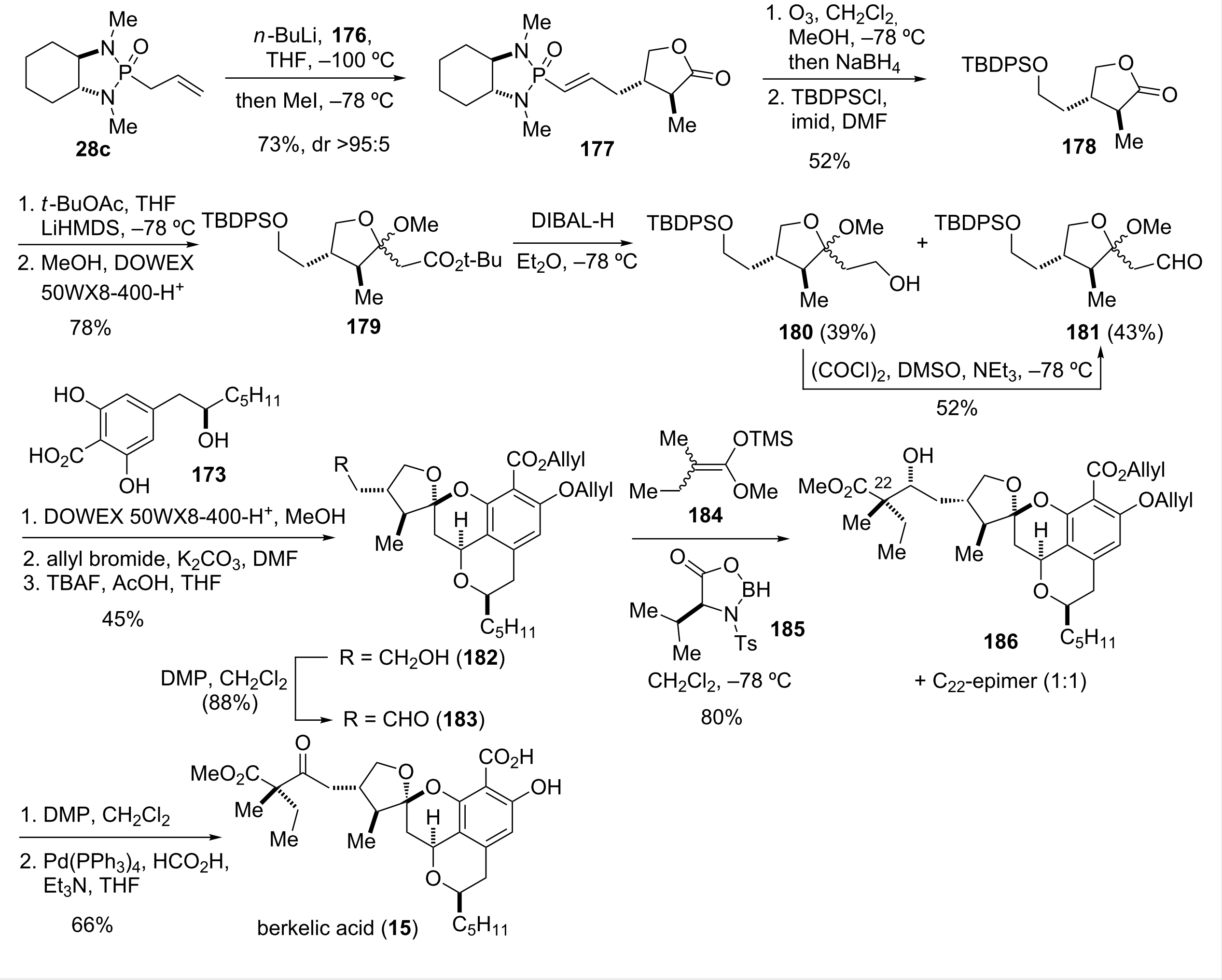


**Figure 10:** Key assembly strategy of berkelic acid (**15**) [43].

Thus, deprotonation of chiral phosphonamide **28c** and addition of the anion to 2(5*H*)-furanone (**176**) at −100 °C, followed by trapping with excess methyl iodide afforded adduct **177** with excellent selectivity (dr > 95:5) (Scheme 22). Ozonolysis with reductive work-up and ensuing protection of the formed hydroxy group as TPDPS ether provided lactone **178**. Addition



**Scheme 21:** Stereoselective synthesis of mGluR agonist **21** [124].



**Scheme 22:** Total synthesis of berkelic acid (**15**) [43].

of the enolate of *tert*-butyl acetate to **178** and ketal formation afforded **179**. Reduction with DIBAL-H gave ketal aldehyde **181**, which was then condensed with 2,6-dihydroxybenzoic acid **173** in a oxa-Pictet–Spengler reaction to form the tetracyclic core of berkelic acid. Treatment of the obtained tetracyclic salicylic acid with allyl bromide and desilyation with TBAF/AcOH provided **182**. The primary alcohol of the side chain was oxidized with Dess–Martin periodinane (DMP) to give aldehyde **183**. The latter was subsequently reacted with trimethylsilyl ketene acetal **184** in the presence of oxazaborolidinone **185** to afford aldol product **186** and the $C_{22}$-epimer as only isomers in a 1:1 mixture. Dess–Martin oxidation and deprotection of both allyl groups with formic acid under palladium catalysis finally provided berkelic acid (**15**). Thus, total synthesis of both epimers established the relative configuration of the side chain at $C_{22}$ which was previously unknown, as well as helped to determine the absolute stereochemistry of the molecule [43,126-132].

## Ambruticin S and jerangolid A (2010)

The jerangolids [133,134] and the ambruticins [135-137] are part of two closely related families of linear polyketides with potent antifungal properties produced by a variety of myxobacteria. Besides the biochemical profile, the two families share common structural features and a common biosynthesis [138,139]. Among the five members of the jerangolid family, which may be considered as tunctated analogs of the ambruticins, jerangolid A is reported to be the most potent [133,134]. The ambruticin family currently consists of eight known members [140]. Since the “eastern” segment of jerangolid A (**22**) and ambruticin S (**14**) is identical, a synthetic strategy was considered for this segment that would allow for the total synthesis of both molecules (Figure 11) [27,28].

The strategy for the first synthesis of jerangolid A (**22**) is depicted in retrosynthetic format featuring dihydropyran **188**, lactone **187**, and phosphonamide **189a** originating from the

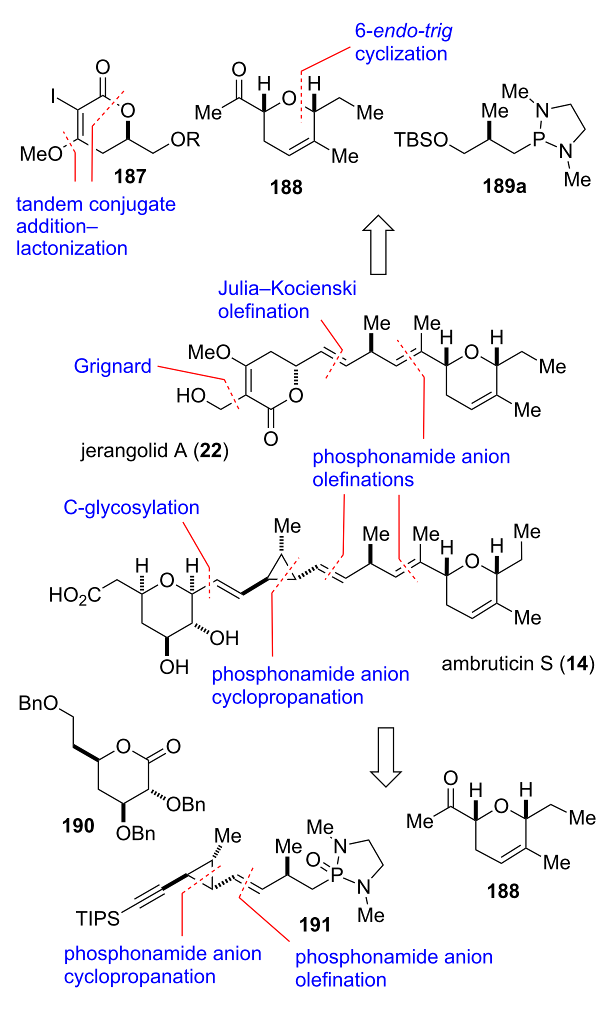
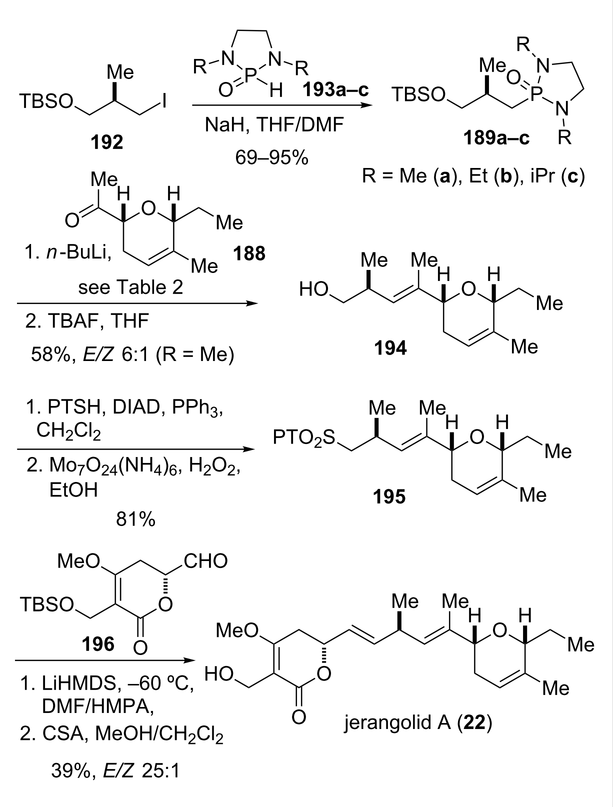


**Figure 11:** Key assembly strategy of jerangolid A (**22**) and ambruticin S (**14**) [27,28].

Roche ester (Figure 11) [27]. Lactone **187** ring was thought to be formed from addition of ethyl propiolate to (*S*)-glycidol, and ensuing conjugate addition of methanol and lactonization. The second cyclic building block, *syn*-dihydropyran **188**, could be synthesized by a highly diastereoselective 6-*endo-trig* cyclization of an allylic 1,3-diol, which was developed by Hanessian and co-workers [141]. The required allylic 1,3-diol would also be accessed from (*S*)-glycidol. The assembly of the two cyclic building blocks and the Roche ester derived middle fragment under formation of the *trans*-double bonds would utilize phosphonamide and sulfone anion coupling strategy, respectively. A similar strategy was employed for the assembly of ambruticin S (**14**). Disconnection at logical sites led to lactone **190** derived from D-glucose, dihydropyran methyl ketone **188**, and phosphonamide **191** as advanced intermediates [28]. Building block **191** and three of its four stereocenters would be constructed via phosphonamide-mediated olefination and cyclopropanation reactions [51-55]. The remaining stereocenter would originate from Roche ester as a readily available chiron.

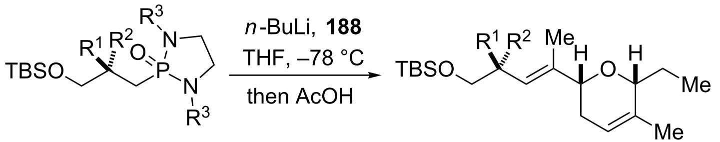
The final steps in the assembly of jerangolid A (**22**) are shown in Scheme 23. The required cyclic phosphonamide reagent **189** for the olefination of methyl ketone **188** was obtained from alkylation of 1,3-dialkyl-2-oxo-1,3,2-diazaphospholidines **193a–c** [69-71] with iodide **192**. The latter was prepared from (*S*)-Roche ester in a three step sequence. Coupling of methyl ketone **188** with phosphonamides **189a–c** afforded separable mixtures of *E/Z* isomers of TBS ether **197**, gratifyingly with the desired *E*-isomer as the major product (Table 2).



**Scheme 23:** Final assembly steps in the total synthesis of jerangolid A [27].

The reaction conditions, the steric nature of the phosphonamide *N*-substituents as well as its absolute configuration had a significant impact on the stereoselectivity of the olefination. Thus, treatment of methyl ketone **188** with dimethyl phosphonamide **189a** afforded the corresponding olefin **197** in a 3:1 *E/Z* ratio (Table 2, entry 1). Equilibrating the reaction mixture at ambient temperature before adding acetic acid helped to improve the *E/Z* ratio to 6:1 (Table 2, entry 2). The *E/Z* selectivity could further be enhanced by increasing the steric demand of the phosphonamide substituents. Replacing methyl with isopropyl improved the selectivity from 3:1 to 13:1, albeit to the

**Table 2:** Olefination of ketone **188** employing cyclic phosphonamides **189** [27].[a]



(*S*)-**189**: $R^1$ = Me, $R^2$ = H
(*R*)-**189**: $R^1$ = H, $R^2$ = Me

**197**: $R^1$ = Me, $R^2$ = H
**198**: $R^1$ = H, $R^2$ = Me

| Entry | Phosphonamide | Product | Yield (%) | *E*/*Z* |
|---|---|---|---|---|
| **1** | (*R*)-**189a**: $R^3$ = Me | **197** | 57 | 3:1 |
| **2** | (*R*)-**189a**: $R^3$ = Me | **197** | 62 | 6:1[b] |
| **3** | (*R*)-**189b**: $R^3$ = Et | **197** | 38 | 5:1 |
| **4** | (*R*)-**189c**: $R^3$ = iPr | **197** | 20 | 13:1 |
| **5** | (*S*)-**189a**: $R^3$ = Me | **198** | 63 | 19:1 |

[a]Reaction conditions: **189**, *n*-BuLi, THF, −78 °C, 1 h; **188**, −78 °C, 1 h; then AcOH (xs), −78 °C to rt. [b]Addition of AcOH at rt.

expense of lower conversion and increased recovery of starting material (Table 2, entry 1 and 4). Remarkably, the (*S*)-enantiomer of dimethyl phosphonamide **189a** furnished an excellent *E*/*Z* ratio of 19:1 in the olefination of **188** to afford diastereomer **198** (Table 2, entry 5).

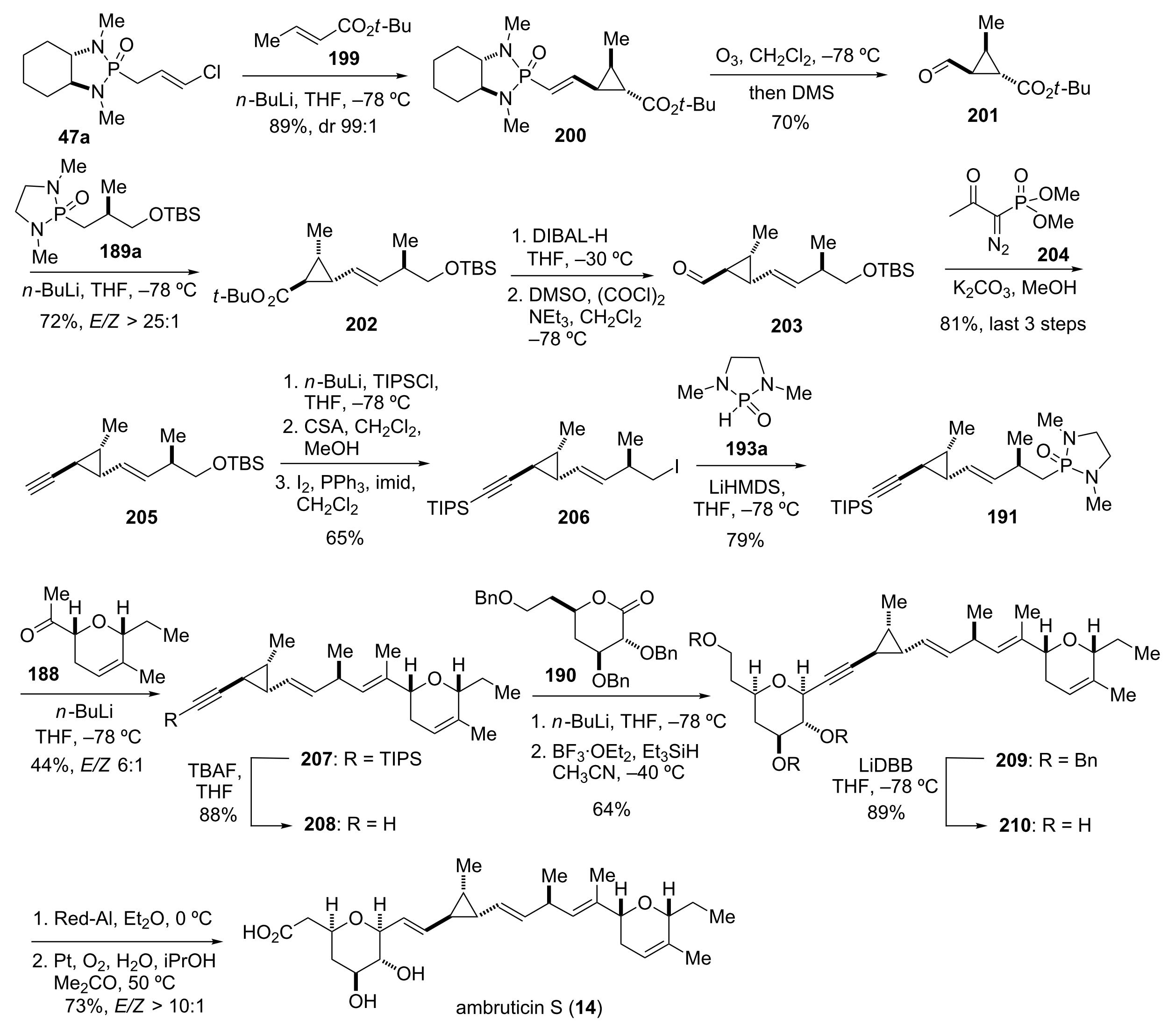
Deprotection of TBS ether **197** with TBAF provided alcohol **194** which was then transformed into known phenyltetrazole (PT) sulfone **195** [142,143] through Mitsunobu reaction with 1-phenyltetrazole-5-thiol (PTSH), followed by oxidation of the intermediate sulfide. Coupling of the lactone building block in form of aldehyde **196** with the fully elaborated PT-sulfone **195** provided the corresponding olefin with the correct double-bond geometry in moderate yield and excellent selectivity (*E*/*Z* > 25:1). Lastly, cleavage of the TBS ether under mild acidic conditions afforded jerangolid A (**22**) [27,143,144].

The synthesis of ambruticin S commenced with the 1,4-conjugate addition of the anion of chiral *trans*-chlorallyl phosphonamide *ent*-**47a** to *tert*-butyl crotonate (**199**) to give cyclopropane **200** as a single diastereomer with the desired relative and absolute stereochemistry (Scheme 24) [28]. Removal of the chiral auxiliary by oxidative cleavage of the olefin furnished aldehyde **201**, which was coupled with phosphonamide **189a** to afford olefin **202** in good yield and excellent selectivity (*E*/*Z* > 25:1). The latter was then converted into alkyne **205** via DIBAL-H reduction of the *tert*-butyl ester moiety followed by Swern oxidation to give aldehyde **203**, and treatment with the Ohira–Bestmann reagent **204** [145,146]. Protection of the alkyne CH as its TIPS-derivative, chemoselective removal of the TBS group using CSA and transformation of the obtained primary alcohol with iodine and $PPh_3$ gave iodide **206**. The latter was then converted into phosphonamide **191** by treatment with the lithium anion of 1,3-dimethyl-2-oxo-1,3,2-diazaphospholidine (**193a**). Coupling with methyl ketone **188** was performed in a similar fashion as described for jerangolid A. Thus, deprotonation of phosphonamide **191** with *n*-butyllihium and treatment with methyl ketone **188** followed by addition of acetic acid provided triene **207** as the desired major isomer with moderate selectivity (*E*/*Z* 6:1). Treatment of **207** with TBAF liberated alkyne **208**, which was coupled with lactone **190** in a two-step sequence to give the desired *syn*-dihydrofuran **209** as a single diastereomer. Next, cleavage of the three benzyl ether moieties without reducing any of the double-bonds was achieved using lithium 4,4-di-*tert*-butylbiphenylide (LiDBB) to deliver alkyne **210**. The homopropargylic system was reduced with sodium bis(2-methoxyethoxy)aluminum hydride to afford the corresponding olefin with good selectivity (*E*/*Z* > 10:1). Finally, selective oxidation of the primary hydroxy group was achieved using a method that was chosen before by Jacobsen for the same transformation [147]. Thus, treatment of the intermediate triol with oxygen under platinum catalysis efficiently oxidized the primary alcohol group to the carboxylic acid without affecting the two secondary hydroxy groups and provided (+)-ambruticin S (**14**) [28,142,147-151].

## Estrone (2010)

Estrone (**12**), an aromatized C18 steroid with a 3-hydroxy group and a 17-ketone, is a member of the estrogenic hormones, which also include estriol and estradiol. In humans, it is produced primarily by the cyclic ovaries, placenta, and the adipose tissue of men and postmenopausal women [152].

A classic problem in steroid synthesis is the selective formation of the *trans*-fused ring junction. A common strategy to circumvent this issue is to employ a cyclization strategy that



Scheme 24: Key assembly steps in the total synthesis of ambruticin S (**14**) [28].

commences from a D-ring precursor already containing the correct stereochemistry at the future CD ring junction [153,154]. Linclau and co-workers developed this concept further and a general steroid construction strategy based on the formation of a D-ring template that contains the correct configuration of three stereocenters C8, C13 and C14 with suitable functionalization for the following C- and B-ring cyclizations (Figure 12). The applicability of this approach to steroid synthesis was validated using estrone as target [44]. A key requirement for the strategy was a highly diastereo- and enantioselective formation of the D-ring intermediate **211** and flexibility in introducing different $R^1$ and $R^2$ groups to enable the synthesis of diverse steroids targets. Intermediate **211** was envisioned to come from a one-pot process involving the conjugate addition of a chiral phosphonamide anion to cyclopentenone **48** followed by an alkylation to introduce $R^1$. Furthermore, the obtained vinylic phosphonamide was thought to be an excellent reactive handle for the following C-ring cyclization.

The synthesis of the required *Z*-allylic phosphonamide **216** began from dibromide **213** by benzylic displacement with allenylmagnesium bromide followed by reaction with paraformaldehyde to give propargylic alcohol **214** (Scheme 25). Alkyne reduction was performed with Zn and dibromoethane to give selectively the corresponding *cis*-alkene. The Zn/dibromoethane system proved to be more reliable for this reduction than using hydrogen and poisoned Pd-catalysts. Chlorination with hexachloroacetone gave allylic chloride **215**, which was then converted to phosphonamide **216** via an Arbuzov reaction with phospholane **60**. Deprotonation of **216** and addition to cyclopentenone **48** followed by alkylation with allyl bromide afforded adduct **217** as a single diastereomer.

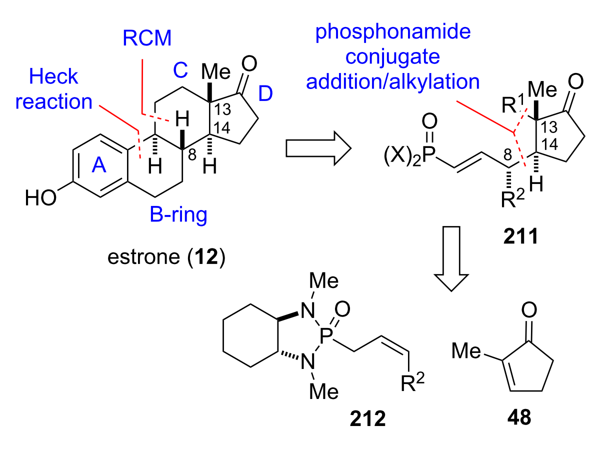
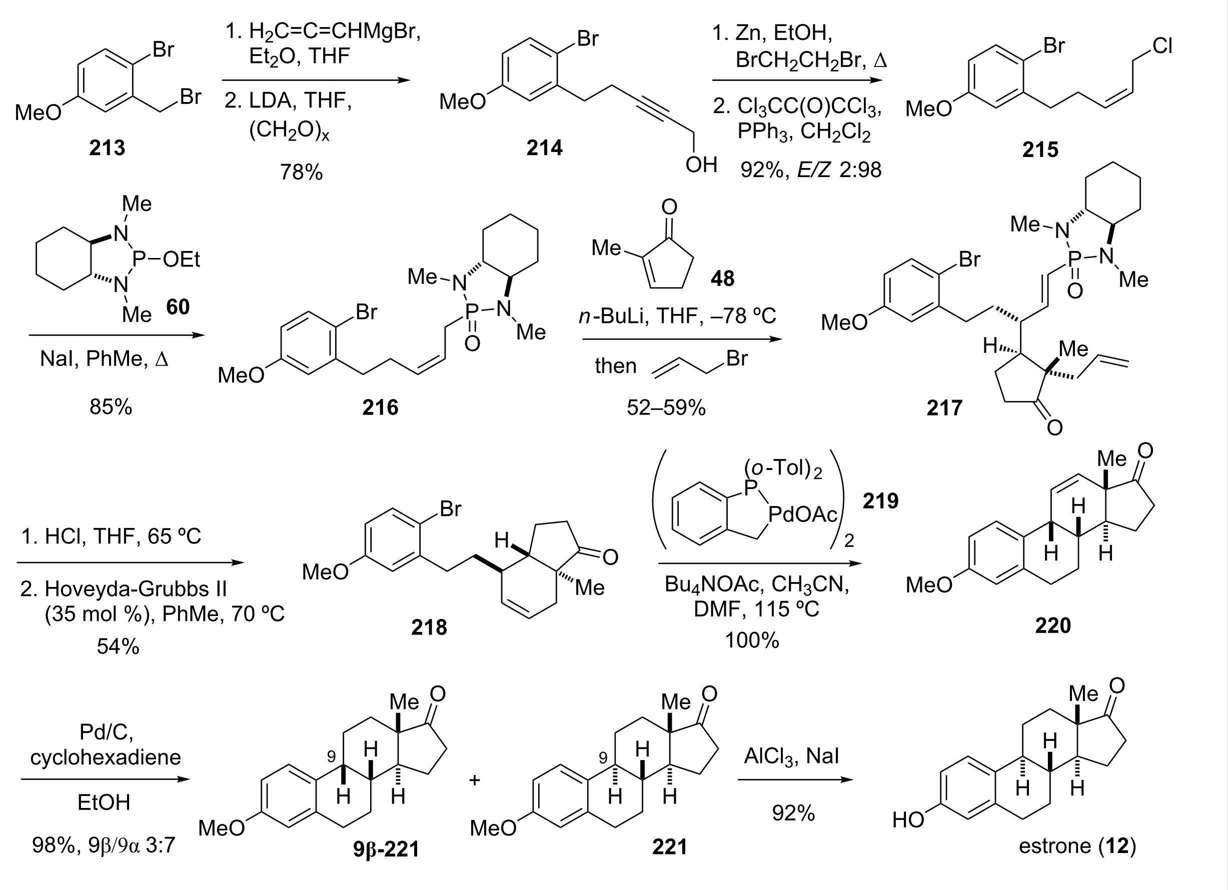


**Figure 12:** General steroid construction strategy based on conjugate addition of **212** to cyclopentenone **48**, exemplified with estrone (**12**) [44].

With key intermediate **217** in hand, the B and C ring systems were then constructed by two subsequent cyclizations. Thus, treatment of the phosphonic acid obtained from acid hydrolysis of **217** with Hoveyda–Grubbs II catalyst afforded *trans*-hydrindene **218**, with the Δ9,11 double bond perfectly positioned for the subsequent Heck B-ring closure. Cyclization product **220** was then obtained in quantitative yield by treatment of **218** with catalytic amounts of palladacycle **219** at elevated temperature, albeit with the undesired 9β-configuration. Inversion of the C9 stereocenter and reduction of **220** was achieved by an isomerization/hydrogenation process using Pd/C and cyclohexadiene, which produced **221** and its C9 epimer **9β-221** in a 7:3 mixture. Separation of the desired isomer by crystallization and cleavage of the methyl ether finally gave estrone (**12**). Three of the four stereocenters of estrone [155-163] were set in a single conjugate addition and enolate alkylation reaction with excellent stereocontrol [44].

## Conclusion

In this review we summarized a substantial volume of work dealing with the preparation, reactivity, and utility of cyclic phosphonamides as versatile reagents for the asymmetric synthesis of a variety of acyclic and carbocyclic chiral non-racemic compounds. The focus was placed on enantiomerically pure pentacovalent $C_2$-symmetrical phosphonamides, whose stabilized anions have been used as nucleophilic reagents toward



**Scheme 25:** Total synthesis of estrone (**12**) [44].

electrophiles in a variety of applications. Especially useful among others are tandem conjugate additions to α,β-unsaturated carbonyl substrates followed by alkylation of the resulting enolates to give diastereomerically enriched acyclic, carbocyclic, and azacyclic molecules harboring as many as three contiguous stereogenic centers. These have been useful starting materials for the synthesis of a number of natural products and biologically active molecules such as enzyme inhibitors, bioisosteres, and receptor agonists to mention a few. Although the initial products must be oxidatively cleaved to obtain the corresponding aldehydes, thereby sacrificing the original phosphonamide portion, the benefits are in the highly functionalized products that are obtained, many of which are not easily attainable by other means. The methods are also of great utility for the stereocontrolled synthesis of the medicinally important α-substituted phosphonic acids in the case of alkyl halides as electrophiles. The utility of chiral non-racemic phosphonamides in organic synthesis extends beyond their uses as mild carbon-based nucleophilic reagents for stereoselective alkylation, amination, Michael addition, cyclopropanation and aziridination reactions.

For example, diastereoselective *o*-metalation of ferrocenes was mediated by (*R*,*R*)-*N*,*N*'-dimethyl-1,2-diaminocyclohexane [164]. 2-Dimethylamino-*N*,*N*'-diphenyl-1,3,2-diazaphospholidine is an excellent reagent for the conversion of alcohols to the corresponding crystalline 2-alkoxy-*N*,*N*'-diphenyl-1,3,2-diazophospholidines, simply by heating in toluene with elimination of dimethylamine [165]. The resulting products are excellent substrates for Arbuzov-type $S_N2$ halogenations with methyl iodide or bromine as halogen sources. Related $C_2$-symmetrical diazaphospholidines can be used for the determination of enantiomeric excesses of chiral alcohols by $^1$H NMR [166] and carboxylic acids [167].

The possibility to perform ring-closing metathesis reactions with α,β-unsaturated phosphonic acids resulting from the hydrolysis of the initially formed phosphonamide, as in the recent synthesis of estrone [44], adds a new and exciting dimension to the utility of phosphonamides in asymmetric synthesis.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

# Relay cross metathesis reactions of vinylphosphonates

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Full Research Paper

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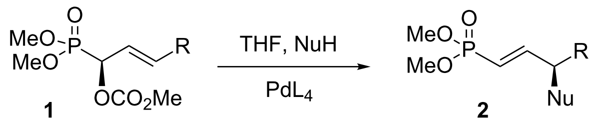
## Abstract

Dimethyl (β-substituted) vinylphosphonates do not readily undergo cross metathesis reactions with Grubbs catalyst and terminal alkenes. However, the corresponding mono- or diallyl vinylphosphonate esters undergo facile cross metathesis reactions. The improved reactivity is attributed to a relay step in the cross metathesis reaction mechanism.

## Introduction

Over the last two decades, we have developed reactions for the formation of chiral non-racemic γ-substituted vinylphosphonates [1-9]. In particular, carbonate derivatives **1** (phosphono allylic carbonates) of allylic hydroxy phosphonates undergo palladium-catalyzed addition of nucleophiles to give γ-substituted vinylphosphonates **2** in high yield (Scheme 1). The nucleophile adds exclusively to the 3-position, with migration of the double bond into "conjugation" with phosphoryl group. As expected, the reactions generally proceed with complete chirality transfer. Various carbon, nitrogen, and oxygen nucleophiles participate in the palladium-catalyzed substitution reactions of phosphono allylic carbonates **1**. Vinylphosphonates formed in this way, for example **2a–e** (Figure 1), have been used in the synthesis of the natural products turmerone [4] and enterolactone [5], the phosphonate derivatives of the natural product cyclophostin [6], the C18–C34 fragment of amphidinolide C [7], and the oxylipids from Australian brown algae [8].



**Scheme 1:** Palladium catalysed reaction of phosphono allylic carbonates.

The potential of vinylphosphonates as intermediates in organic synthesis is limited by their chemistry. Unlike the parent compound, vinylphosphonates substituted with an aryl or alkyl group on the alkene appear to have somewhat limited reactivity. This lack of reactivity is exemplified by the Grubbs cross metathesis reaction [10]. Grubbs and co-workers classified terminal vinylphosphonates as type III substrates [11]. Type III alkenes do not homodimerize, but will engage in alkene cross metathesis reactions. However, we have observed that β-substi-

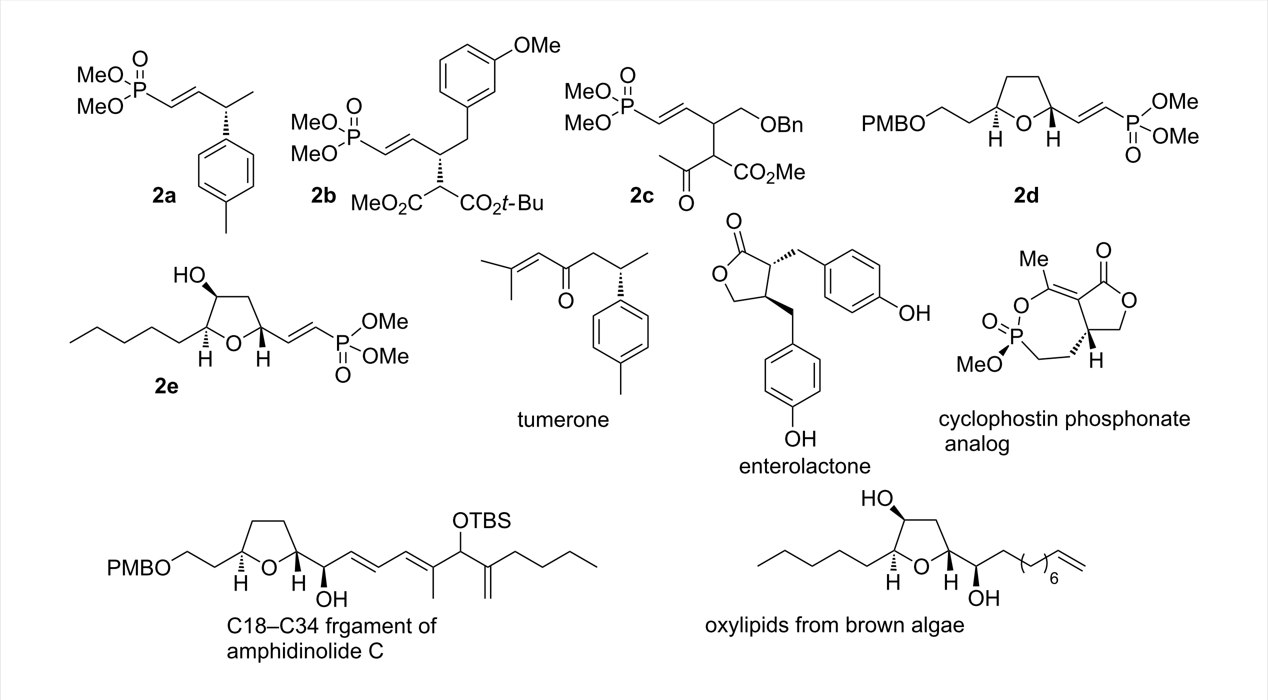
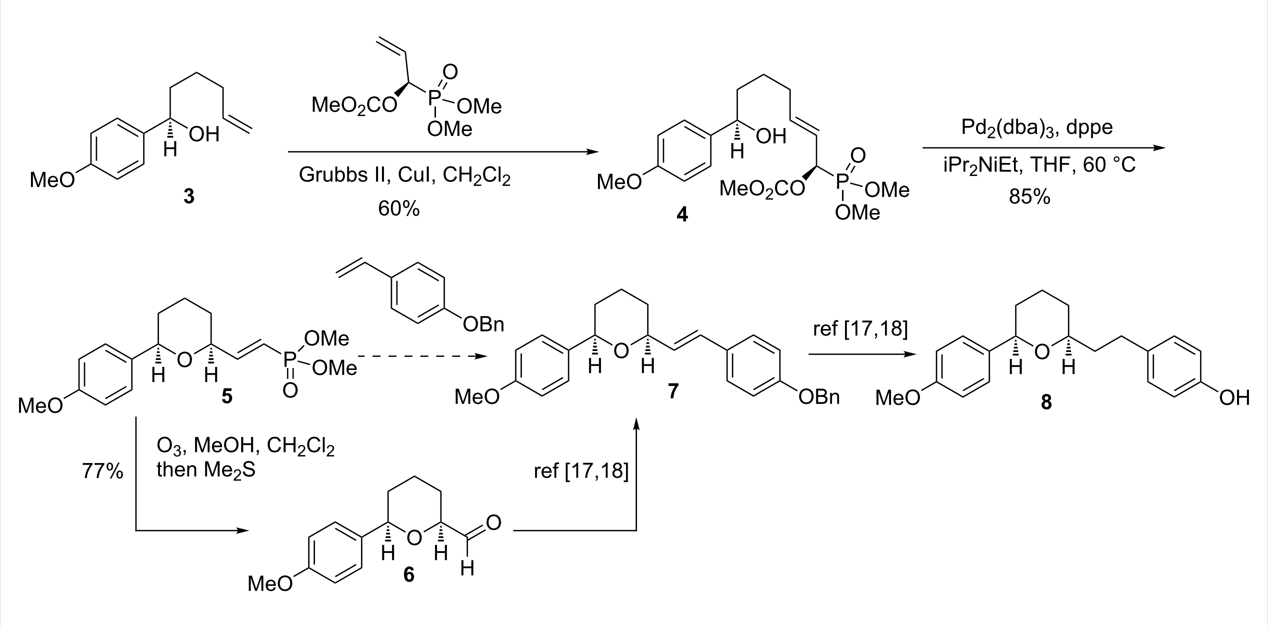


**Figure 1:** Natural products prepared using vinyl phosphonate intermediates.

tuted vinylphosphonates are unreactive towards cross metathesis and are therefore type IV substrates. Since alkene cross metathesis is a powerful method of combing organic fragments in natural product synthesis, the value of vinylphosphonates as synthetic intermediates would increase if their reactivity could be enhanced to a level where they would participate in cross metathesis reactions.

As an example, we recently described a method for the formal synthesis of centrolobine (**8**) [9], an antileishmananial compound isolated from the heartwood of various *Centrolobium* species [12-16] (Scheme 2). The *cis*-THP substituted vinylphosphonate **5**, formed by a stereospecific palladium-catalyzed cyclization of phosphono allylic carbonate **4**, was cleaved via ozonolysis to the aldehyde **6**, a known intermediate [17,18] on



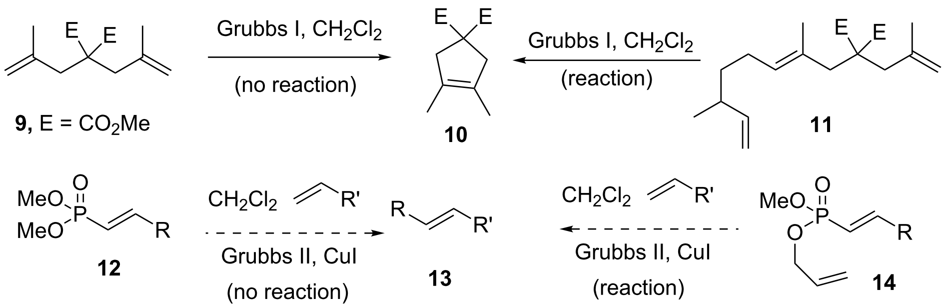
**Scheme 2:** Approaches to the synthesis of centrolobine.

route to (−)-centrolobine (**8**). An alternative approach could involve an alkene cross metathesis reaction between the vinylphosphonate and a styrene (**5** to **7**).

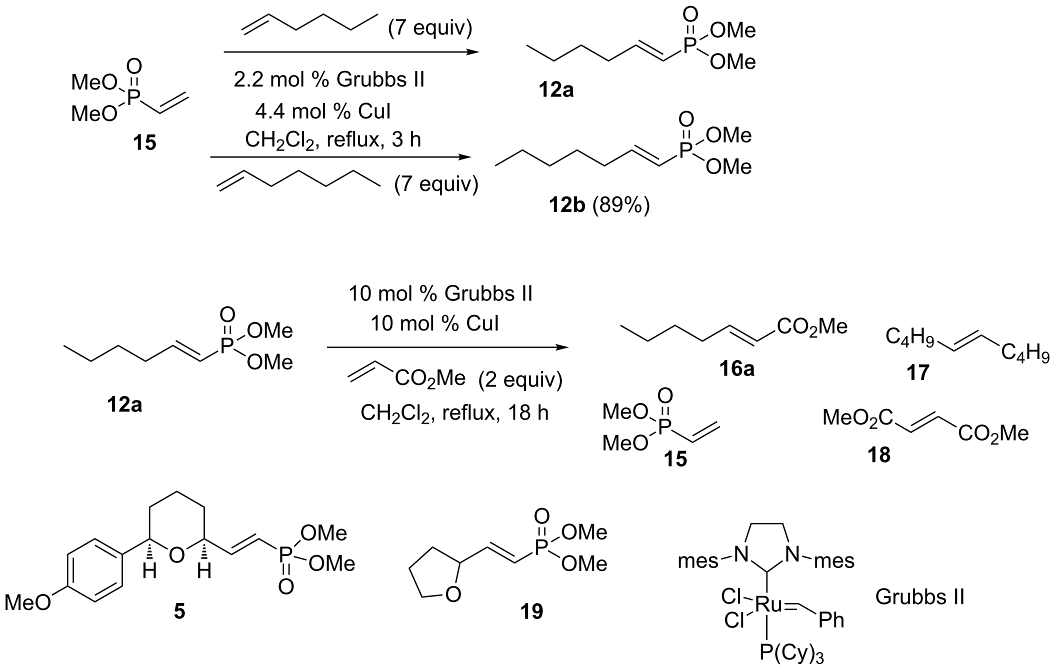
Since substituted vinylphosphonates are reluctant to participate in cross metathesis reactions (Scheme 3), this approach to the synthesis of cetrolobine appeared to have little merit. However, Hoye et al. reported the concept of "relay ring closing metathesis (RRCM)", wherein typically unreactive α,ω-dienes bearing 1,1-disubstituted ethylene moieties **9** would react via the intermediacy of an additional terminal alkene **11** (Scheme 3) [19-21]. Similarly, Hansen and Lee employed an allyl ether to activate enynes toward cross metathesis [22]. Furthermore, there are several examples of vinylphosphonates participating in ring closing metathesis (RCM) reactions [23-25]. Therefore, given the propensity for vinylphosphonates to undergo RCM, it was proposed that an allyl phosphonate ester **14** would act as an initial site of metathesis, which would lead to a relay cross metathesis and thus render vinylphosphonates reactive.

## Results and Discussion

A series of cross metathesis reactions were performed to establish the baseline reactivity of vinylphosphonates (Scheme 4). Not surprisingly, the terminal vinylphosphonate **15** underwent smooth cross metathesis with either 1-hexene or 1-heptene using our standard conditions (2% Grubbs II, 4% CuI, $CH_2Cl_2$ reflux) [2,26,27] to give the substituted vinylphosphonates **12a** or **12b** in good yield. In contrast, when vinylphosphonate **12a** was subjected to a cross metathesis reaction with methyl acrylate, the cross metathesis product **16a** was formed in low yield



**Scheme 3:** Relay ring closing metathesis and relay cross metathesis.



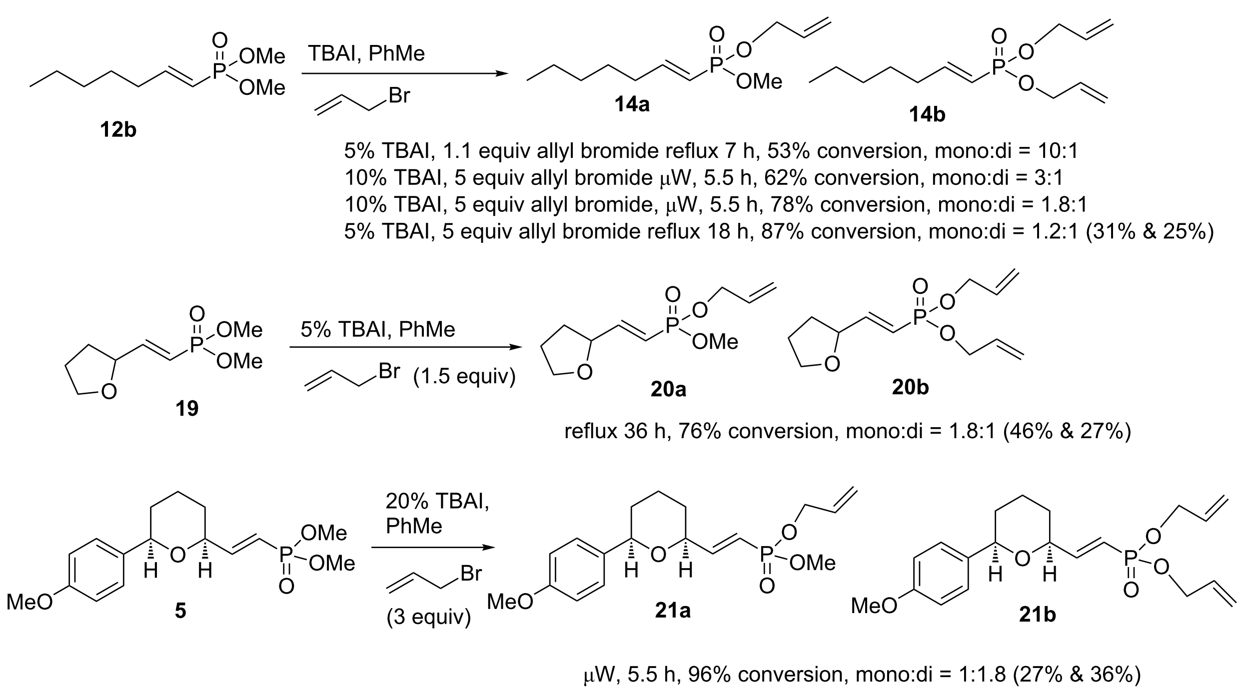
**Scheme 4:** Cross metathesis reactions of vinyl phosphonates.

(~11%) as part of a complex mixture. More highly substituted vinylphosphonates (**5** and **19**) failed to react at all with methyl acrylate under similar conditions, even with higher catalyst loading and extended reaction times.

Initially, the synthesis of the allyl vinylphosphonate esters was achieved using a transesterification reaction catalysed by tetra *n*-butylammonium iodide (TBAI) (Scheme 5) [28]. A solution of the vinylphosphonate **12b**, 1.1 equivalents of allyl bromide and 5 mol % TBAI in toluene was heated at reflux for 7 hours to give a 53% conversion to both the mono- and diallyl vinylphosphonates **14a** and **14b** in a 10:1 ratio. The overall conversion could be improved with excess allyl bromide, increasing the amount of TBAI and prolonged heating times, either at reflux or in a microwave reactor. The ratio of di- to mono-allyl phosphonate esters increases with the duration of reaction. A subsequent reaction of vinylphosphonate **12b** employing 5 equivalents of allyl bromide, 5 mol % TBAI and 18 hours at reflux resulted in 87% conversion with 1.2:1 ratio of mono- to diallyl ester (**14a** and **14b**). The products were isolated by silica gel chromatography to give 31% yield of mono-allyl and 25% yield of diallyl phosphonate esters.

Similarly, THF-substituted vinylphosphonate **19** was treated with 5 equivalents of allyl bromide and 5 mol % TBAI in refluxing toluene for 36 hours to give a 76% conversion with 1.8:1 ratio of mono- to diallylated vinyl phosphonates **20a** and **20b** (Scheme 5). The products were isolated by silica gel chromatography to give 46% yield of mono-allyl and 27% yield of diallyl phosphonate esters. Finally, THP-vinylphosphonate **5** was subjected to transesterification by reaction with 20 mol % of TBAI and 5 equivalents of allyl bromide in toluene solution and heating in a microwave reactor for 5.5 hours. The reaction proceeded to 96% conversion and gave 1:1.8 ratio of mono- and diallyl vinylphosphonates **21a** and **21b**. The products were isolated by silica gel chromatography to give 27% yield of the mono-allyl and 36% yield of the diallyl phosphonate esters.

With the mono- and diallyl vinylphosphonates in hand, the cross metathesis reactions with methyl acrylate (a type II olefin) were examined (Scheme 6). The mono-allyl vinylphosphonate **14a** was treated with methyl acrylate, 10 mol % Grubbs catalyst and 10 mol % CuI in refluxing $CH_2Cl_2$. The unsaturated ester **16b** [29] was formed in 78% yield (estimated from NMR). However, ester **16b** is volatile and isolation by column chromatography resulted in some loss of material leading to an isolated yield of 45%. In addition, the $^{31}P$ NMR spectrum of the crude reaction mixture indicated the formation of a new phosphorus-containing product with a signal at 43 ppm, consistent with formation of the oxaphosphole **22** [25]. An impure sample of the oxaphosphole **22** was isolated by column chromatography, but it decomposed during attempts of further purification [23]. However, the $^{31}P$ NMR signal and the chemical shifts, multiplicities and coupling constants for the vinylic protons [Hα 7.16

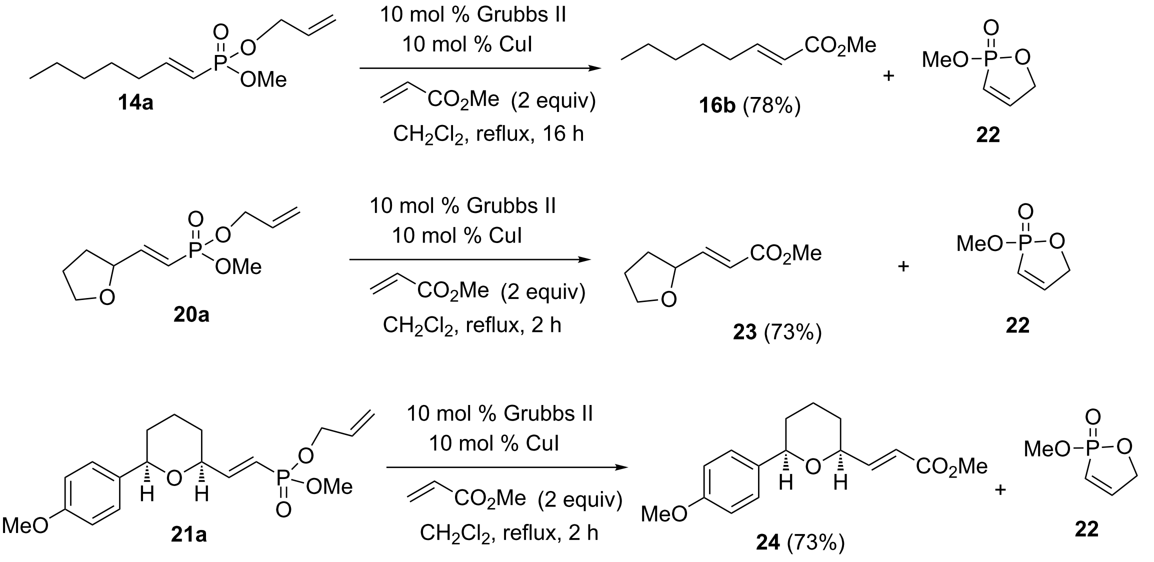


5% TBAI, 1.1 equiv allyl bromide reflux 7 h, 53% conversion, mono:di = 10:1
10% TBAI, 5 equiv allyl bromide µW, 5.5 h, 62% conversion, mono:di = 3:1
10% TBAI, 5 equiv allyl bromide, µW, 5.5 h, 78% conversion, mono:di = 1.8:1
5% TBAI, 5 equiv allyl bromide reflux 18 h, 87% conversion, mono:di = 1.2:1 (31% & 25%)

reflux 36 h, 76% conversion, mono:di = 1.8:1 (46% & 27%)

µW, 5.5 h, 96% conversion, mono:di = 1:1.8 (27% & 36%)

**Scheme 5:** Transesterification of phosphonate esters.



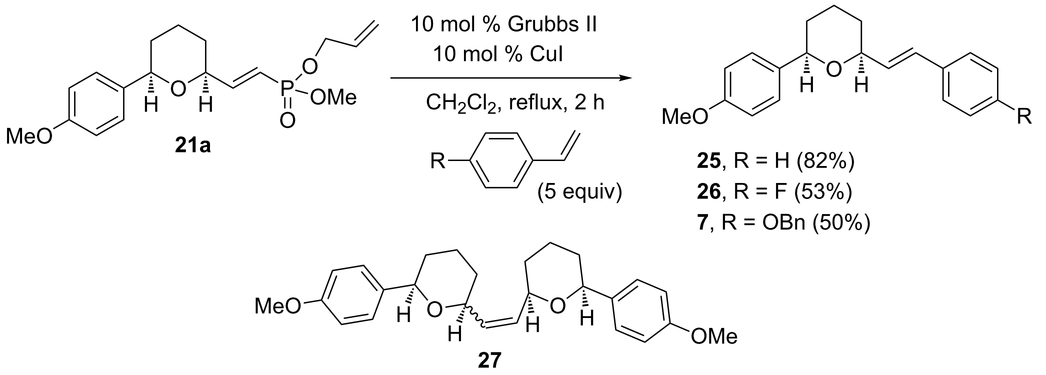
**Scheme 6:** Relay cross metathesis of mono-allyl vinylphosphonates with methyl acrylate.

(ddt, $J_{HH}$ = 8.6, ~1 Hz, $J_{Hp}$ = 46.9 Hz, 1H) and Hβ, 6.2 (ddt, $J_{HH}$ = 8.6, 2.3 Hz, $J_{HP}$ = 33.9 Hz, 1H] in the $^1$H NMR spectrum were very similar to those reported for similar structures [25] giving confidence in the structural assignment. The THF-substituted allyl vinylphosphonate **20a** and THP-substituted allyl vinylphosphonate **21a** reacted under similar conditions to yield the unsaturated esters **23** [30] and **24**, respectively.

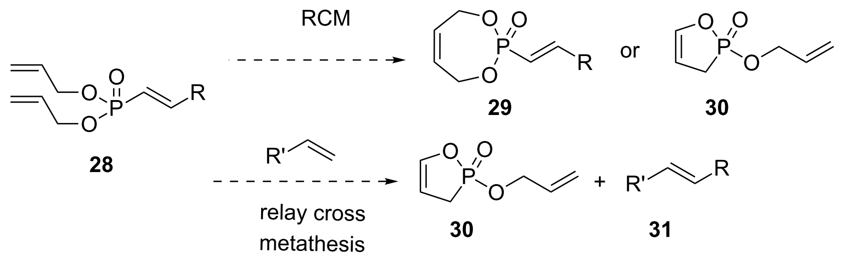
The proposed synthesis of centrolobine (and analogs) (Scheme 2) required the cross metathesis reaction of the THP-substituted allyl vinylphosphonate **21a** with substituted styrenes. *p*-Substituted styrenes are type I substrates and should readily engage in the metathesis reaction. Thus, reaction of the mono-allyl vinylphosphonate **21a** with 5 equivalents of styrene using 10 mol % Grubbs second generation catalyst and 10 mol % CuI in refluxing $CH_2Cl_2$ for two hours gave tetrahydropyran **25** in 82% isolated yield (Scheme 7). Similarly, reaction of vinylphosphonate **21a** with 4-fluorostyrene and 4-benzyloxystyrene gave the tetrahydropyrans **26** and **7**, respectively. Tetrahydropyran **7** is a known intermediate and can be converted to centrolobine by hydrogenation [17].

Surprisingly, the dimer **27** was isolated in small amounts (~20%) from the reaction of vinylphosphonate **21a** with styrenes. The dimeric product **27** was not observed during the cross metathesis of the vinylphosphonate **21a** with methyl acrylate.

Diallyl vinylphosphonates (**28**) are reported to undergo ring closing metathesis to give either 7-membered (**29**) or 5-membered (**30**) phosphorus heterocycles (Scheme 8) [23,24]. The mode of cyclization depends upon the geometry and substi-



**Scheme 7:** Relay cross metathesis of mono-allyl vinylphosphonates with styrenes.

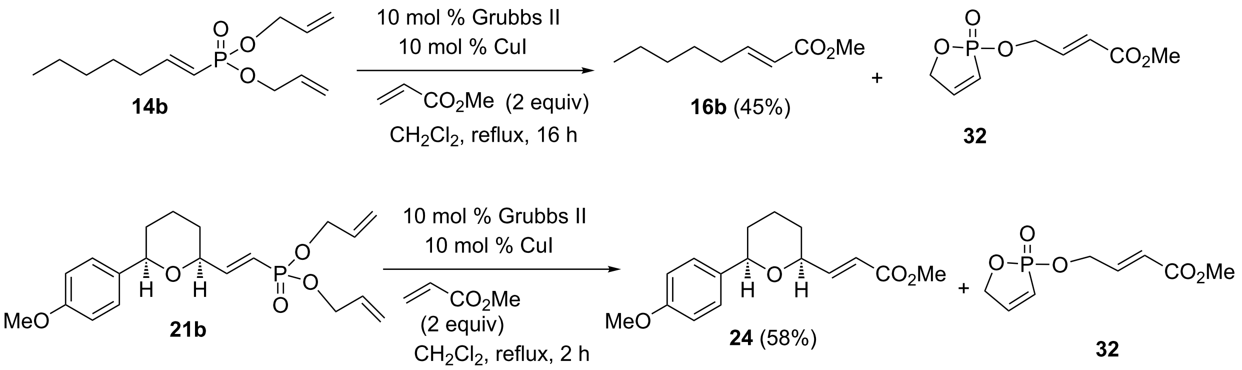


**Scheme 8:** Ring closing vs relay cross metathesis.

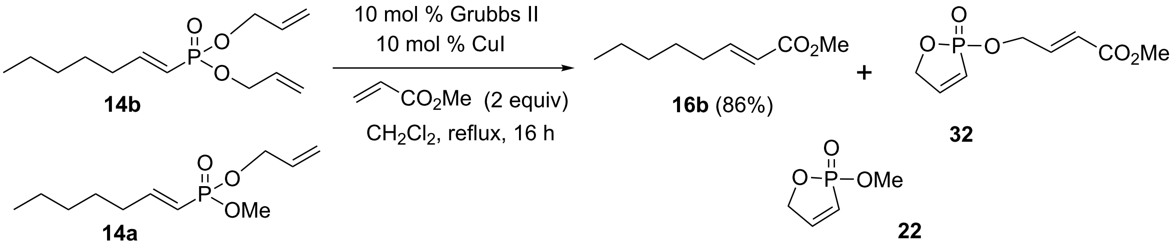
tution of the vinylphosphonate. It was proposed that (*E*) diallyl vinylphosphonates would prefer to form the 5-membered ring oxaphosphole **30** and therefore, like the corresponding mono-allyl phosphonates, should engage in relay cross metathesis reactions.

To test the hypothesis, the diallyl vinylphosphonate **14b** was subjected to cross metathesis with methyl acrylate using standard conditions (Scheme 9). The corresponding cross metathesis product, unstaurated ester **16b**, was obtained with 45% conversion. Again, isolation resulted in some loss of product. $^{31}$P NMR measurements also confirmed the formation of the 5-membered phosphate heterocycle **32**. Similarly, diallyl phosphonate **21b** was reacted with methyl acrylate to give the corresponding unsaturated ester **24** in good yield along with the phosphonate heterocycle **32**. In general, reaction of either mono- allyl or diallyl vinylphosphonates with methyl acrylate proceeded with comparable yields.

The mono- and diallyl vinylphosphonates were first synthesized and then chromatographically separated before they were subjected to the cross metathesis reaction. In an ideal case, a single cross metathesis product would be formed from a crude mixture of mono-allyl and diallyl vinylphosphonates, avoiding the inefficiencies of chromatographic separation. A mixture of mono- and diallyl vinylphosphonates **14a** and **14b** was subjected to cross metathesis reaction with methyl acrylate (Scheme 10). The reaction progress was monitored by



**Scheme 9:** Relay cross metathesis of diallyl vinylphosphonates with methyl acrylate.



**Scheme 10:** A cross metathesis reaction of both mono- and diallyl vinylphosphonates with methyl acrylate.

$^{31}$P NMR spectroscopy. After the reaction was complete, the $^{31}$P NMR spectrum showed the formation of the two oxaphospholes **22** and **32** in a ratio corresponding to the amount of vinylphosphonates **14a** and **14b** in the starting material. Chromatographic separation of the crude product gave the unsaturated ester **16b** in 86% isolated yield.

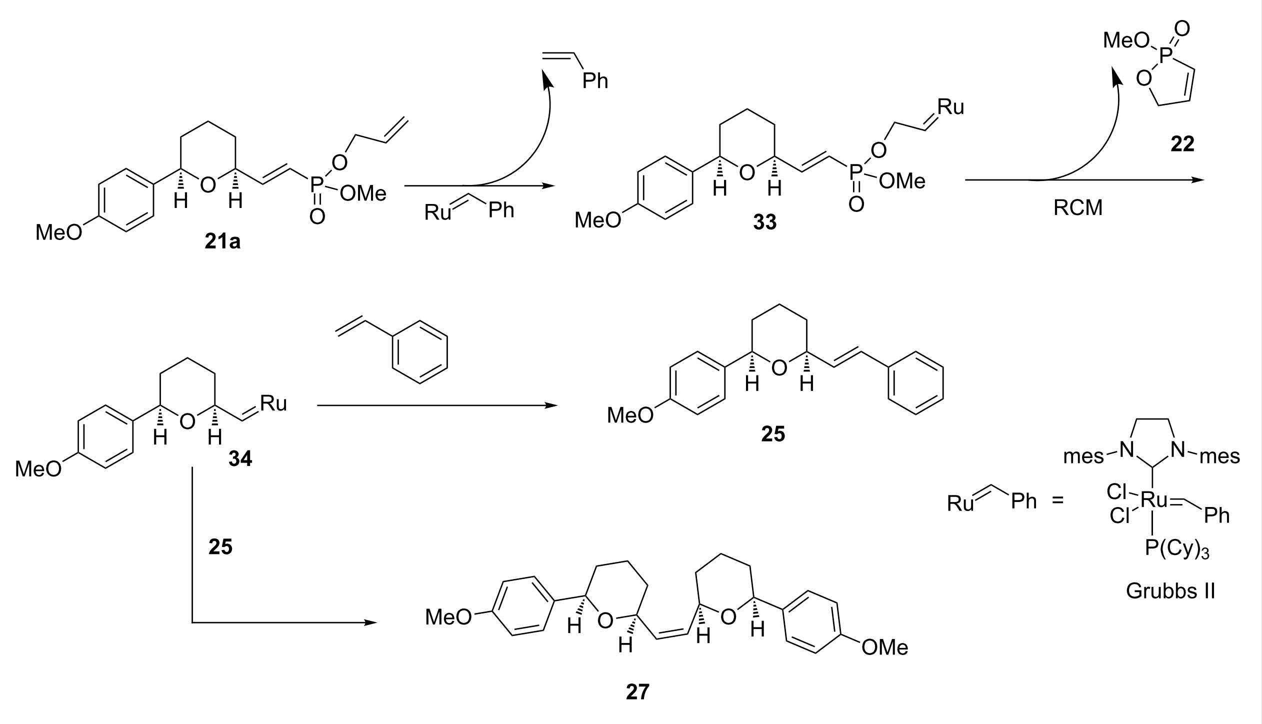
It is proposed that the Grubbs catalyst first reacts with the terminal alkene (Scheme 11) of the allyl phosphonate ester **21a** to give the metal alkylidene **33**. The metal alkylidene then reacts with the vinylphosphonate in a ring closing metathesis (RCM) to generate the oxaphosphole **22** and a new metal alkylidene **34**. The sequence is completed by reaction of the metal alkylidene **34** with the metathesis partner (styrene) to give the tetrahydropyran **25**. The formation of the dimeric product **27** is probably the result of a competitive cross metathesis reaction between the tetrahydropyran **25** and the metal alkylidene **34** [31].

Once the activation of vinylphosphonates toward cross metathesis was established, it became clear that the overall success of this method would depend on a selective, high yielding synthesis of mono-allyl phosphonates. The proposed mechanism of the TBAI catalyzed allylation (Scheme 12) involves cleavage of the Me–O bond to form a phosphonate anion **35**. The anion is re-alkylated with allyl bromide to produce the mono-allyl phosphonate **14a**. The major weakness of this approach is that the mono-allyl phosphonate can further react with iodide leading ultimately to the diallyl phosphonate **14b**. Early in the reaction, the mono-allyl phosphonate is the dominant product. However, attempts to force the reaction with longer reaction times, increased TBAI, or increased ally bromide, leads to an increase in diallyl phosphonate **14b**.

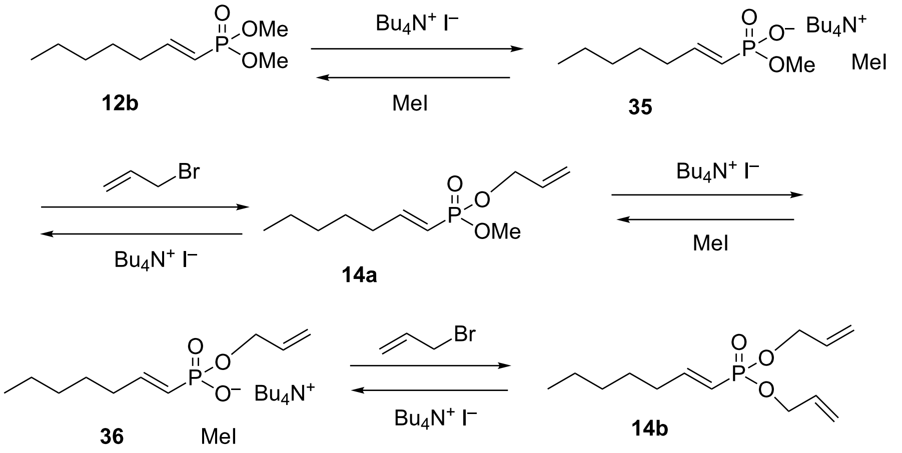
Analysis of the TBAI allylation mechanism suggested that a good approach to mono-allyl phosphonate **14a** would be a stoichiometric demethylation followed by a rapid allylation under ambient conditions. During the synthesis of phosphonate based ionic liquids, Sachnov et al. showed that ethylimidazole would reacted with dimethyl methylphosphonate to give ethylimidazolium methylphosphonate in quantitative yield [32]. We were pleased to observe [$^{31}$P NMR] that dimethyl vinylphosphonate **12b** reacted with neat methylimidazole at 100 °C to give the imidazolium salt **37** (Scheme 13). Treatment of the salt with 5 equivalents of allyl bromide at room temperature for two days gave the mono-allyl phosphonate in 71% isolated yield (two steps). It is probable that this transesterification reaction can be further optimized to both increase yields and decrease the reaction time.

## Conclusion

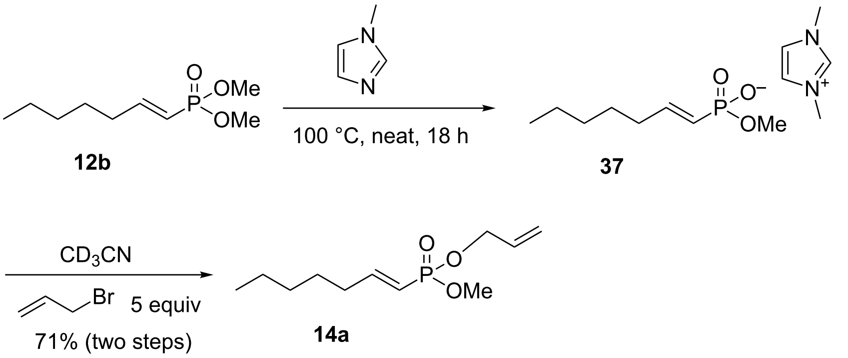
The experiments presented above have demonstrated that whereas the dimethyl esters of substituted vinylphosphonates are characterized as type IV substrates in alkene cross



**Scheme 11:** A proposed mechanism for the relay cross metathesis reaction of allyl vinylphosphonates.



**Scheme 12:** A proposed mechanism for the TBAI catalysed transesterification.



**Scheme 13:** A selective synthesis of mono-allyl phosphonates.

metathesis reactions and are unreactive, the corresponding allyl esters show significantly improved reactivity. The improved reactivity is attributed to relay step in the cross metathesis reaction mechanism.

## Supporting Information

### Supporting Information File 1

Experimental procedures, characterization data, $^1H$ and $^{13}C$ spectra for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-201-S1.pdf]

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# Photorelease of phosphates: Mild methods for protecting phosphate derivatives

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Full Research Paper

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## Abstract

We have developed a new photoremovable protecting group for caging phosphates in the near UV. Diethyl 2-(4-hydroxy-1-naphthyl)-2-oxoethyl phosphate (**14a**) quantitatively releases diethyl phosphate upon irradiation in aq MeOH or aq MeCN at 350 nm, with quantum efficiencies ranging from 0.021 to 0.067 depending on the solvent composition. The deprotection reactions originate from the triplet excited state, are robust under ambient conditions and can be carried on to 100% conversion. Similar results were found with diethyl 2-(4-methoxy-1-naphthyl)-2-oxoethyl phosphate (**14b**), although it was significantly less efficient compared with **14a**. A key step in the deprotection reaction in aq MeOH is considered to be a Favorskii rearrangement of the naphthyl ketone motif of **14a**,**b** to naphthylacetate esters **25** and **26**. Disruption of the ketone-naphthyl ring conjugation significantly shifts the photoproduct absorption away from the effective incident wavelength for decaging of **14**, driving the reaction to completion. The Favorskii rearrangement does not occur in aqueous acetonitrile although diethyl phosphate is released. Other substitution patterns on the naphthyl or quinolin-5-yl core, such as the 2,6-naphthyl **10** or 8-benzyloxyquinolin-5-yl **24** platforms, also do not rearrange by aryl migration upon photolysis and, therefore, do not proceed to completion. The 2,6-naphthyl ketone platform instead remains intact whereas the quinolin-5-yl ketone fragments to a much more complex, highly absorbing reaction mixture that competes for the incident light.

## Introduction

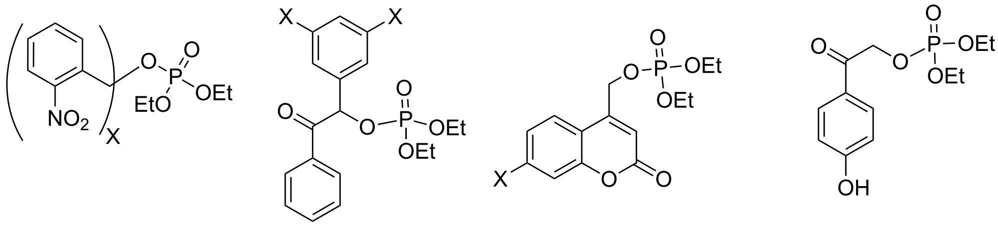
Phosphates have long held an important formative position in the development of organic photochemistry beginning with the seminal report by Havinga [1] of the unusual substituent effects in the photosolvolysis of aryl phosphates that showed unexpectedly pronounced *meta* activation of substituted aryl phosphates. A strong ‘*meta* effect’ resulting in enhanced reaction efficiency by electron withdrawing, *meta* substituents is contrary to their ground state effects on solvolysis reactions which, instead, display enhanced reactivity for *para* substituents. This contrasting substituent reactivity is a consequence of two different potential energy surface (PES) contours that control the reactivity, an observation first rationalized by Zimmerman through a comparison of the change in PES electron distribution in the ground (HOMO) and excited states (LUMO) using Hückel molecular orbital theory [2,3], subsequently attributed by him to the positioning of conical intersections between the HOMO–LUMO PE surfaces [4,5]. He termed this phenomenon the "*meta* effect", and generalized it for photochemical solvolysis reactions. Several additional photosolvolysis studies substantiated the generality of the *meta* effect for phosphate leaving groups in heterolytic photoreactions.

Over the past four decades, additional examples of phosphate esters attached to reactive chromophores other than phenyl and benzyl [6-11] have been investigated for their propensity to undergo heterolytic photosolvolysis reactions, most notably *o*-nitrobenzyl (o-NB) [12], benzyl phenyl ketone (benzoin) [13,14], coumarin-4-ylmethyl [15], and, more recently, *p*-hydroxyphenacyl (pHP) [15] phosphate esters (Figure 1). While these chromophores exhibit a range of photophysical properties, all share a conjugated aromatic structural motif that facilitates UV–vis absorption and serves as a traceless reagents, orthogonal to common ground state deprotection processes and essentially independent of pH effects. Thus, the chromophores are particularly useful at neutral pH and no added reagents are required for protecting group release.

Many photosolvolysis studies have targeted key biological substrates [6,8-12] for mechanistic and phenomenological studies. The culmination of these studies has resulted in the development of an entirely new branch of photochemistry with application in both organic chemistry and biochemistry. The reagents are generally described as "caged" compounds or photoremovable protecting groups (PPGs) in which the attached chromophore masks the biological activity of a substrate. Irradiation releases the substrate, allowing it to return to its normal bioactivity.

The desirable properties of any new PPG candidate are 1) absorption at wavelengths near or above 400 nm, 2) enhanced chemical and photochemical quantum yields and 3) improved rate of release, ideally in the range of ps to ns time constants; all three are useful properties for applications in organic chemistry and biochemistry, but they are particularly important for mechanistic studies in biochemistry and biophysics [6,8-11]. Most PPG candidates require sufficiently high energy excited states for heterolysis of a carbon–oxygen or carbon–heteroatom bond that binds the chromophore to a substrate. This limits the useful absorption range to ca. 350 to 400 nm for heterolysis by a primary photochemical pathway.

Phosphates hold a central historic position in caged photochemistry through their cross-disciplinary significance in both biology and chemistry. Nucleotides (especially ATP, cAMP, and GTP) were among the first to be covalently bound to chromophores in a cage or PPG format that were demonstrably released upon photolysis. Benzoin caged cAMP and *o*-nitrophenethyl caged ATP, seminal examples of caged phosphates, are often the two classic caged biochemical substrates cited [6-13,15-17]. Subsequent interest in and application of PPGs has exploded largely because they provide researchers in interdisciplinary fields with a tool for initiating biological [18] and chemical processes [6,8,10,11] by remote control with light as the activator. Spatial, temporal and concentration parameters for releasing substrates are controlled by adjusting the focus, time resolution, and intensity of the light source in conjunction with other variables such as the photochemical reactivity and molecular reaction pathway. Since photolysis reactions are generally considered to be kinetically much faster than ground state processes (most photorelease rates have sub µsec time



*o*-nitrobenzyl (o-NB)
**1a**, X = 1
**1b**, X = 2

benzoin
**2a**, X = H
**b**, X = OMe

coumarin-4-ylmethyl
**3a**, X = OH
**b**, X = OMe
**c**, X = $NMe_2$

*p*-hydroxyphenacyl (pHP)
**4a**

**Figure 1:** Common photoremovable protecting groups (PPGs) for phosphates depicted as diethyl phosphate (DEP) esters.

constants), the use of time resolved lasers to activate PPGs offers much greater temporal resolution and more precise spatial control of the reaction variables in chemical processes, increasingly important features for biophysics and biochemistry.

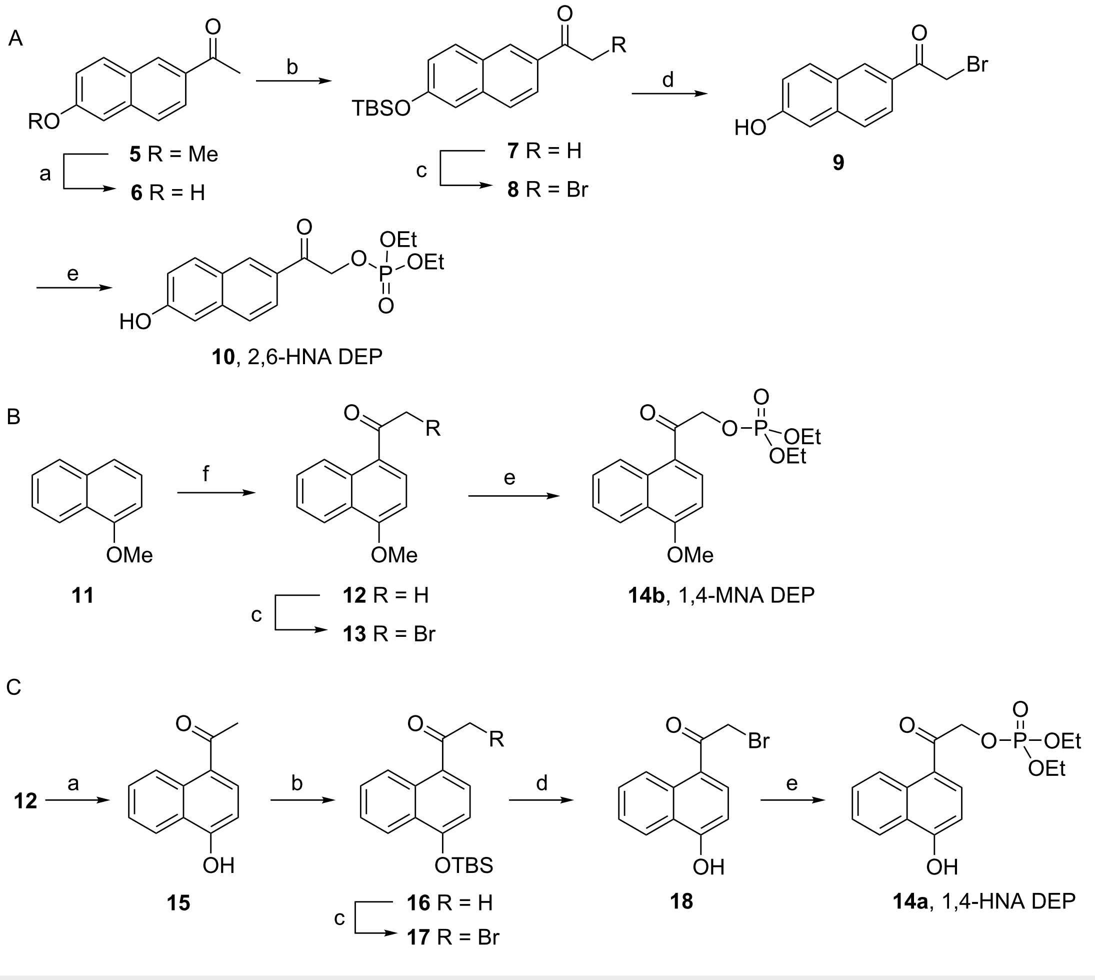
Our studies on photosolvolysis reactions have uncovered several new chromophores with superior PPG properties amenable to photodeprotection. Earlier work defined the advantages and limitations of *p*-hydroxyphenacyl (pHP, **4**), a PPG that is now finding application in biochemistry and chemistry [15]. We now report new pHP analogs with a fused aromatic or heteroaromatic extension of pHP. Our intent was to impose the pHP motif on the naphthyl and indolin-5-yl platforms (maintaining the critical substituent pattern) in order to foster aryl ketone migration by a photo-Favorskii rearrangement concomitant with ligand release. The combination of these features shifts and extends the chromophore, exhibiting a more intense, broader absorption band closer to the visible region, making the PPG more accessible for photodeprotection. Thus, elaborating the two motifs by optimally appending a hydroxy and carbonyl positioned for excited state interaction, in accord with the pHP motif **4a**, invited serious examination.

# Results

## Synthesis of phosphate esters

A series of diethyl phosphate (DEP) esters caged with extended 2-(6-hydroxynaphthalen-2-yl)-2-oxoethyl (2,6-HNA, **10**), 2-(4-hydroxynaphthalen-1-yl)-2-oxoethyl (1,4-HNA, **14a**) and its methoxy ether (1,4-MNA, **14b**)**,** and 8-(benzyloxy)quinolin-5-yl)-2-oxoethyl (5,8-BQA, **24**), each modeled after the *p*-hydroxyphenacyl (pHP, **4**) chromophore were synthesized as illustrated in Scheme 1 and Scheme 2.

Synthesis of the extended 2,6-HNA phosphate ester **10** was accomplished by first demethylating 2-acetyl-6-methoxynaph-



**Scheme 1:** Synthesis of 2,6-HNA DEP (**10**), 1,4-HNA DEP (**14a**), and 1,4-MNA DEP (**14b**) DEP esters. Reagents and conditions: a) PhSH, $K_2CO_3$, *N*-methyl-2-pyrrolidinone, 194 °C, 45 min; b) TBSCl, $Et_3N$, DBU, $CH_2Cl_2$, rt, 28 h; c) $CuBr_2$, 1:1 $CHCl_3$/EtOAc; d) $KHSO_4$, MeOH (aq), $CH_2Cl_2$, rt, 43 h; e) tetramethylammonium diethyl phosphate, DMF, 55 °C, 2–3 h; f) $Ac_2O$, $AlCl_3$, $CH_2Cl_2$, 0 °C to rt over 3 h then stirred at rt.

thalene (**5**) with thiophenol and 0.1 mol percent potassium carbonate in *N*-methyl-2-pyrrolidinone at 194 °C [19] to generate the hydroxynaphthalene **6** (72%) followed by protecting the hydroxy group with TBSCl to give **7** (89%, Scheme 1A). α-Bromination with copper(II) bromide [20] gave **8** (96%, direct bromination of **6** gave poor yields). The TBS group was removed in 30% aqueous methanol containing 10–20% methylene chloride and several molar equivalents of potassium hydrogen sulfate to provide hydroxy bromo ketone **9** (yield, 75%) [21], which was reacted with tetramethylammonium diethyl phosphate under anhydrous conditions to afford diethyl (2-(6-hydroxynaphthalen-2-yl)-2-oxoethyl) phosphate (2,6-HNA DEP, **10**, 62%) [22].

Diethyl (2-(4-methoxynaphthalen-1-yl)-2-oxoethyl) phosphate (1,4-MNA DEP, **14b**) was obtained, as shown in Scheme 1B, beginning with Friedel–Crafts acylation of 1-methoxynaphthalene (**11**) yielding 1-acetyl-4-methoxynaphthalene (**12**, 73%). α-Bromination with copper(II) bromide gave **13** (44%) which was converted to the phosphate ester using tetramethylammonium diethyl phosphate in dimethoxyethane (DME) at room temperature to give diethyl (2-(4-methoxynaphthalen-1-yl)-2-oxoethyl) phosphate (1,4-MNA DEP, **14b**, 92%).

The hydroxy analog (1,4-HNA DEP, **14a**, Scheme 1C), was synthesized from methoxynaphthone **12** by demethylation with thiophenol giving acetylnaphthol **15** in moderate yield (42%). Protection with TBSCl gave **16** (86%) followed by α-bromination to **17** (89%). TBS deprotection gave 2-bromo-1-(4-hydroxy-1-naphthyl)ethanone, (**18**, 59%) which was converted to diethyl (2-(4-hydroxynaphthalen-1-yl)-2-oxoethyl) phosphate (1,4-HNA DEP, **14a**, 31%) with tetramethylammonium diethyl phosphate.

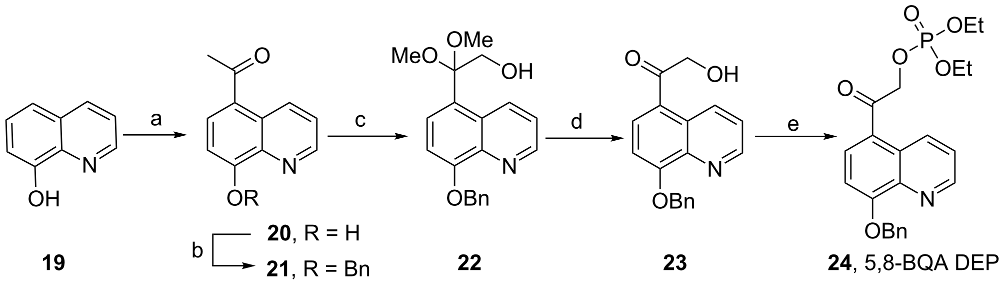
Benzyl protected diethyl 2-(8-hydroxyquinolin-5-yl)-2-oxoethyl phosphate (**24**) was synthesized from 8-hydroxyquinoline (**19**) by first performing acylation [23] with acetyl chloride and then quantitatively protecting the hydroxy group as its benzyl ether [24] followed by installation of ketal protection with iodobenzene diacetate in alkaline methanol [25] to give **22** (90%, Scheme 2). Deprotection of **22** with 50% acetic acid gave the α-hydroxy ketone **23** (98%) which was esterified with diethyl phosphoryl chloride in pyridine [26] to afford 2-(8-(benzyloxy)quinolin-5-yl)-2-oxoethyl diethyl phosphate (5,8-BQA DEP, **24**, 30%).

The UV–vis spectra of 1,4-substituted esters **14a,b** ($\lambda_{max}$ range from 319 to 325 nm) are substantially red-shifted relative to the pHP ester **4a** ($\lambda_{max}$ at 287 nm) and exhibit molar extinction coefficients (ε) of ca. $10^4$ $M^{-1}cm^{-1}$ in aq MeCN (Figure 2). For the 2,6-HNA DEP (**10**) and 2,6-HNA GABA, the $\lambda_{max}$ appears at 325 nm whereas the $\lambda_{max}$ for the 5,8-BQA phosphate **24** occurs at 321 nm in 10% aq MeCN. For the 2,6-HNA series, a strong fluorescence emission is observed at 470 nm as shown here for the more aqueous soluble GABA ester derivative. The 2,6-HNA GABA had better aqueous solubility for fluorescence studies. (See Supporting Information File 1 for synthetic and spectral details).

## Photolysis of phosphate esters

Irradiation of **14a** at 350 nm in Pyrex vessels under ambient conditions in 1% aq $CD_3OD$ resulted in the release of diethyl phosphate as confirmed by NMR (Scheme 3, Table 1). The protecting group underwent a photo-Favorskii rearrangement (Scheme 4), yielding predominantly methyl 4-hydroxy-1-naphthylacetate (**25**) with a trace amount of reduction product **15** (Scheme 3). In anhydrous methanol, the ratio of **25**/**15** was approximately 3:1. When the photolysis was performed in 10% aq MeCN, **15** was the only assigned structure from the $^1H$ NMR spectrum of a complex product mixture.

Photolysis of the methoxy analog **14b** under similar conditions either in $CD_3OD$ or 1% aq MeCN resulted in the release of DEP and formation of **12** as confirmed by reversed-phase HPLC



**Scheme 2:** Synthesis of diethyl 8-(benzyloxy)quinolin-5-yl)-2-oxoethyl phosphate (5,8-BQA DEP, **24**). Reagents and conditions: (a) $CH_3COCl$, $AlCl_3$, nitrobenzene, 14 h, 40%; (b) $PhCH_2Br$, $K_2CO_3$, DMF, rt, 24 h, 100%; (c) $PhI(OAc)_2$, MeOH, KOH, 0 °C to rt, 24 h, 90%; (d) 50% $CH_3COOH$, rt, 12 h, 98%; (e) $P(O)Cl(OEt)_2$, pyridine, −5 °C to rt, 24 h, 30%.

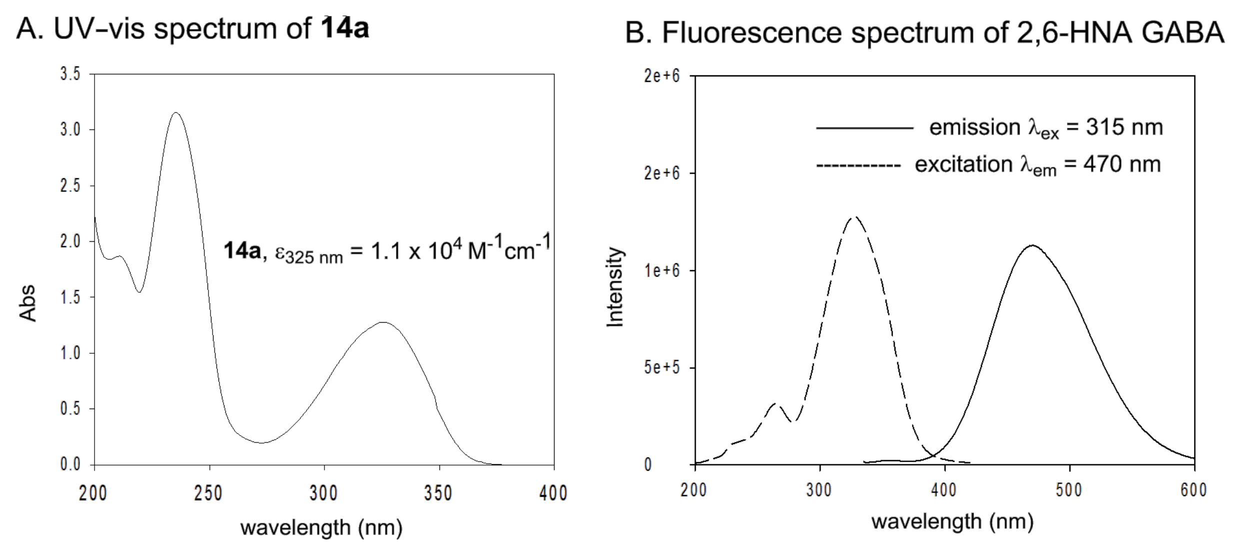
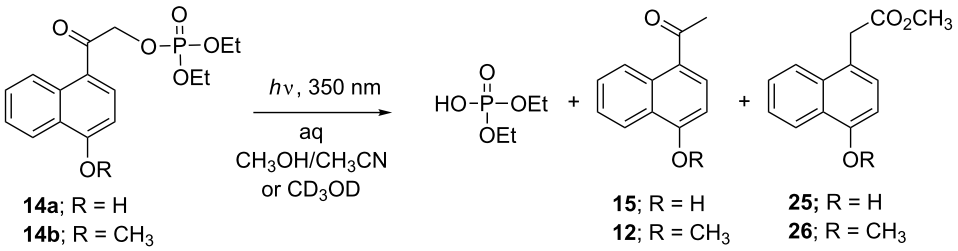


**Figure 2:** A. UV–vis spectrum of **14a** (1,4-HNA DEP) in 1% aq MeCN. B. Fluorescence emission/excitation spectra of 2,6-HNA GABA (0.042 mM) in pH 7.3 TRIS buffer containing 1% MeCN.



**Scheme 3:** Photolysis of 1,4-HNA and 1,4-MNA diethyl phosphates **14a** and **14b** in aq MeOH.

**Table 1:** Photolysis efficiencies and product yields for 1,4-HNA DEP (**14a**) and 1,4-MNA DEP (**14b**).

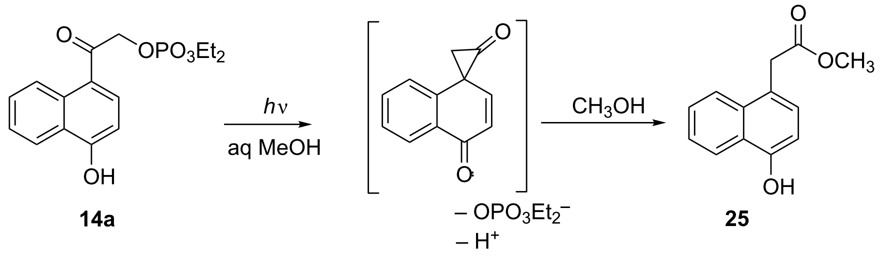
| ester | % conversion[a] | deprotection % yield[b] | $\Phi_{dis}$[c] |
|---|---|---|---|
| **14a** OH | 98 | 100 | 0.028 |
| **14b** OMe | 40 | 90 | 0.0076 |

[a]One hour photolysis in $CD_3OD$ at 350 nm, determined by $^1H$ NMR using DMF as an internal standard, [b]diethyl phosphate, corrected for conversion, [c]determined by RP-HPLC; photolysis in 1% aqueous MeOH.

(RP-HPLC) and NMR (Scheme 3, Table 1) but the conversion was not complete and the reaction was lethargic due to competitive absorption by the unrearranged product chromophore **12**. In 1% aq MeOH, however, the major product from the protecting group was methyl 4-methoxy-1-naphthylacetate (**26**) which was characterized by the signals at δ 4.02 and 3.68 ppm and confirmed by FAB–MS (*m*/*z* 230) and comparison with an independently synthesized sample obtained from Friedel–Crafts alkylation of 1-methoxynaphthalene (**11**) with methyl bromoacetate and ferric oxide [27].

Quantum yields for disappearance and percentage conversions for **14a** are higher than that of **14b** as indicated in Table 1. After one hour of photolysis at 350 nm in $CD_3OD$, **14a** reached 98% conversion whereas **14b** managed to attain only 40% conversion. The disappearance quantum efficiency ($\Phi_{dis}$) for **14a** in 1% aq $CD_3OD$ was 0.028, more than three times that for **14b** under the same conditions. However, the deprotection yields for both esters were excellent, resulting in quantitative release of DEP based on conversion.

The quantitative conversion and apparent good efficiency of the 1,4-derivative **14a** prompted further investigation. The quantum yield for disappearance of **14a** in 1% aq MeCN ($\Phi_{dis}$ = 0.021) is comparable to that observed in aq MeOH ($\Phi_{dis}$ = 0.028, Table 1 and Table 2) but the product mixture was more complex (vide infra). Interestingly, quantum yields for the disappearance for **14a** are enhanced three-fold ($\Phi_{dis}$ = 0.067) when the photolysis



**Scheme 4:** The photo-Favorskii rearrangement of **14a**.

solution was purged free of oxygen (Table 2). The quantum yield of **14a** for the triplet sensitized photolysis in the presence of benzophenone (BP), a well-established triplet sensitizer, at 254 nm under $O_2$-free conditions was $\Phi_{dis} = 0.022$. These combined results demonstrate that the reactive excited state is a triplet that is partially quenched by $O_2$ under ambient conditions.

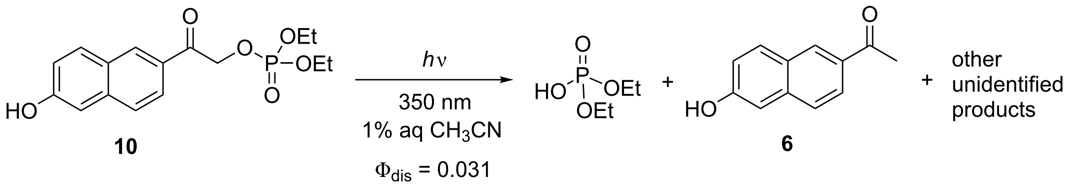
**Table 2:** Photolysis of 1,4-HNA diethyl phosphate (**14a**) in the presence and absence of $O_2$ and benzophenone in 1% aq MeCN.

| $\Phi_{dis}$[a] | conditions |
|---|---|
| 0.067[b] | degassed with Ar |
| 0.022 | BP sensitized[c] |
| 0.021 | saturated with Air |

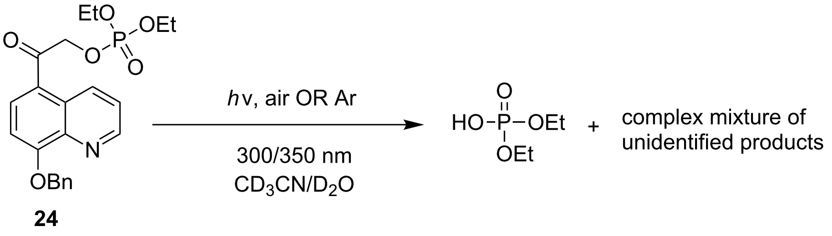
[a]Determined with RP-HPLC; [b]Estimated value (see experimental section); [c]Benzophenone (11 mM) as the sensitizer and **14a** (0.59 mM) in 1% aq MeCN at 254 nm and purged with Ar.

Irradiation of 2,6-HNA DEP (**10**) at 350 nm in 1% aq MeCN under conditions comparable to those employed with **14a**,**b** also released phosphate. The disappearance quantum yield for **10** ($\Phi_{dis} = 0.031$) was nearly the same as that obtained for **14a** but the conversion after a 10 min irradiation was only 67%. Unlike **14a**,**b**, however, the chromophore did not undergo the photo-Favorskii rearrangement, forming only the reduction product 2-acetyl-6-hydroxynaphthalene (**6**) in addition to other unidentified photoproducts (Scheme 5). These results paralleled our observations for **14a**,**b** in aq MeCN.

Finally, photolysis of 5,8-BQA diethyl phosphate (**24**) in 10% aq MeCN at 300 or at 350 nm under degassed conditions released DEP at only 30% conversion, even after 18 hours as confirmed by both $^1$H and $^{31}$P NMR analyses (Scheme 6). The quantum yields for disappearance and product appearance ($\Phi_{dis} = \Phi_{app} = 0.00024$) were exceptionally low (Table 3), considerably less than any of the naphthyl (**10** and **14**) or



**Scheme 5:** Photolysis of 2,6-HNA DEP (**10**) in 1% aq MeCN.



**Scheme 6:** Photolysis of 5,8-BQA diethyl phosphate (**24**).

**Table 3:** Quantum yields and conversions of **24** with and without Ar purging.[a]

| ester | % conversion[b] ambient $O_2$ | % conversion[b] Ar purged | $\Phi_{dis}$ (× $10^3$)[c] ambient $O_2$ | $\Phi_{app}$ (× $10^3$)[d] ambient $O_2$ |
|---|---|---|---|---|
| **24** | 32 | 30 | 0.24 | 0.24 |

[a]Solvent was 10% $H_2O$ in MeCN. Photolyses were conducted with 300 or 350 nm lamps. [b]Determined using $^1H$ NMR in 10% $D_2O$ in $CD_3CN$; [c]Determined with $^1H$ NMR for the disappearance of the starting material at 350 nm with air; [d]Determined with $^1H$ NMR for the appearance of diethyl phosphate at 350 nm with air.

phenacyl (**4a**) analogs (see Table 4, Discussion section). A complex product mixture of byproducts of the indolinyl chromophore was obtained which was not investigated further.

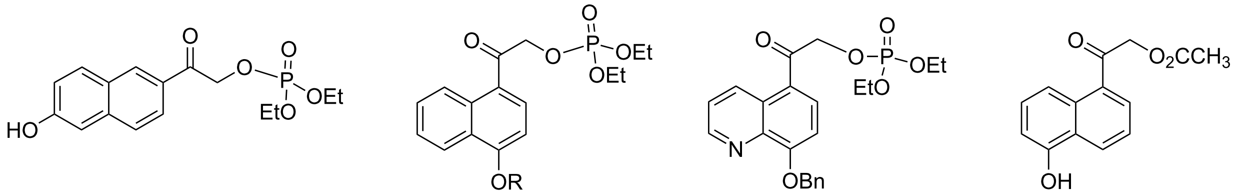
## Discussion

In our design of new PPG chromophores, we have attempted to circumvent or avoid the inherent deficiencies of the classical o-NB, benzoin, and coumaryl analogs (see Figure 1). A noisome limitation of o-NB PPGs that mitigate their general use in biological and mechanistic studies are their inherently slow reaction rates. o-NB rate constants are decidedly among the slowest for a photochemical heterolysis (e.g., usually not larger than μsec time constants) due to mechanistic constraints imposed by the rate determining step of a ground state hemiacetal hydrolysis, generated photochemically, that releases the substrate. Furthermore, the o-NB PPG chromophore, itself, is converted to an *o*-nitroso aldehyde (or ketone) that reacts with endogenous nucleophiles such as amines, thiols, etc. either present on the substrate, on target proteins or in the media. Poignant evidence of these limitations surfaced during mechanistic investigations of GAP protein GTPases and enzymatic studies of ATPase [28-34].

We [15,28,29,35] and others [6-11] have successfully offered alternatives to the o-NB PPG series, initially with benzoin phosphate **2** [13,14] and coumarin-4-ylmethyl phosphate **3**. However, the chromophores for these candidates remain intact or rearrange to more strongly absorbing chromophores which compete for the effective radiation wavelengths, often resulting in incomplete conversions that compromise their synthetic utility. These chromophores and especially their photoproducts are also highly fluorescent, which frequently prove to be disadvantageous.

The recent candidates are based on a pHP motif. Phosphate esters of **10**, **14**, **24**, and acetate **27** [19] each possess a hydroxy donor coupled with an acetyl function bearing the leaving group (Figure 3). One of these, the 5-hydroxy-1-naphthylacetyl motif as its acetate ester **27**, has already been reported to be photochemically inert in 1:1 aq MeCN by Wan [19]. Accordingly, we did not pursue the study of **27** (vide infra). Extending the aromatic portion of the chromophore with either an added benzo or pyridyl group using the pHP model red-shifted the chromophore absorption for the remaining three, **10**, **14**, and **24** (e.g., the maximum of **4a** at 280 nm shifted to 325 nm for **14a** tailing nearly to 400 nm, see Figure 2).

Similar extensions of the benzyl PPG expanding it to naphthylmethyl [35,36] (**28** and **29**, Figure 4) or modifications by attaching substituents to phenacyl (e.g., **4b,c**) or benzyl (**30b–d**) moieties, and naphthylacetyl [37] reportedly lowered the singlet and triplet state energies only modestly [10,11] and were unsuitable because these chromophores remained intact and in competition for incident radiation.



**10**

diethyl 2-(6-hydroxynaphthalen-2-yl)-2-oxoethyl phosphate (2,6-HNA DEP)

**14a**, R = H
**14b**, R = Me

diethyl 2-(4-hydroxy-1-naphthyl)-2-oxoethyl phosphate and diethyl 2-(4-methoxynaphthalen-1-yl)-2-oxoethyl phosphate (1,4-HNA DEP and 1,4-MNA DEP

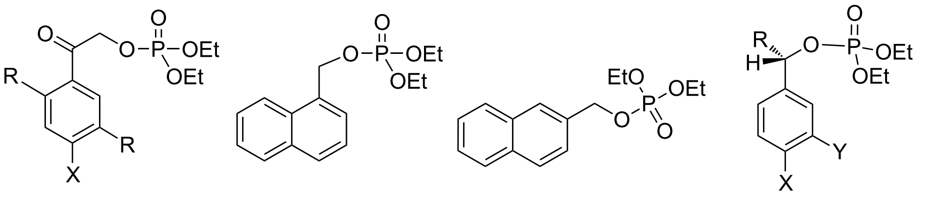
**24**

diethyl 2-(8-(benzyloxy)quinolin-5-yl)-2-oxoethyl phosphate (5,8-BQA)

**27**, acetate

2-(5-hydroxynaphthalen-1-yl)-2-oxoethyl (1,5-HNA) acetate

**Figure 3:** Naphthyl and quinolin-5-yl caged phosphate esters **10**, **14**, **24** and **27** (acetate ester).



**4b**, R = H, X = OMe
**4c**, X = H, R = $CH_3$

**28**

**29**

**30a,** X,Y = H, R = H
**b,** X,Y = H, R = $CH_3$
**c,** X = OMe, Y,R = H
**d,** X,R = H, Y = OMe

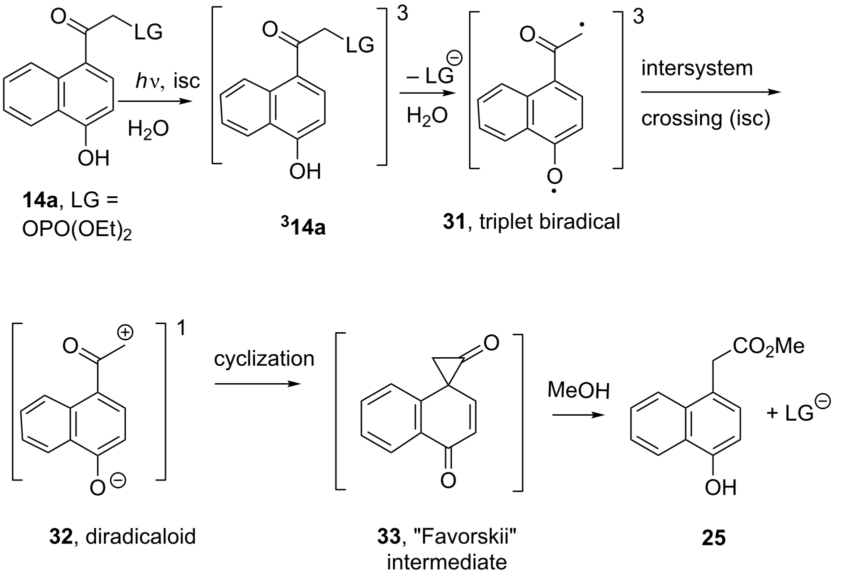
**Figure 4:** Previously studied caged diethyl phosphate PPGs possessing aromatic (benzyl, phenacyl, and naphthylmethyl) phosphates.

Photolysis of 1,4-HNA DEP (**14a**) in 1% aq MeOH released DEP with modest efficiency, Φ = 0.028. Similarly, the methoxy analog, 1,4-MNA DEP (**14b**), released DEP, but with a much lower efficiency (Φ = 0.0078). Both quantitatively produced DEP and, pleasingly, underwent photo-Favorskii rearrangements converting the aryl ketones to methyl naphthylacetates, blue-shifting the byproduct chromophore absorptions.

Both **14a** and **14b** now become the first new examples of photo-Favorskii rearrangements, here on a naphthyl platform. Previous examples are limited to phenacyl frameworks [6-9,15,38,39]. It is interesting to note, however, that replacement of the OH with OMe in the 1,4-HNA series results in both lower efficiency and decreased yield, a further analogy to that found with *p*-methoxy vs *p*-hydroxyphenacyl DEPs **4a,b** (Table 4) [6,13,15,40] and with other leaving groups.

In contrast to the results in 1% aq MeOH, photolysis of **14a**,**b** in anhydrous media or changing the co-solvent to MeCN resulted in a decrease in conversion (40–60%) and more complex reaction mixtures. The only products identified were DEP (quantitative) and reduction products **12** or **15**, signaling a change in mechanism from heterolysis to homolysis. The low conversions are primarily due to competition for incident radiation by the unrearranged byproduct chromophore **12** or **15**.

The role of $H_2O$ and hydroxylic solvents observed in this series is in complete accord with solvent effects on the parent pHP photoreactions [6,13,15,40-46]. The photo-Favorskii reaction (Scheme 7) is favored by aqueous-based solvents that serve both as a proton donor and an acceptor to the conjugate base generated from the chromophore's triplet state heterolytic cleavage of the leaving group. The dual behavior of $H_2O$ is



**14a**, LG = $OPO(OEt)_2$

**$^3$14a**

**31**, triplet biradical

**32**, diradicaloid

**33**, "Favorskii" intermediate

**25**

**Scheme 7:** Photo-Favorskii mechanism based on pHP DEP **4a** photochemistry as applied to 1,4-HNA DEP (**14a**).

manifest in accepting a proton from the naphthol OH while simultaneously solvating the developing anionic charge on the departing nucleofuge. The resulting biradical **31**, which must be a triplet by Wigner's spin rule [47] is formed from the chromophore while on the excited state PES. Intersystem crossing (isc) to a diradicaloid ground state intermediate **32** (vide infra) is followed by cyclization to form the 'Favorskii intermediate' **33** [6,8,15,26,38,39,48].

In contrast to the 1,4-naphthyl design, neither **10** nor **24** underwent Favorskii rearrangements. While both gave stoichiometric release of DEP, the chromophores either remain intact (for **10**) as also reported for other 2-naphthylacetyl analogs [49] or are consumed by oxidation and fragmentation as in the case of **24**. Thus, the conversion and chemical yields were low and the photolysates were complex mixtures of byproducts. In the case of **24**, although the reaction efficiency was insensitive to $O_2$ (implying singlet reactivity, not quenchable by ambient $O_2$), the product mixture included several oxidation byproducts of the chromophore. Thus, photoreactions of **24** with ambient $O_2$ were a complication not encountered with **10** or **14a**,**b**.

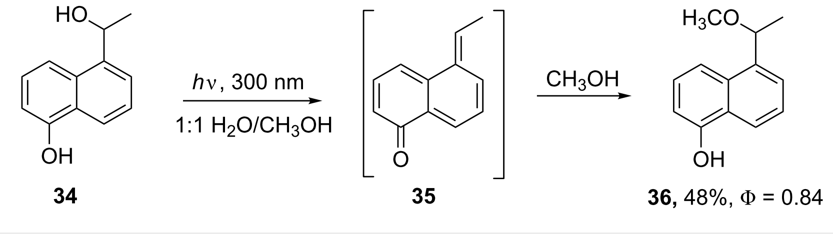
The failure to deconjugate the carbonyl of either chromophore by rearrangement once again impinged on the overall conversion to released substrate. The formation of competing chromophoric byproducts limits the conversion and yields [6,10,11,15]. For example, changing the leaving group for **10**, i.e., photolysis of 6-hydroxy-2-naphthylacetyl GABA ester (Figure 2B) inefficiently released 4-aminobutyrate (GABA) in low yield and is absent of any chromophore rearrangement.

It is surprising that 2,6-HNA DEP (**10**) and Wan's 1,5-HNA acetate **27** [19] do not undergo a photo-Favorskii rearrangement. In the case of **27**, Wan suggested that the lack of reactivity may have arisen from factors such as a lower excited state energy of the naphthyl ketone platform or the disruption of both aromatic rings for the 1,5 substituted analog **27** whereas only one ring is involved for the 1,4 substituted derivative [19].

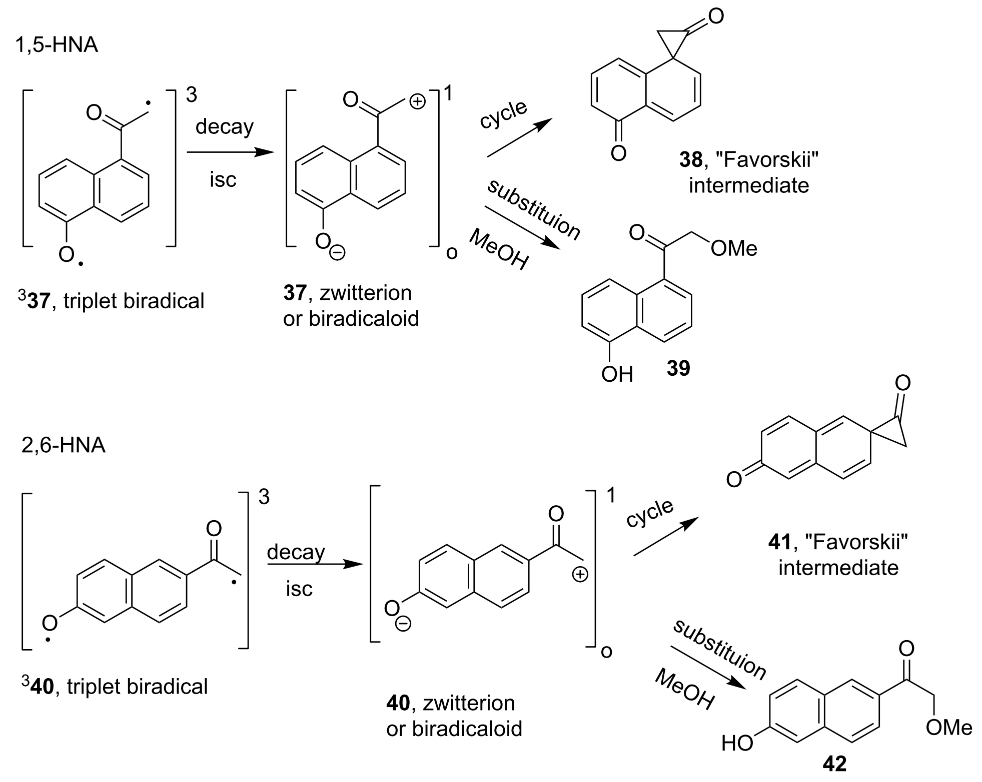
Both of the contributing components of the 2,6 pattern, 2-naphthol ($E_T$ = 60.2 kcal/mol) and 2-acetylnaphthalene ($E_T$ = 59.5 kcal/mol) are higher energy contributors than the same two components of the 1,4 and 1,5 patterns, 1-naphthol ($E_T$ = 58.6 kcal/mol) and 1-acetylnaphthalene ($E_T$ = 56.4 kcal/mol) [10,11]. Of the two motifs, the 1,4 arrangement has the lower energy triplet. Yet the 2,6 pattern with the higher triplet energy is the less reactive and fails to participate in the photo-Favorskii rearrangement.

Wan's work clearly demonstrates, however, that the excited state acidity of 1-naphthols is much greater than 2-naphthols and that excited-state intramolecular proton transfer (ESIPT) for 1-naphthols occurs at both the 5- and 8-positions by H–D exchange [19]. Furthermore, dehydration of 5-(1-hydroxyethyl)-1-naphthol (**34**) is very efficient, leading to quinone methide **35** which is trapped by solvent MeOH (Scheme 8). The corresponding 4-(1-hydroxyethyl)-1-naphthol, however, is unreactive. Comparisons of the two photoreactions, photodehydration and photo-Favorskii [48,50], and Wan's results [19] for H–D exchange reactions demonstrate the importance of the relative location of the two functional groups and the role of ESIPT for both reactions. The hydroxy group, as Wan has elegantly determined, is the source of the acidic proton (especially for singlet state reactions). The carbonyl appendage, however, must be responsible for the enhanced heterolysis efficiency [28,29,38] and may influence the formation of the triplet excited state through intersystem crossing (isc) [26] which is the origin of the heterolysis and rearrangement processes for pHP.

Wan's alternative suggestion that a disruption of both aromatic rings' π-conjugation would be less favorable than only one ring's disruption has merit. For this to be a determining factor, the disruption would have to occur prior to or during the product determining formation of the 'Favorskii' intermediate **33** [38,48,50]. The putative key intermediates for 2,6-HNA and 1,5-HNA photo-Favorskii rearrangements (Scheme 9) illustrate the stage at which disruption in the π-network takes place. As in the case for the 1,4-HNA rearrangement, neither triplet biradical $^3$**37** nor $^3$**40** experience a change in connectivity within the aromatic nucleus. The formation of the triplet biradical is irreversible so that once generated, it must proceed on to a final



**Scheme 8:** Photodehydration and substitution of 5-(1-hydroxyethyl)-1-naphthol **34** [19].



**Scheme 9:** Putative rearrangement intermediates for 1,5- and 2,6- HNA chromophores.

product. Since no rearrangement products are formed for either the 2,6-HNA or 1,5-HNA, it is tempting to conclude that the decay to a ground state biradicaloid or zwitterion is the product determining step. In both cases, the aromaticity of both rings is lost upon formation of the Favorskii cyclopropanone intermediates **38** and **41**.

However, this rationale also falls short because the reactions of the similar biradicaloid or zwitterion are known to undergo nucleophilic substitution and not reduction to the methyl ketone products **6**, **12** or **15** [38,39]. Substitution by solvent would trap the intermediate biradicaloid (or zwitterion) to form, in the case of 2,6-HNA, the α-methoxy ketone **42**, which was not detected among the photoproducts.

The controlling feature leading to the change in mechanism for these two examples is more reasonably imbedded in the route to the reactive triplet excited state configuration [10,11]. For pHP, the reactive excited state is a π,π* triplet that is favored only in hydroxylic solvents, especially $H_2O$ [15,45,46,48]. In non-hydroxylic solvents, the $(n,\pi^*)^3$ dominates which leads to the classical α- and β-homolytic cleavage and H-abstraction reactions. For 2,6-HNA and 5,8-BQA, the reduction product, a methyl ketone, probably results from homolysis. The lower excited state acidity and the poor intersystem crossing in the 2,6-HNA platform and strong fluorescence of the 2,6-HNA chromophore (Figure 2) also diminishes formation of the triplet and, thus, its participation in a photo-Favorskii rearrangement. Finally, an indication of the photostability of the 2,6-HNA derivatives had earlier precedence in the lack of product formation for 2-hydroxy-6-trifluoromethylnaphthylene photo-dehydrofluorination reported by Seiler and Wirz [51]. For the 1,5-HNA acetate, the less reactive (higher p$K_a$) of the leaving OAc group of **27** vs DEP, fluorescence decay and reversible ESIPT processes are major factors disfavoring photorelease.

A summary of the most frequently encountered examples of caged phosphates is given in Table 4. The data are reported for DEP leaving groups, when available, since DEP has proven to be a commonly employed test leaving group for PPG comparisons. It is generally found that the DEP model is reliable when extended to more complex phosphate leaving groups including nucleotides such as ATP and GTP and tyrosyl phosphates and thiophosphates [52-55]. The key comparisons for practical applications of photochemical deprotection are the maximum conversion which controls the chemical yield, the quantum yield (or photochemical efficiency) and the complexity of the photochemical products and byproducts in the photolyzate mixture. Solvents and excitation wavelengths are also given in Table 4 as a guide on selecting a PPG using these reaction parameters.

Table 4 reveals that most chromophores either form complex mixtures of photoproducts complicating the isolation of pure, unprotected phosphates or they remain essentially unchanged (intact) and continue to absorb incident radiation, thus compromising the conversion to products and lengthening exposure of

**Table 4:** A comparison of photorelease from cages for diethyl phosphates. Chemical yields, quantum yields, efficiencies and complexity based on solvents and chromophores.

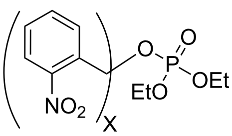
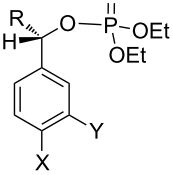
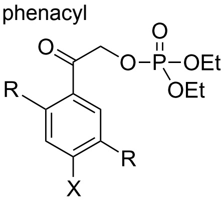
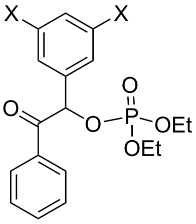
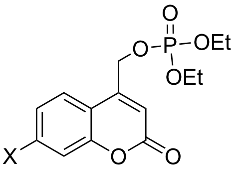
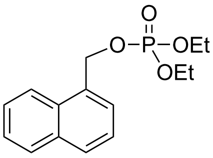
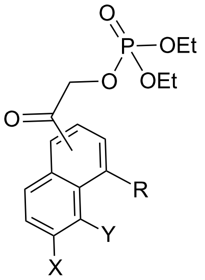
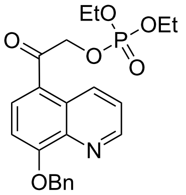
| PPG chromophore | derivatives | solvent$^{a}$ | $\lambda_{exc}$ nm | $\Phi_{dis}$ and (conversion yield/%) | $S^1$ or $T^1$ | chromophore fate$^{b}$ | Ref |
|---|---|---|---|---|---|---|---|
| *o*-nitrobenzyl  | **1a** X=1 | $H_2O$ | 254, 308 | N/A$^{c}$ (28$^{d}$) | | mixture | [56] |
| | **1b** X=2 | $H_2O$ | 308, 355 | N/A (90$^{d}$) | $S^1$ | N/A | [56] |
| benzyl  | **30a** (R, X, Y = H) | MeOH,<br>*n*-BuOH,<br>*t*-BuOH | 254 | 0.39 (50–60) | $S^1$ | intact | [35,57] |
| | S(−)-**30b** (X, Y = H, R = Me) | MeOH<br>*t*-BuOH | 254 | 0.21–0.9$^{e}$ (77/28 rac) | $S^1$ | intact | [35,58] |
| | **30c** (R, Y = H, X = OMe) | *n*-BuOH,<br>*t*-BuOH | 254 | 0.42 (47) | $S^1$ | intact | [58] |
| | **30d** (R, X = H, Y = OMe) | *t*-BuOH | 254 | 0.18 (28) | $S^1$ | intact | [58] |
| phenacyl  | **4a** (R = H, X = OH) | MeOH | 300 | 0.77 (87–96) | $T^1$ | Favorskii | [6,8,15,26, 28,29] |
| | **4b** (R = H, X = OMe) | $H_2O$, MeOH | 300, 355 | 0.42$^{f}$ (27$^{d}$/90$^{f}$) | $S^1$ | mixture | [28,36,57] |
| | **4c** (R = Me, X = H) | MeOH | 313 | 0.71 (94) | nr | intact | [59] |
| benzoin  | **2a** (X = H) | benzene | 350 | 0.28 (72–79) | $T^1$ | benzofuran | [35,56] |
| | **2a** (X = H) | $H_2O$/MeCN | 350 | 0.37<br>(50$^{d}$, 100) | $T^1$ | N/A$^{d}$,<br>benzofuran | [56,58,60] |
| | **2b** (X = OMe) | $H_2O$ | 308, 350 | N/A (55, 100) | | benzofuran | [8,56,61] |
| coumarin-4-ylmethyl  | **3a**<br>(X = OH) | MeOH | 350 | 0.038 (<50) | $S^1$ | intact | [62,63] |
| | **3b**<br>(X = OMe) | $H_2O/CH_3CN$,<br>MeOH | 333–350 | 0.04–0.08 | $S^1$ | intact | [58,60] |
| | **3c**<br>(X = $NMe_2$) | $H_2O$ | 389 | 0.0041 (N/A) | $S^1$ | intact | [62,64] |
| naphthylmethyl  | **28** α | MeOH | 300 | 0.08 (N/A) | $S^1$ | intact | [35,58] |
| | **29** β | MeOH | 300 | 0.3 (N/A) | $S^1$ | intact | [35,58] |

**Table 4:** A comparison of photorelease from cages for diethyl phosphates. Chemical yields, quantum yields, efficiencies and complexity based on solvents and chromophores. (continued)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| naphthylacetyl<br> | **10** (2,6)<br>(X = OH, R, Y = H) | 1% aq MeCN | 350 | 0.031 (67) | $T^1$ | intact | this work |
| | **14a** (1,4)<br>(X, Y = H, R = OH) | 1% aq MeOH | 350 | 0.028 (98) | $T^1$ | Favorskii | this work |
| | **14b** (1,4)<br>(X ,Y = H, R = OMe) | 1% aq MeOH | 350 | 0.0076 (40) | $T^1$ | Favorskii | this work |
| | **27** (1,5)<br>(X, R = H, Y = OH) | $MeCN/H_2O$ | 300 | nr (nr[g]) | | intact | [19] |
| hydroxyindolinyl<br> | **24** | $MeCN/H_2O$ | 350 | $24 \times 10^{-5}$ (30–44) | $S^1$ | mixture | this work |

[a]The ratio of $H_2O$/MeCN was 1:1 unless stated otherwise. [b]When the chromophore is unchanged upon photolysis, fate of the chromophore is noted as “intact”. When the chromophore rearranges by the photo-Favorskii migration or closure to a benzofuran group, the fate is noted as Favorskii or benzofuran, respectively. When complex photoreactions occur with the chromophore, it is noted as “mixture”. [c]N/A = not available. [d]Inorganic phosphate released in $H_2O$ ([56]), [e]When internal return is included. [f]In MeOH, [g]nr = no reaction (leaving group was acetate).

the sample to radiation. Three chromophores, benzoin, pHP, and now 1,4-hydroxynaphthylacetyl substrates cleanly undergo rearrangements that shift the absorption chromophore. Benzoins form benzofurans that, in fact, exacerbate the problem of light competition and fluorescence. Only pHP and 1,4-substituted naphthylacetyl **14** generate a less competitive chromophore allowing maximum conversion and quantitative chemical yield.

While pHP is highly efficient as a PPG (Φ’s approach 1.0) [15] the lower efficiency of 1,4-HNA (0.028) is competitive with many currently available PPGs. A measure often applied in biological decaging studies is the product of absorptivity and efficiency ($\varepsilon_{max} \times \Phi$) which is 232 for photolysis of 1,4-HNA DEP at 325 nm, competitive with PPGs listed in Table 4. By comparison, although its absorptivity is very low at 325 nm, pHP DEP has a much larger $\varepsilon_{max}$ at 280 nm that gives a value of 6000 for excitation at 280 nm, an excitation wavelength that is biologically harmful [6,8,9].

## Conclusion

We have designed and tested several new candidates for near-UV absorbing photoprotecting groups. 1,4-HNA DEP (**14a**) and 1,4-MNA DEP (**14b**) upon irradiation at 350 nm in 1% aq MeOH quantitatively release diethyl phosphate concomitant with a photo-Favorskii rearrangement with quantum yields of 0.028 for 1,4-HNA DEP and 0.0076 for 1,4-MNA DEP. The lower quantum efficiency of 1,4-MNA in MeOH is fully in accord with a similar methylation of the hydroxy group of pHP DEP, emphasizing the role of the phenolic OH on the reaction and rearrangement [6,15,46,48]. In anhydrous, non hydroxylic media, the mechanism of the reaction changes from heterolysis and reverts to the more traditional photochemically induced homolysis mechanism, leading to more complicated product mixtures and poor conversions.

The heterolysis mechanism of the photo-Favorskii rearrangement and release of DEP is initiated at the triplet state of **14** and proceeds according to the more extensively characterized rearrangement for pHP DEP. Due to a more favorable excitation wavelength of 350 nm for 1,4-HNA (vs 280 nm for pHP), it is anticipated that the 4-hydroxy-1-acylnaphthyl PPG will find more favorable applications as a PPG not only for phosphates but many other acidic functional groups. Additional studies on 2PE activation of 1,4-HNA DEP at 650 nm are also in progress.

2,6-HNA DEP and 5,8-BQA DEP also release DEP but do not undergo the beneficial aryl ketone deconjugative rearrangement, instead follow a homolytic pathway. This results in lower yields, poorer efficiencies, and incomplete conversion for 2,6-HNA, and intractable mixtures of chromophoric byproducts and secondary oxidation reactions with $O_2$, for 5,8-BQA. Neither chromophore is suitable for application as a PPG.

# Experimental

## Synthesis

The details on the synthesis of all new compounds can be found in the Supporting Information File 1. The synthetic procedures and spectral data for all new compounds are reported in Supporting Information File 1.

## Photochemistry

### General methods

Photolyses were performed in a Rayonet RPR-100 photochemical reactor fitted with a merry-go-round apparatus and 16 × 350 nm (RPR 3500 Å) or 16 × 300 nm (RPR 3000 Å) lamps. The Rayonet reactor was turned on to warm up the lamps for 15 minutes prior to the irradiation. Samples were irradiated in NMR tubes or Pyrex test tubes at 40–45 °C in the presence of air unless indicated otherwise. The tubes were placed in a merry-go-round apparatus and the time of irradiation was recorded. Light output for the determination of quantum efficiencies was measured by using the potassium ferrioxalate method [65] under identical conditions used for the photolysis of the esters. Photolysis samples were analyzed for product formation and ester disappearance using $^1$H NMR and RP-HPLC methods. Dimethylformamide (DMF, 2 μL, $2.6 \times 10^{-2}$ mmol) was used as an internal standard in $^1$H NMR analyses. For HPLC analyses the solvent was 70% $CH_3CN$ and 30% $H_2O$ unless otherwise noted. The detection wavelength varied depending on the ester analyzed as noted and the flow rate was 1.0 mL/min. Sample injections were performed in triplicate.

### Photolysis of diethyl (2-(4-methoxynaphthalen-1-yl)-2-oxoethyl) phosphate (**14b**)

An NMR tube was charged with **14b** (16 mg, 0.045 mmol) along with $CD_3OD$ (0.95 mL) and DMF (2 μL) as an internal standard. The sample was irradiated at 350 nm and $^1$H NMR scans were collected after 0, 30, and 60 min of photolysis. The depletion of **14b** and the appearance of released diethyl phosphate were quantified from the integrations of the signals at δ 5.4 and 4.1 ppm, respectively. Results are shown in Table 1.

**1. Quantum efficiency determination.** A Pyrex tube was charged with **14b** (6.2 mg, 0.018 mmol) in methanol (5 mL) and water (50 μL) and the contents were mixed thoroughly. The sample was irradiated at 350 nm and sample aliquots (150 μL) were taken after 0, 15, 30, and 45 min. The aliquots were analyzed by HPLC with a mobile phase of 90% acetonitrile and 10% water and a detection wavelength of 319 nm. The depletion of **14b** was quantified from the peak areas of the signal at 3.5 min corresponding to the phosphate ester. The quantum efficiency was determined as described above. Results are shown in Table 1.

**2. Photoproduct analysis in aqueous methanol.** The photolysis mixture of **14b** from the previous experiment was concentrated under reduced pressure and the residue washed with water and extracted with ethyl acetate. The organic extract was concentrated under vacuum and the residue analyzed with $^1$H NMR ($CD_3OD$) and FAB–MS. The data for the major product matched that of an authentic sample of methyl (4-methoxy-1-naphthyl)acetate (**26**).

**3. Photoproduct analysis in aqueous acetonitrile.** Diethyl (2-(4-methoxynaphthalen-1-yl)-2-oxoethyl) phosphate (**14b**, 6 mg, 0.017 mmol) was dissolved in acetonitrile (5 mL) containing water (50 μL) in a Pyrex tube and irradiated at 350 nm with 9–3500 Å bulbs. Sample aliquots were taken after 0, 45, and 90 min of photolysis and analyzed by HPLC. The detection wavelength was 319 nm. The phosphate ester had a retention time of 5.6 min. A new peak emerged at 6.3 min that grew in intensity throughout the photolysis. Co-injection with an authentic sample of 1-acetyl-4-methoxynaphthalene (**12**) confirmed the ketone as a photoproduct from the reaction.

**4. Diethyl (2-(4-methoxynaphthalen-1-yl)-2-oxoethyl) phosphate (14b): Dark reaction control experiment.** An NMR tube was charged with **14b** (ca. 5 mg), which was dissolved in methanol-$d_4$ (<1 mL). The sample was heated to 46 °C in a warm water bath in the dark for 1 h. $^1$H NMR scans were taken before and after heating; no significant difference was observed in the NMR spectra. Also, **14a** was shown to be stable for 30 h in 10% aq MeCN at rt in the dark.

### Photolysis of diethyl (2-(4-hydroxynaphthalen-1-yl)-2-oxoethyl) phosphate (**14a**)

An NMR tube was charged with **14a** (17 mg, 0.05 mmol) along with $CD_3OD$ (0.95 mL) and DMF (2 μL). The sample was irradiated at 350 nm and the percent conversion and deprotection % yield were determined as described above for **14b**. Results are shown in Table 1.

**1. Quantum efficiency determination in aqueous methanol.** The same general procedure and HPLC conditions were employed as described for **14b**. Amounts used: **14a** (7.6 mg, 0.022 mmol), methanol (5 mL), water (50 μL). The detection wavelength was 323 nm. The phosphate ester had a retention time of 3.1 min. Results are shown in Table 1.

**2. Quantum efficiency determination in aqueous acetonitrile.** A Pyrex tube was charged with **14a** (4.7 mg, 0.014 mmol), acetonitrile (5 mL) and water (50 μL). The sample was irradiated at 350 nm; aliquots (200 μL) were taken after 0, 2, 5, 7, and 10 min of photolysis and analyzed by HPLC on a C18 analytical column. The mobile phase contained 70% acetonitrile and 30% water, and the detection wavelength was 323 nm. The phosphate ester had a retention time of 3.5 min. The depletion of **14a** was accompanied by the appearance of four new peaks at 1.7, 2.3, 2.6, and 3.9 min, which were not identified. Results are shown in Table 2.

**3. Quantum efficiency determination in aqueous acetonitrile (degassed).** A Pyrex tube was charged with **14a** (5 mg, 0.015 mmol) along with acetonitrile (5 mL) and water (50 μL). The tube was fitted with a rubber septum and sparged with argon for 15 min. Sample aliquots (0.2 mL) were taken after 0, 2, 5, 7, and 10 min of photolysis using a needle syringe to avoid the introduction of air into the sample during irradiation. The aliquots were analyzed as described above. The percent conversion was 44% after 2 min of photolysis, thus the first two data points from a plot of mmol **14a** vs time were used to estimate the slope of the regression line for depletion of **14a** which led to an approximate value of 0.067 for the disappearance quantum efficiency (Table 2).

**4. Triplet sensitization experiment.** A quartz tube was charged with **14a** (2.0 mg, 0.0059 mmol) and benzophenone (20 mg, 0.11 mmol), and the contents were dissolved in acetonitrile (10 mL) to which was added water (100 μL) to make a 1% aqueous solution. The solution was degassed with argon and irradiated with 6-RPR 2540 Å bulbs. Sample aliquots (0.2 mL) were taken after 0, 2, 5, 7, and 10 min of photolysis and analyzed by HPLC on a C18 analytical column with a mobile phase containing 70% acetonitrile and 30% water. The detection wavelength was 323 nm. The benzophenone had a retention time of 6.5 min and remained constant throughout the photolysis. The phosphate ester had a retention time of 3.6 min and its depletion was accompanied by the appearance of three new peaks at 1.6, 1.9, and 4.4 min, which were not assigned. The quantum efficiency was determined as described above. Results are shown in Table 2.

**5. Photoproduct analysis in aqueous methanol.** A Pyrex tube was charged with **14a** (5 mg, 0.015 mmol), methanol (5 mL) and water (50 μL). The sample was irradiated at 350 nm for 15 min. After photolysis the solution changed from colorless to light yellow in appearance. The solvent was removed under reduced pressure and the remaining residue was dissolved in methylene chloride and washed with water. The organic extract was collected and the solvent concentrated to afford ca. 3 mg of an orange-colored residue. The residue was analyzed with $^1$H NMR in methanol-$d_4$. Two signals were observed in the spectrum at δ 4.00 and 3.68 ppm, in a ratio of ca. 1:1.5, which were assigned to the methylene and methyl protons of methyl (4-hydroxy-1-naphthyl)acetate (**25**), based on the similar chemical shifts observed for methyl (4-methoxy-1-naphthyl)acetate (**26**).

**6. Photoproduct analysis in aqueous acetonitrile.** An NMR tube containing **14a** (ca. 5 mg) was charged with $CD_3CN$ (1 mL) and $D_2O$ (0.1 mL). The solution was mixed thoroughly and irradiated at 350 nm for 30 min. The $^1$H NMR spectrum contained a singlet at δ 2.66 ppm that was assigned to the methyl protons of 1-acetyl-4-hydroxynaphthalene (**15**). The presence of **15** was confirmed upon spiking with an authentic sample.

## Photolysis of diethyl (2-(6-hydroxynaphthalen-2-yl)-2-oxoethyl) phosphate (**10**)

**Quantum efficiency determination.** A Pyrex tube was charged with **10** (2.2 mg, 0.0065 mmol) along with acetonitrile (5 mL) and water (50 μL). The solution was irradiated at 350 nm and sample aliquots (200 μL) were taken after 0, 2, 5, 7, and 10 min of photolysis. The aliquots were analyzed by HPLC. The detection wavelength was 315 nm. The phosphate ester had a retention time of 3.4 min and its depletion was accompanied by the appearance of signals at 1.8 and 4.0 min. The quantum efficiency was determined as described above and displayed in Scheme 5 ($\Phi_{dis}$= 0.031).

## Photolysis of 4-[2-(6-hydroxy-2-naphthyl)-2-oxoethoxy]-4-oxobutan-1-aminium trifluoroacetate (2,6-HNA GABA)

**Photoproduct analysis.** A Pyrex tube was charged with 2,6-HNA GABA (19.5 mg, 0.068 mmol) along with acetonitrile (1.0 mL) and 50 mM TRIS buffer (9.0 mL, pH 7.3). The solution was photolyzed at 350 nm for 1 h, and sample aliquots of 50 μL were taken after 0, 30, and 60 min of photolysis. The aliquots were diluted with 150 μL of TRIS buffer and injected into an Econosphere C18 analytical column. The mobile phase contained 90% $CH_3CN$ with 0.1% TFA and 10% $H_2O$. The flow rate was 1.0 mL/min and the detection wavelength was 244 nm. The depletion of 2,6-HNA GABA (retention time ca. 6 min) was accompanied by an increase in a peak with a retention time of ca. 3 min corresponding to the photoproduct(s). At the end of the photolysis, the solution contained an orange-colored precipitate. The organic soluble components were extracted with ethyl acetate, and the organic extract was washed with water, dried over magnesium sulfate, and the solvent removed under reduced pressure to afford ca. 6 mg of a yellow residue. The residue was dissolved in acetonitrile and injected into the HPLC column, resulting in a peak with a retention time of ca. 3 min. Co-injection of an authentic sample of 2-acetyl-6-hydroxynaphthalene (**6**) also produced the same peak. The residue was analyzed with $^1$H NMR ($CDCl_3$) and found to contain the characteristic methyl singlet at δ 2.7 ppm corresponding to **6**, in addition to other unassignable peaks further downfield in the spectrum. TLC analysis with 2:1 hexane/ethyl acetate further suggested the presence of **6** as a photoproduct from the reaction.

**Fluorescence measurements.** A solution of 2,6-HNA GABA (0.042 mM in pH 7.3 TRIS buffer containing 1% acetonitrile) was placed in a quartz cell in a Carey Eclipse fluorescence spectrometer. Measurements were made under ambient conditions.

### Photolysis of 2-(8-(benzyloxy)quinolin-5-yl)-2-oxoethyl diethyl phosphate (**24**)

An NMR tube was charged with **24** (5.0 mg, 0.01 mmol) dissolved in $CD_3CN$ (900 µL), $D_2O$ (100 µL), and DMF (2 µL, $2.6 \times 10^{-2}$ mmol). The sample was irradiated without degassing with 16 × 300 nm or 16 × 350 nm lamps and $^1H$ NMR spectra (16 scans) were collected after 0, 30, 60, 90, and 120 min of photolysis. The depletion of **24** and the appearance of released diethyl phosphate were quantified from the integrations of the methylene signals at δ 5.30 ppm and 3.89 ppm, respectively.

**1. Photolysis of 24 in the absence of oxygen.** Using the same general procedure, the photolysis was repeated under degassed conditions. In these experiments, photolysis samples were purged with argon for 30 min before photolysis. The results are shown in Table 3.

**2. Photoproduct analysis by $^1$H NMR.** An NMR tube was charged with **24** (10 mg, 0.02 mmol) which was dissolved in $CD_3CN$ (900 µL) and $D_2O$ (100 µL). The contents were mixed thoroughly and the sample irradiated with air or under Ar purged conditions with 16 × 300 or 350 nm lamps. $^1H$ NMR spectra were collected after 60 min of photolysis and used to calculate the percent conversion. The depletion of **24** and the appearance of released diethyl phosphoric acid were determined from the NMR signals for the methylene protons of the phosphate ester and methylene hydrogens of diethyl phosphoric acid at δ 5.30 ppm and 3.88 ppm, respectively. The photolysis sample was spiked with an authentic sample of diethyl phosphoric acid synthesized from diethyl chlorophosphate [66]. A dramatic increase in the intensities of the new methylene and methyl signals at 3.88 and 1.19 ppm, respectively, confirmed the presence of diethyl phosphate.

**3. Control experiments with 24; stability in the absence of irradiation.** An NMR tube was charged with **24** (10.0 mg, 0.02 mmol) along with 900 µL of $CD_3CN$ and 100 µL of $D_2O$. The contents were mixed thoroughly and warmed in a water bath at 40 °C in the dark for 2 h. $^1H$ NMR analysis before and after the heating showed no significant change in the NMR spectrum. No significant change was observed when the sample was re-examined 48 h later.

## Supporting Information

### Supporting Information File 1

Synthetic procedures and spectral data for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-212-S1.pdf]

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# $P(O)R_2$-directed Pd-catalyzed C–H functionalization of biaryl derivatives to synthesize chiral phosphorous ligands

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Letter

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chiral synthesis; Pd-catalysis; organophosphorus; phosphorus ligands; $P(O)R_2$-directing

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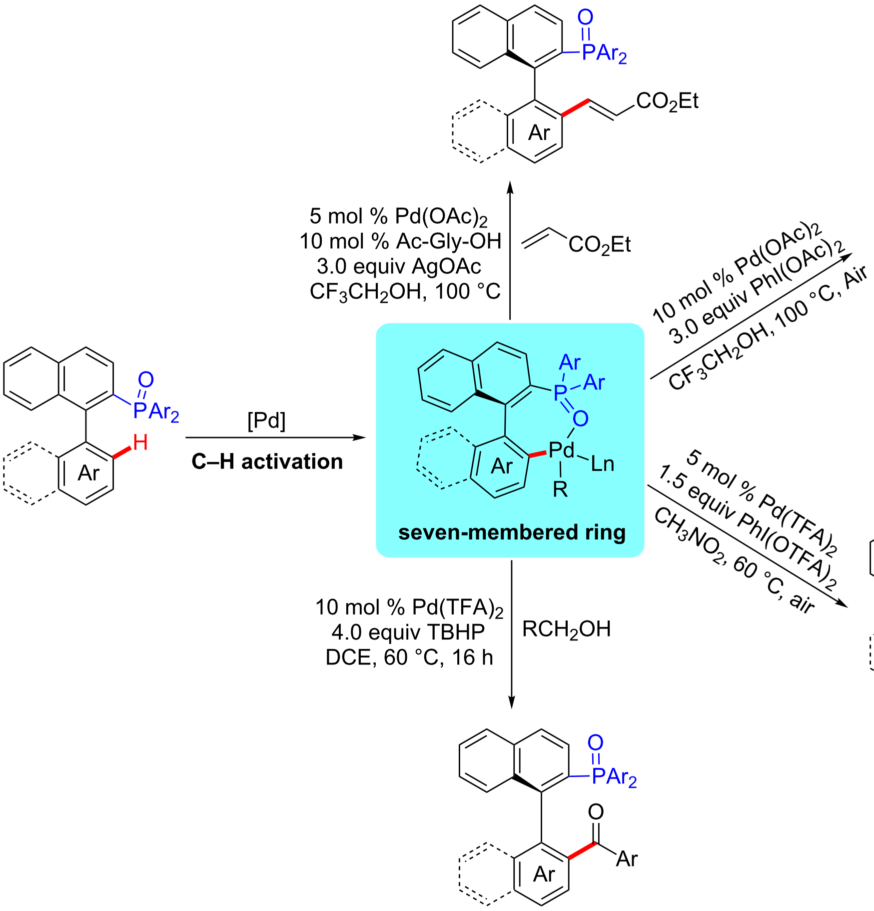
## Abstract

Chiral phosphorus ligands have been widely used in transition metal-catalyzed asymmetric reactions. Herein, we report a new synthesis approach of chiral biaryls containing a phosphorus moiety using $P(O)R_2$-directed Pd-catalyzed C–H activation; the functionalized products are produced with good enantioselectivity.

## Introduction

In the past decades, phosphorus ligands have been demonstrated to be efficient ligands in many metal-catalyzed organic reactions [1-4]. In particular, their special effects of enhancing the metal-catalyst efficiency and of controlling chiral induction has continually prompted synthetic chemists to probe efficient methods generating access to chiral, enantiomerically pure phosphorus compounds used in pharmaceutical, agrochemical and perfume industries [5-10]. However, the difficulty of synthesizing such ligands hampered their wide application, mainly due to the challenging formation of P–X (X = N, O, C…), especially C–P bond formation.

At present, the traditional strategy to introduce phosphorus atoms requires prefunctionalization or lithiation of substrate. However, these methods are not compatible for some activated functional groups in precursor compounds. Over the past several years, we have achieved reactions of C–P bond formation with new and efficient protocols via transition metal-catalysis [11-16]. Despite the progress in this area, only limited development has been accomplished through metal-catalyzed C–H activation to build C–P bonds [17,18]. As an alternative, we disclosed a novel protocol of palladium-catalyzed C–H functionalization by using the $P(O)R_2$ moiety as a new directing group to synthesize a series of phosphorus-containing compounds in a straightforward and atom-efficient way (Scheme 1) [19-23]. In our system, we proposed a seven-membered cyclopalladium transition state instead of the common five or six-membered transition state [24-30]. The $P(O)R_2$ group not only



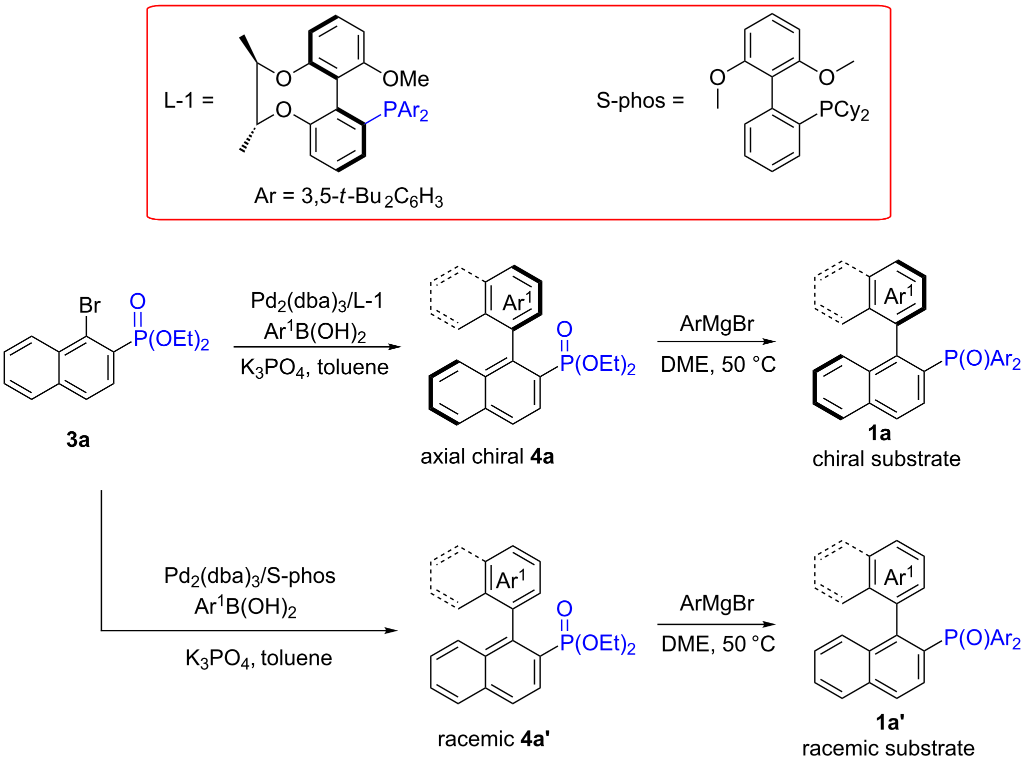
**Scheme 1:** C–H functionalization of P(O)R$_2$ directed through a seven-membered cyclopalladium transition state.

achieved the directing role but also acts as an important component unit of the C–H functionalized products. In this paper, we use the axially chiral biaryl phosphine oxides as substrates and report the synthesis of various chiral phosphorus ligands with high enantiomeric selectivity using palladium-catalyzed C–H functionalization.

## Results and Discussion

To obtain the axially chiral phosphorus compounds, we first synthesized the special chiral-bridged atropisomeric monophosphorus ligand L-1 through an eight-step reaction sequence starting from 1,3-dimethoxybenzene. According to the reported operation, the substrates of biaryl derivatives that contained phosphate with axial chirality were obtained in high yields using the Suzuki–Miyaura coupling reaction with the assistance of this versatile chiral ligand [31-34]. We used substituted naphthylboronic acid or *ortho*-substituted-phenylboronic acid to synthesize the corresponding substituted binaphthyl or phenylnaphthyl skeleton substrates with axial chirality. To maintain the axial chirality within the substrates, a steric hindrance effect at the ortho position of phenylboronic acids was required, rendering the *non-ortho* substituted-phenylboronic acid that is not applicable in these reactions. As the P(O)Ar$_2$ group showed a better directing ability in the process of C–H activation, the axial chiral P(O)(OEt)$_2$ **4a** was transformed into P(O)Ar$_2$ by reacting with an arylgrignard reagent (Scheme 2) [32]. At the same time, the racemic substrates were produced using the nonchiral S-phos ligand. By using 2-chlorophenylboronic acid as coupling component, we demonstrated that we could obtain the phosphate compound, but it failed to yield the P(O)Ph$_2$ group in the arylation step. In addition, in the processes of hydroxylation, arylation, alkenylation, the P(O)(iPr)$_2$ group showed a good guiding ability, but the corresponding substrates could not be obtained because the phosphate moiety did not react with the (iPr)MgBr.

Under the optimized conditions, we started to investigate the scope and applicability of our strategies. Initially, we used



**Scheme 2:** Synthesis of chiral and racemic substrates.

chiral [1,1'-binaphthalen]-2-yldiphenylphosphine oxide as a substrate [35]. In the process of alkenylation and acetoxylation, the corresponding products **2a** and **2b** were obtained in moderate yields and high enantioselectivities. Next, we examined the substituent effect with P(O)(*p*-Tol)$_2$ as a directing group: The reactions of alkenylation, acetoxylation, hydroxylation and acylation occurred smoothly. Even if the products were obtained in low to moderate yields, they were optically pure (Figure 1, **2c–f**). For the substrate of 4-methoxy substituted binaphthyl, we could achieve the alkenylation product **2g** in moderate yield and with high ee. When a fluorine substituent was used, the acetoxylated product **2h** was obtained in moderate yield and high ee. Even if the alkenylation product **2i** was obtained when the substituent was methyl, we failed to produce the desired chromatogram; however, it did exhibit a good optical rotation. Those results showed that the products of C–H functionalization were maintained with high enantioselectivities when the substrates were optically pure, even when these reactions were carried out in air atmosphere and at high temperature. Herein, we provided a method to synthesize the substituted axially chiral binaphthyl compounds with a phosphorus moiety. Moreover, these products can be further transformed into other functional groups.

Next, the substrates of the phenyl-naphthyl framework were examined. For the ortho-OMe substituted substrate, we achieved the products of alkenylation, acetoxylation and hydroxylation. The OMe group is a relatively small group, so the ee was not very high. If the substituent was OEt, the products of alkenylation and acetoxylation (Figure 1, **2m** and **2n**) were obtained in moderate yield and the results showed good enantioselectivities. Although the yields were not very high in these processes, the starting materials were completely converted except for the acylation reaction, presumably due to partial decomposition of the starting materials. These functionalized products showed that the axially chiral substrates could be well maintained in our system of P(O)R$_2$-directed Pd-catalyzed C–H activation. These compounds could be transformed to trivalent phosphorus compounds by silane to obtain the corresponding phosphorous ligands.

## Conclusion

In summary, a series of substrates with axially chiral biaryl compounds containing a P(O)Ar$_2$ directing group were successfully synthesized using the Suzuki–Miyaura coupling reaction under the assistance of a chiral ligand. Moreover, the substrates were further C–H functionalized using the P(O)Ar$_2$ directing

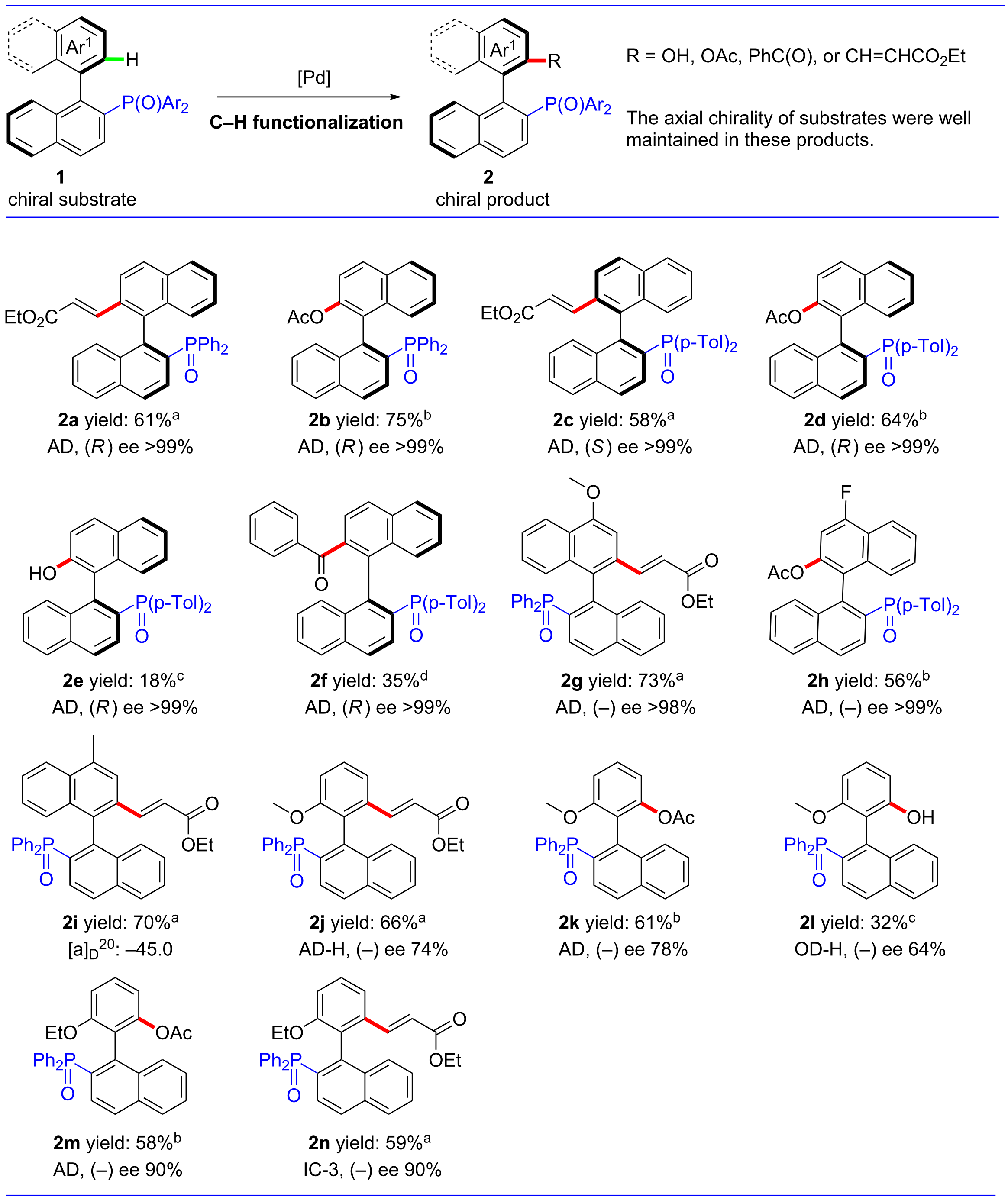


**Figure 1:** C–H functionalization of axially chiral phosphorus substrates. The yields are isolated yields and the ee values are determind by HPLC. [a]Reaction conditions: substrate (0.3 mmol), ethyl acrylate (1.5 mmol), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), AgOAc (1.5 mmol), TFE (3.0 mL), 100 °C, 24 h, air atmosphere; [b]Substrate (0.3 mmol), $PhI(OAc)_2$ (0.9 mmol), $Pd(OAc)_2$ (10 mol %), TFE (3.0 mL), 100 °C, 24 h, air atmosphere; [c]Substrate (0.3 mmol), TBHP (1.2 mmol), benzyl alcohol (0.75 mmol), $Pd(TFA)_2$ (10 mol %), DCE (3.0 mL), 60 °C, air atmosphere; [d]Substrate (0.3 mmol), $PhI(TFA)_2$ (0.45 mmol), $Pd(OAc)_2$ (10 mol %), $MeNO_2$ (3.0 mL), 60 °C, 24 h, air atmosphere.

role with Pd salt as catalyst. Notably, the reactions took place in air atmosphere and at high temperature and the corresponding functionalized products exhibited good enantioselectivities. We propose a unique seven-membered cyclopalladium transition state for this transformation and provide a new and efficient route to synthesize the substituted axially-chiral oxygen–phosphine or alkene–phosphine ligand analogues.

# Experimental

See Supporting Information File 1.

## Supporting Information

### Supporting Information File 1

Experimental details, characterization data ($^1$H, $^{13}$C, $^{31}$P spectra) of products.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-215-S1.pdf]

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The [1, 1'-binaphthalen]-2-yldiphenylphosphine oxide compounds were synthesized following this reference.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

# Chiral phosphines in nucleophilic organocatalysis

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Review

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## Abstract

This review discusses the tertiary phosphines possessing various chiral skeletons that have been used in asymmetric nucleophilic organocatalytic reactions, including annulations of allenes, alkynes, and Morita–Baylis–Hillman (MBH) acetates, carbonates, and ketenes with activated alkenes and imines, allylic substitutions of MBH acetates and carbonates, Michael additions, γ-umpolung additions, and acylations of alcohols.

## Introduction

During the past two decades, tertiary phosphine catalysts have been applied extensively in a wide range of carbon–carbon and carbon–heteroatom bond-forming transformations [1-18]. Many phosphine-catalyzed reactions have been developed for the syntheses of various biologically important acyclic and cyclic molecules. Asymmetric variants of these reactions have evolved relatively slowly. Indeed, very little research on chiral tertiary phosphine-catalyzed asymmetric reactions occurred prior to the year 2000 [19,20]. Over the last decade, however, and especially since 2005, considerable progress has been made in asymmetric phosphine catalysis. As a result, phosphine-catalyzed asymmetric reactions are now powerful and versatile tools for the construction of C–C, C–N, C–O, and C–S bonds and for the syntheses of functionalized carbocycles and heterocycles [11,13,14]. In offering a general account of this field, herein we summarize the major developments in nucleophilic chiral phosphine-catalyzed asymmetric reactions, including annulations of allenes, ketenes, alkynes, and Morita–Baylis–Hillman (MBH) carbonates with activated alkenes and imines, allylic substitution of MBH acetates and carbonates, Michael additions, γ-umpolung additions, and acylations of alcohols. Our discussion is organized according to the structural features of the chiral phosphines, the reaction types, and the nature of the substrate. Because chiral phosphine-promoted Rauhut–Currier (RC) reactions [9,10] and MBH/aza-MBH reactions [21-26] have been summarized splendidly in several reviews, we do not cover these transformations, except for selected examples related to other reactions.

# Review

## 1 Chiral phosphine catalysts

Nucleophilic phosphine catalysis often involves the formation of Lewis adducts, namely phosphonium (di)enolate zwitterions, as reaction intermediates [1,3,6,17]. These intermediates are formed through nucleophilic attack of the phosphine catalysts at electron-poor nuclei (normally carbon atoms) and then proceed through several steps to form new chemical bonds. Generally, the efficiency of nucleophilic phosphine catalysis often depends on the nature of the tertiary phosphine. Although many reactions require more nucleophilic trialkylphosphines as catalysts, only a few chiral trialkylphosphines are available. The synthesis of novel trialkylphosphines can be quite difficult, thereby limiting the scope of their chiral variants. Moreover, because of inherent air-sensitivity, the storage of trialkylphosphines can be problematic. On the other hand, thousands of arylphosphines have been used as chiral ligands for metal-catalyzed asymmetric reactions [27-30]. Most of these phosphines are acyclic, usually possess low nucleophilic activity, and generally display poor enantioselectivities for phosphine organocatalysis. For example, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) is an excellent chiral diphosphine ligand for metal-catalyzed asymmetric reactions, but it displays extremely poor reactivity and enantioselectivity in many nucleophilic phosphine-catalyzed reactions. For these reasons, effective chiral catalysts for nucleophilic phosphine catalysis are scarce, seriously limiting the development of asymmetric variants. At present, the synthesis of new chiral phosphines designed specifically for nucleophilic organocatalysis remains a significant challenge.

In the early exploration stage of asymmetric nucleophilic phosphine organocatalysis, chiral phosphines that had originally been designed as ligands for metal-catalyzed reactions were selected and examined for their reactivity. Although several cyclic phosphines were found to have excellent catalytic activities and enantioselectivities, only a few acyclic phosphines were effective. In this context, inspired by polyfunctional chiral small-molecule catalysts, particularly amino acid and thiourea-based systems [31,32], multifunctional chiral phosphines were constructed by installing a nucleophilic phosphine and a hydrogen bonding moiety on a molecular chiral backbone. These units served as active functional groups to synergistically activate the substrates in an assembled chiral environment, providing excellent catalytic activities and enantioselectivities that could not be accomplished using conventional chiral phosphines lacking hydrogen bonding moieties. Such multifunctional phosphines are readily accessible from simple chiral starting materials through a molecular building block approach, allowing combinatorial syntheses of new multifunctional chiral phosphines with diversity and, consequently, improving the probability of discovering an excellent catalyst.

In this review, we divide chiral phosphines into three classes: cyclic phosphines (Figures 1–5), acyclic phosphines (Figure 6), and multifunctional acyclic phosphines (Figures 7 and 8). Generally, the cyclic phosphines have been constructed based on bridged-ring (Figure 1), binaphthyl (Figure 2), ferrocene (Figure 3), spirocyclic (Figure 4), and five-membered phospholane ring (Figure 5) skeletons. Multifunctional chiral phosphines have generally been constructed based on binaphthyl

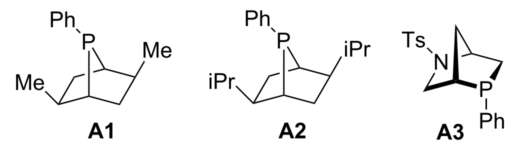


**Figure 1:** Cyclic chiral phosphines based on bridged-ring skeletons.

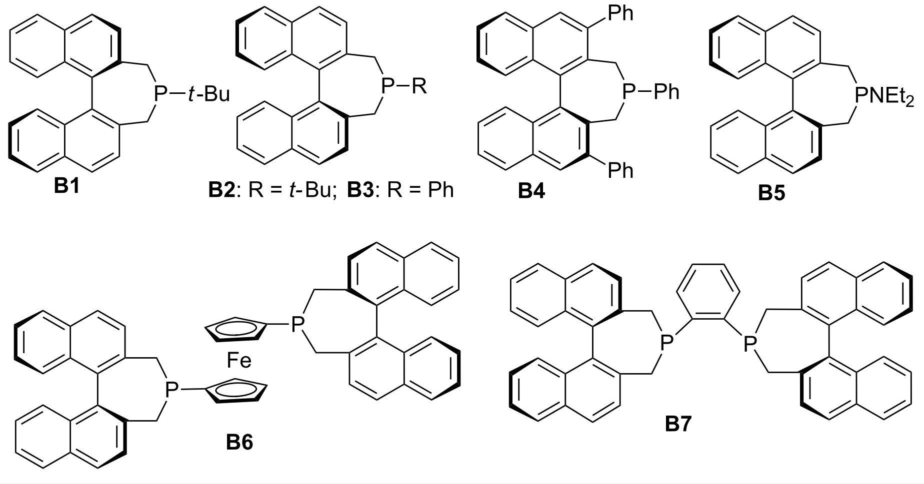


**Figure 2:** Cyclic chiral phosphines based on binaphthyl skeletons.

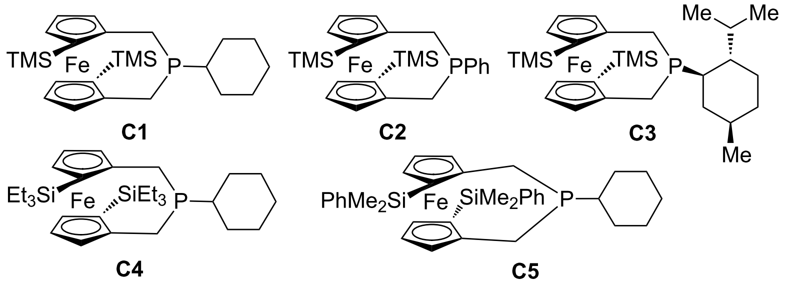


**Figure 3:** Cyclic chiral phosphines based on ferrocene skeletons.

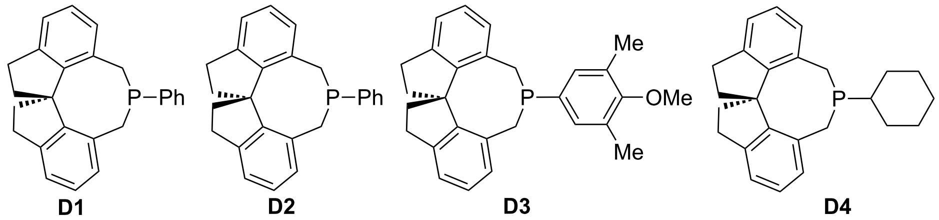


**Figure 4:** Cyclic chiral phosphines based on spirocyclic skeletons.

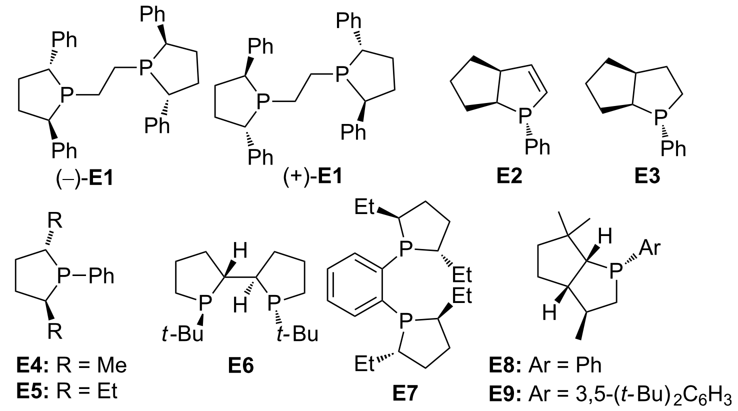


**Figure 5:** Cyclic chiral phosphines based on phospholane ring skeletons.

skeletons (Figure 7) and amino acids (Figure 8). These structurally different chiral phosphines can be selected to catalyze appropriate asymmetric nucleophilic reactions. The electronic and steric properties of these phosphines can be tailored elaborately through modification of functional groups and the introduction of chiral elements, thereby providing suitable chirality, nucleophilicity, basicity, functionality, and rigidity.

## 2 Enantioselective reactions catalyzed by chiral phosphines

Using the chiral phosphines described above as catalysts, a number of highly enantioselective reactions have been achieved, offering a wide variety of methods for enantioselect-

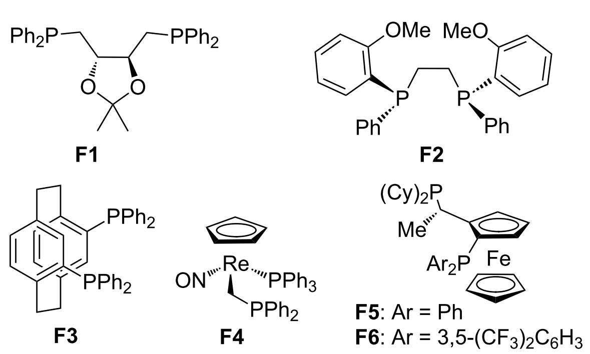
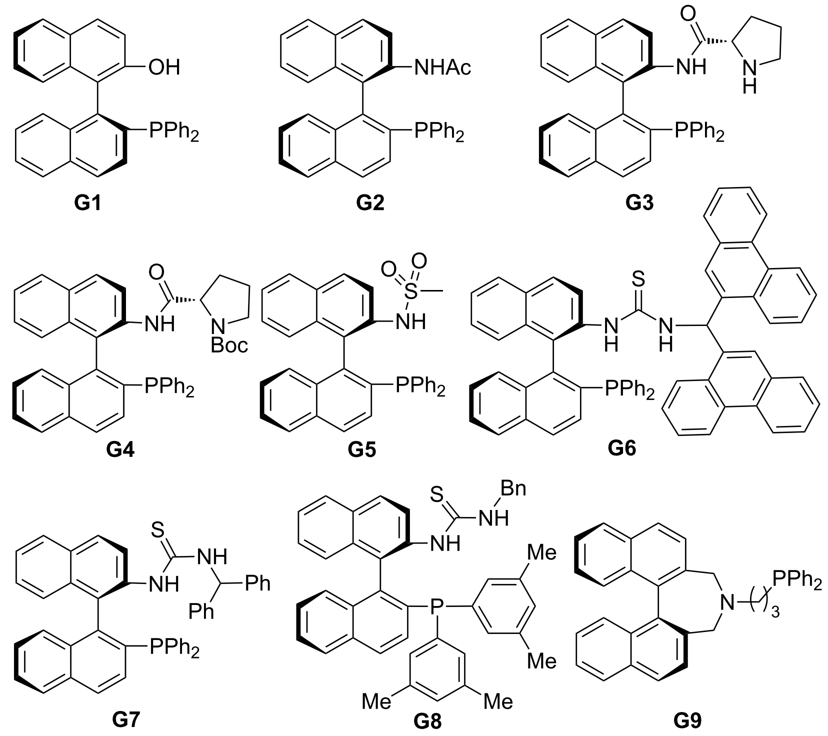
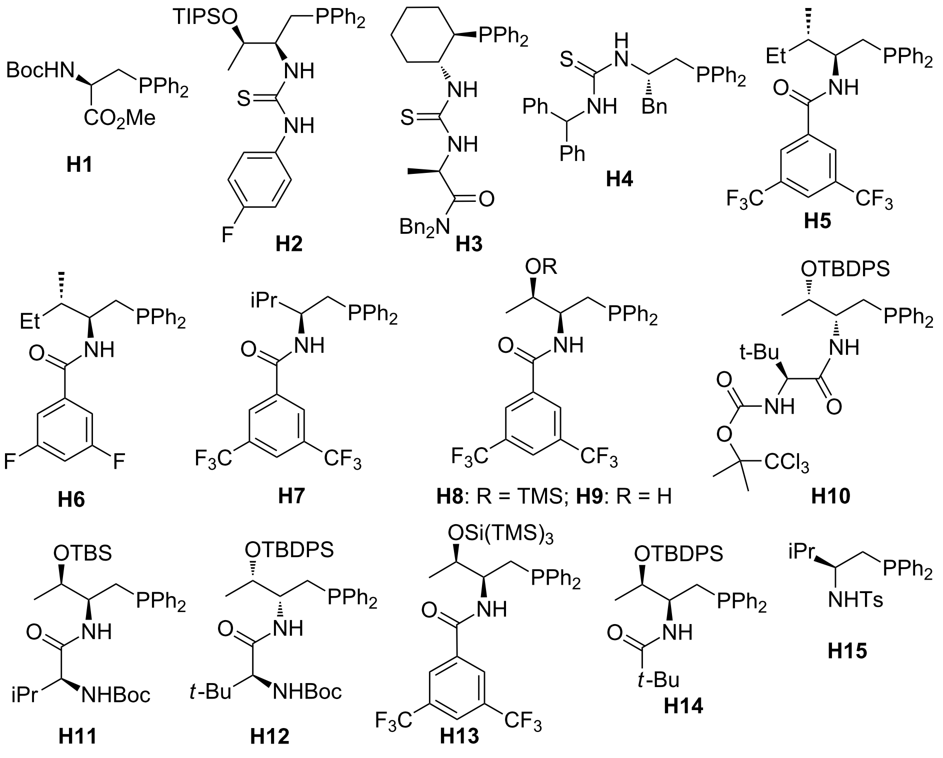


**Figure 6:** Acyclic chiral phosphines.



**G1** **G2** **G3** **G4** **G5** **G6** **G7** **G8** **G9**

**Figure 7:** Multifunctional chiral phosphines based on binaphthyl skeletons.



**H1** **H2** **H3** **H4** **H5** **H6** **H7**

**H8**: R = TMS; **H9**: R = H

**H10** **H11** **H12** **H13** **H14** **H15**

**Figure 8:** Multifunctional chiral phosphines based on amino acid skeletons.

ive syntheses of structurally diverse acyclic, carbocyclic, and heterocyclic compounds.

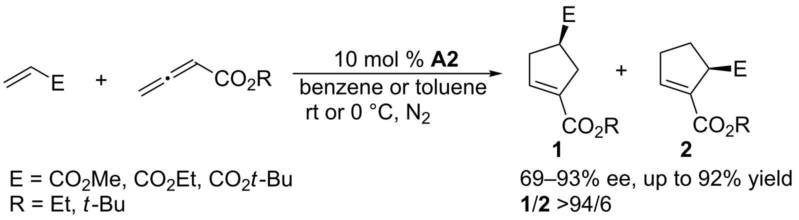
## 2.1 [3 + 2] Annulation of allenes with activated alkenes

Nucleophilic phosphine-catalyzed annulations have been established as very useful tools for the syntheses of carbo- and heterocycles from simple starting materials [1-17]. Although a diverse set of annulations, including [2 + 1], [2 + 2], [4 + 1], [3 + 2], [2 + 2 + 1], [2 + 2 + 2], [3 + 2 + 3], [3 + 3], [4 + 2], [4 + 3], [6 + 3], [8 + 2], and [8 + 3] annulations, has been developed, asymmetric variants exist for only a few of them. In particular, chiral phosphine-catalyzed [3 + 2] annulations of allenes, alkynes, and MBH adducts with electron-deficient olefins and imines, resulting in cyclopentenes and pyrrolidines, have been the most studied, with many successful reported examples.

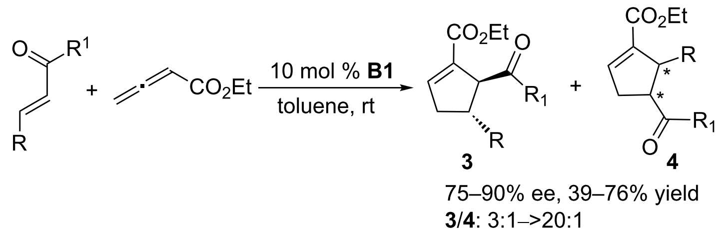
**2.1.1 [3 + 2] Annulations using cyclic phosphines as chiral catalysts:** The first appearance in the literature of a chiral phosphine-catalyzed annulation was reported by Zhang and co-workers in 1997 [33]. Based on Lu’s work on phosphine-catalyzed annulation [34], Zhang et al. employed (Scheme 1) a chiral bicyclic phosphine **A2** to achieve asymmetric [3 + 2] annulations between several allenoates and electron-deficient olefins in benzene at room temperature with excellent regioselectivities (**1**:**2** >94/6) and enantioselectivities (**1**, 69–93% ee). This catalyst features a rigid bridged [2.2.1] bicyclic structure. The excellent regioselectivities and enantioselectivities resulted from the existence of the two isopropyl substituents in the chiral phosphine **A2**, which effectively controlled the approach of the acrylate toward the plausible phosphine/allenoate zwitterionic intermediate. Although the yields were not always very high, this inspiring study provided invaluable insight into asymmetric annulations catalyzed by chiral phosphines.

Until 2006, almost one decade later, no reports appeared of novel phosphine-catalyzed asymmetric [3 + 2] annulations. Then, using a chiral phosphepine **B1** based on a binaphthyl skeleton, Fu and co-workers developed the first asymmetric [3 + 2] annulation of ethyl allenoate with various α,β-unsaturated enones to provide functionalized cyclopentenes (Scheme 2) [35]. The key structural feature of the chiral catalyst **B1** is its rigid binaphthyl skeleton. This approach allowed the preparation of a wide array of cyclopentenes with two adjacent chiral centers, with good enantiomeric excesses and satisfactory to good regioselectivities. These transformations were slightly influenced by electronic effects. Notably, Fu et al. successfully applied this approach to construct spirocyclic compounds containing two neighboring quaternary and tertiary stereocenters in modest to excellent yields (up to 97%) and high enantioselectivities (up to 95% ee).

Subsequently, the Fu group applied this approach to the [3 + 2] annulation of allenes with 1,1-disubstituted olefins to synthesize highly functionalized cyclopentenes that bear an array of heteroatom-substituted quaternary stereocenters [36]. From a screening of catalysts, they carefully examined the effect of substitution of the binaphthyl framework of chiral phosphines, identifying the 3,3′-diphenyl-substituted phosphepine **B4** as the



**Scheme 1:** Asymmetric [3 + 2] annulations of allenoates with electron-deficient olefins, catalyzed by the chiral bicyclic phosphine **A2**.

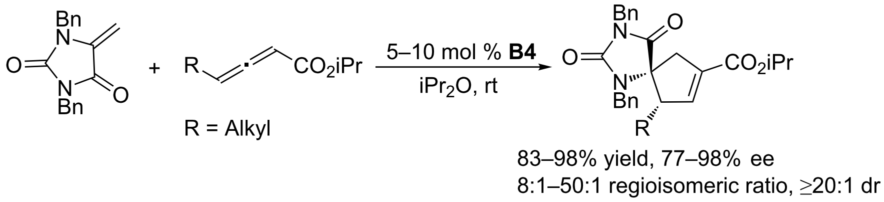


**Scheme 2:** Asymmetric [3 + 2] annulations of allenoate and enones, catalyzed by the chiral binaphthyl-based phosphepine **B1**.

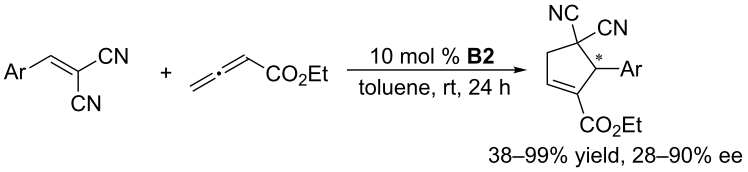
optimal catalyst. Based on the X-ray crystal structure of the catalyst, they proposed that the chiral microenvironment of the binaphthyl-based phosphepine was amplified by its 3,3′-diphenyl substituents. In the presence of the chiral phosphepine **B4**, the reactions of allenes with electron-deficient 1,1-disubstituted olefins proceeded smoothly to give functionalized cyclopentenes in satisfactory yields with up to 98% ee (Scheme 3). That study extended the substrate scope of known asymmetric phosphine-catalyzed [3 + 2] annulation reactions to diverse heteroatom-substituted olefins and allenamides. Nitrogen-, phosphorus-, oxygen-, and sulfur-substituted olefins and allenamides were compatible with these **B4**-catalyzed reactions. Fu's results provided useful hints for further expansion of the substrate scope.

Using **B2** as the chiral catalyst, Marinetti and co-workers also developed several asymmetric [3 + 2] annulations of allenoates with activated alkenes. In the presence of chiral phosphine **B2**, the [3 + 2] annulations between allenoates and 2-aryl-1,1-dicyanoethylenes allowed convenient syntheses of functionalized cyclopentenes with both aryl and heteroaryl substituents on the stereogenic carbon atom, in high yields and with up to 90% ee (Scheme 4) [37]. 3-Alkylideneindolin-2-ones underwent [3 + 2] annulations with allenoates, affording various biologically relevant spirocyclic oxindolic cyclopentanes in excellent yields and greater than 97% ee (Scheme 5) [38]. Enantioselective [3 + 2] annulations of 4-substituted 2,6-diarylidenecyclohexanones with allenoates occurred with high diastereo- and enantioselectivity, providing spirocyclic compounds in satisfactory yields with up to 92% ee (Scheme 6) [39]. Using the catalyst **B2**, Jørgensen and co-workers developed a sequential annulation/alcoholysis reaction. Alkylidene azlactones, among the most widely used starting materials for the syntheses of quaternary amino acids, were cyclized with ethyl allenoate and, subsequently, alcoholyzed in situ to afford highly functionalized, optically active amino esters in moderate to good yields and with 79–94% ee (Scheme 7) [40].

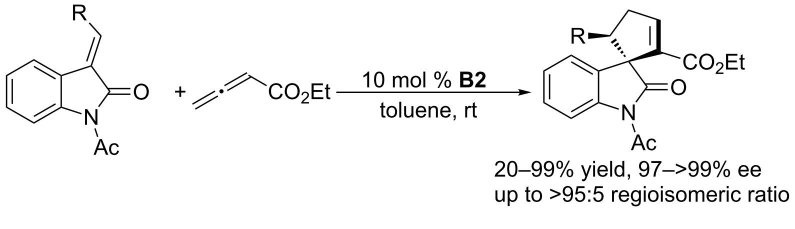
Very interestingly, when using the chiral phosphine (*S*,*S*)-*f*-binaphane **B6** as the catalyst, [60]fullerene also reacted with



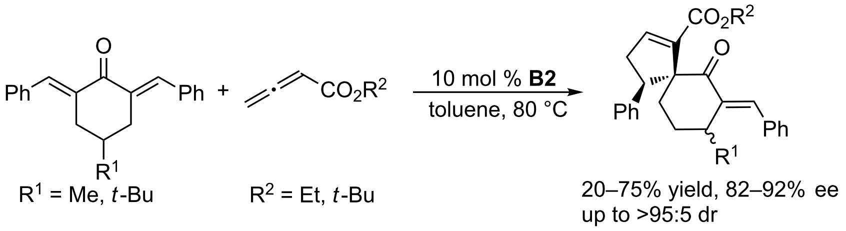
**Scheme 3:** Asymmetric [3 + 2] annulations of *N*-substituted olefins and allenoates, catalyzed by the chiral binaphthyl-based phosphepine **B4**.



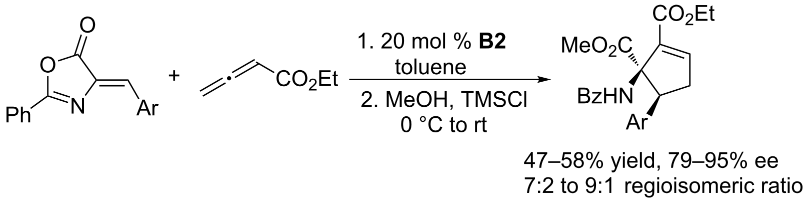
**Scheme 4:** Asymmetric [3 + 2] annulations of 2-aryl-1,1-dicyanoethylenes with ethyl allenoate, catalyzed by the chiral binaphthyl-based phosphepine **B2**.



**Scheme 5:** Asymmetric [3 + 2] annulations of 3-alkylideneindolin-2-ones with ethyl allenoate, catalyzed by the chiral binaphthyl-based phosphepine **B2**.



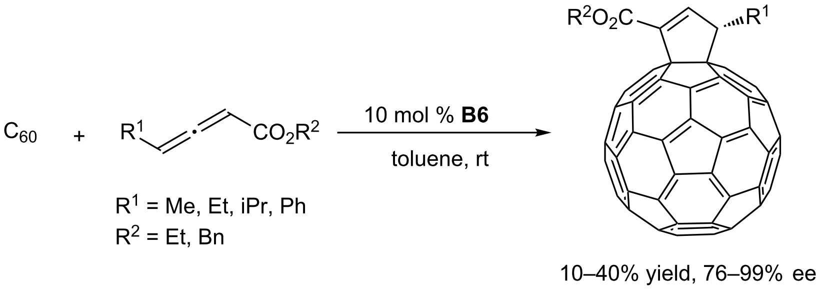
**Scheme 6:** Asymmetric [3 + 2] annulations of 2,6-diarylidenecyclohexanones with allenoates, catalyzed by the chiral binaphthyl-based phosphepine **B2**.



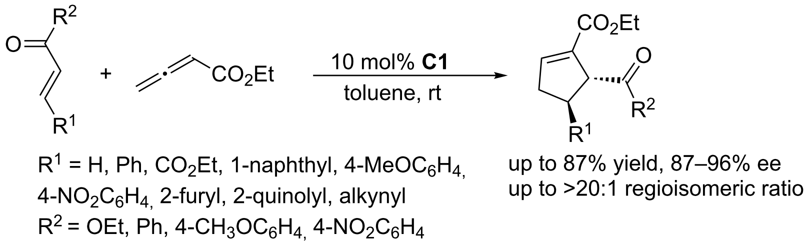
**Scheme 7:** Asymmetric [3 + 2] annulations of allenoate with alkylidene azlactones, catalyzed by the chiral binaphthyl-based phosphepine **B2**, and subsequent alcoholysis in methanol.

allenoates at room temperature, providing a wide range of optically pure (*S*)-cyclopenteno[60]fullerenes in up to 99% ee (Scheme 8) [41]. This study provided a versatile and promising strategy for tailoring carbon materials (e.g., fullerenes, carbon nanotubes), imparting them with desired properties for applications in materials chemistry [42,43].

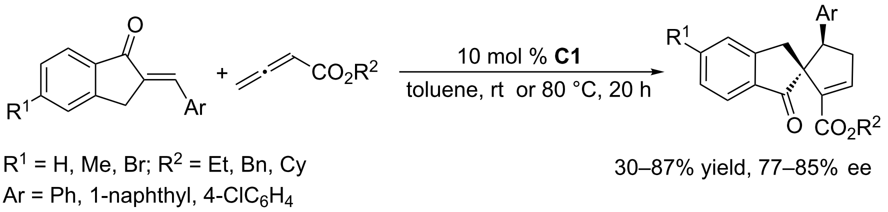
To further develop nucleophilic phosphine-catalyzed asymmetric reactions, Marinetti and co-workers synthesized a series of ferrocene-modified planar chiral phosphines featuring a new skeleton (Figure 3) [44,45]. Among these compounds, the *P*-cyclohexyl phosphine **C1** proved to be the most efficient catalyst for [3 + 2] cycloadditions of ethyl 2,3-butadienoate with activated enones, fumarate esters, and acrylates. In the presence of 10 mol % of the catalyst in toluene at room temperature, the [3 + 2] annulations of allenoates with alkenes proceeded smoothly, providing functionalized cyclopentenes in moderate to good yields (up to 87%) with excellent enantioselectivities (87–96% ee) and regioisomeric ratios of up to >20:1 (Scheme 9) [44,45]. The bulky ferrocene was presumably responsible for the high enantioselectivities. Notably, the presence of the electron-rich ferrocene unit inhibited oxidation of the phosphines, imparting them with air-stability and easy-to-handle properties [45]. Subsequently, Marinetti and co-workers found that these chiral phosphines had very broad substrate scope and could be applied in [3 + 2] annulations of allenes with various activated alkenes. For example, the chiral phosphine **C1** mediated [3 + 2] annulations of a range of di- and trisubstituted alkenes with allenes under mild conditions, providing a variety of functionalized cyclopentenes, cyclopentenylphosphonates, spirooxindoles, heterocyclic spiranes, cyclopentene-fused chromanones, and dihydroquinolinones enantioselectively (Schemes 10–17) [38,39,46-48]. These products can be quite biologically active and many have been applied in medicine and other fields.



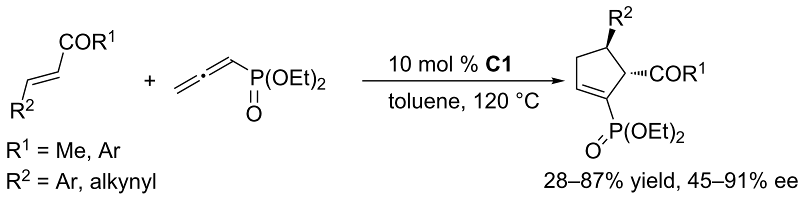
**Scheme 8:** Asymmetric [3 + 2] annulations of $C_{60}$ with allenoates, catalyzed by the chiral phosphine **B6**.



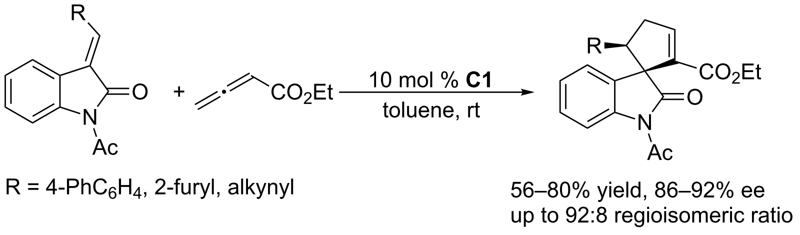
**Scheme 9:** Asymmetric [3 + 2] annulations of α,β-unsaturated esters and ketones with an allenoate, catalyzed by the ferrocene-modified phosphine **C1**.



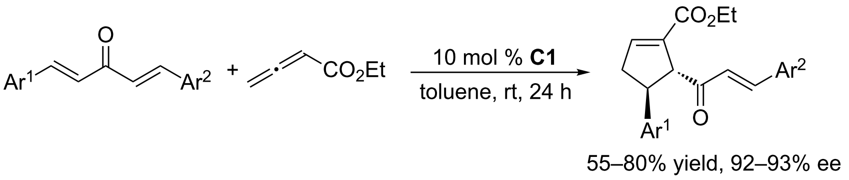
**Scheme 10:** Asymmetric [3 + 2] annulations of exocyclic enones with allenoates, catalyzed by the ferrocene-modified phosphine **C1**.



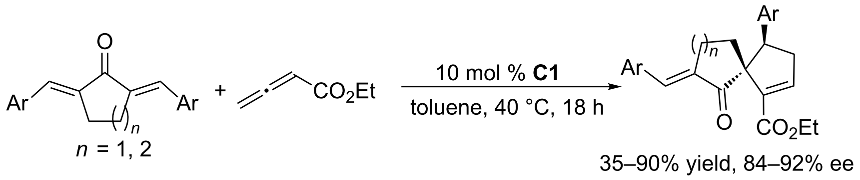
**Scheme 11:** Asymmetric [3 + 2] annulations of enones with an allenylphosphonate, catalyzed by the ferrocene-modified phosphine **C1**.



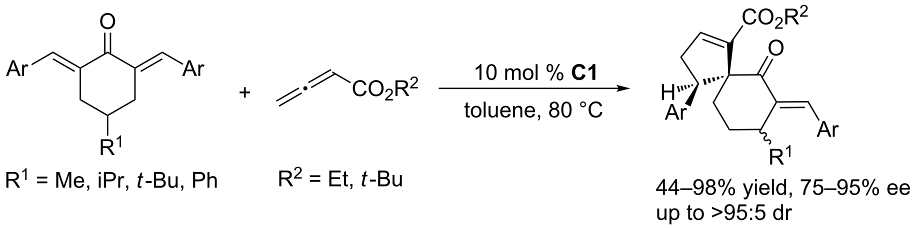
**Scheme 12:** Asymmetric [3 + 2] annulations of 3-alkylidene-oxindoles with ethyl allenoate, catalyzed by the ferrocene-modified phosphine **C1**.



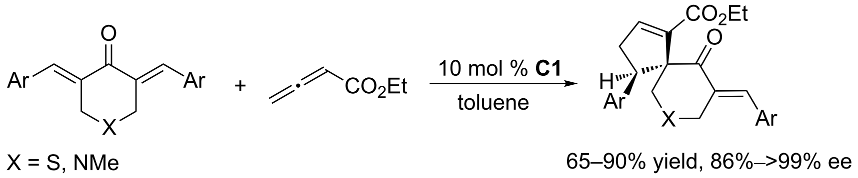
**Scheme 13:** Asymmetric [3 + 2] annulations of dibenzylideneacetones with ethyl allenoate, catalyzed by the ferrocene-modified phosphine **C1**.



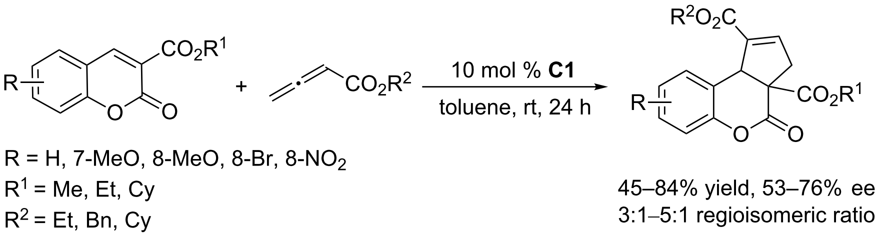
**Scheme 14:** Asymmetric [3 + 2] annulations of trisubstituted alkenes with ethyl allenoate, catalyzed by the ferrocene-modified phosphine **C1**.



**Scheme 15:** Asymmetric [3 + 2] annulations of 2,6-diarylidenecyclohexanones with allenoates, catalyzed by the ferrocene-modified phosphine **C1**.



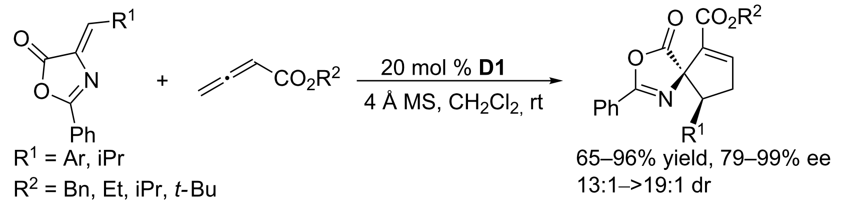
**Scheme 16:** Asymmetric [3 + 2] annulations of α,β-unsaturated ketones with ethyl allenoates, catalyzed by the ferrocene-modified phosphine **C1**.



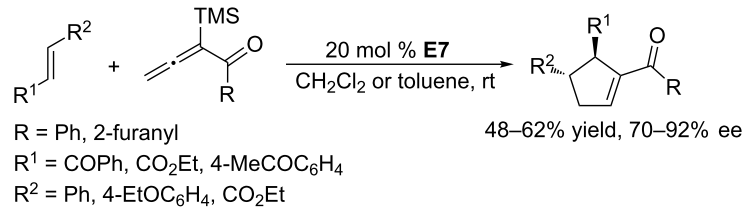
**Scheme 17:** Asymmetric [3 + 2] annulations of α,β-unsaturated esters with allenoates, catalyzed by the ferrocene-modified phosphine **C1**.

Using the axially chiral spirophosphine **D1**, Shi and co-workers accomplished highly regioselective, diastereoselective, and enantioselective [3 + 2] annulations of a series of alkylidene azlactones with allenoates (Scheme 18) [49]. Under mild conditions, the reactions worked efficiently to afford corresponding functionalized spirocyclic products with adjacent spiro-quaternary and tertiary stereocenters in good to excellent yields. These products were readily transformed into a variety of useful optically active amino acid analogues, including various aspartic acid derivatives.

Using the commercially available chiral catalyst (*S*,*S*)-Et-Duphos **E7**, Loh and co-workers developed the asymmetric [3 + 2] annulations of phenyl allenone and furanyl allenone with electron-deficient olefins, namely enones, maleates, and fumarates, to give corresponding functionalized cyclopentenes in moderate yields with moderate to high enantioselectivities (Scheme 19) [50]. The presence of a trimethylsilyl group at the α-position of the allenone was key to achieving a regioselective [3 + 2] annulation. This remarkable steric effect probably suppressed the [4 + 2] self-condensation of the allenone [51].



**Scheme 18:** Asymmetric [3 + 2] annulations of alkylidene azlactones with allenoates, catalyzed by the chiral spiro phosphine **D1**.

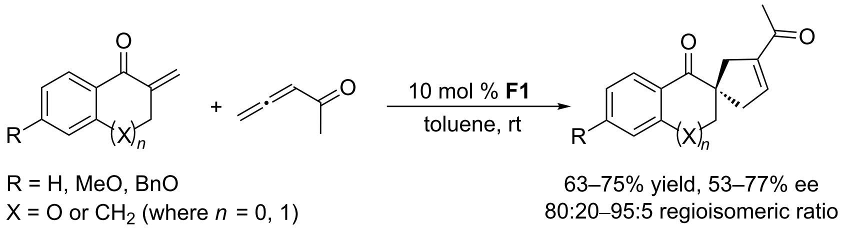


**Scheme 19:** Asymmetric [3 + 2] annulations of α-trimethylsilyl allenones and electron-deficient olefins, catalyzed by the chiral phosphine **E7**.

**2.1.2 [3 + 2] Annulations using acyclic phosphines as chiral catalysts:** In 2007, Wallace and co-workers employed the commercially available chiral phosphine (*S*,*S*)-DIOP **F1** in asymmetric [3 + 2] annulations of allenic ketones with a diverse array of exocyclic enones, providing a series of spirocyclic compounds – promising drug precursors – in good yields and with modest enantioselectivities (Scheme 20) [51]. Generally, it is difficult to control an enantioselective annulation when using an acyclic chiral phosphine lacking additional functionality. This example is one of the few asymmetric reactions catalyzed by an acyclic chiral phosphine.

**2.1.3 [3 + 2] Annulations using multifunctional phosphines as chiral catalysts:** In addition to cyclic chiral phosphines, multifunctional chiral phosphines can also display excellent catalytic activity and enantioselectivity in the asymmetric [3 + 2] annulations. Through intramolecular hydrogen bonding, the bond-forming transition-state geometry between electrophile and the zwitterionic intermediate formed from the allenoate and the multifunctional chiral phosphine can be better organized, thereby delivering annulation products in high yields and ee's.

In 2007, based on their peptide catalyst studies, the Miller group developed the first α-amino acid-based phosphine catalyst **H1** for enantioselective [3 + 2] annulations of allenoates with enones (Scheme 21) [52]. This catalyst performed multiple roles during the catalytic process, with the amino acid moiety providing a chiral environment and acting as a hydrogen bond donor while the phosphine unit functioned as the nucleophile. In the presence of 10 mol % of **H1**, they treated both cyclic and acyclic enones with the allenoates in toluene at −25 °C to generate corresponding cyclopentenes as single regioisomers with high enantioselectivities. Interestingly, single amino acid-based phosphines were better than di-, tri-, and tetrapeptide-based catalysts. Of particular note, when they treated γ-substituted racemic allenoates with acyclic enones, unique dynamic kinetic asymmetric transformations occurred in the presence of

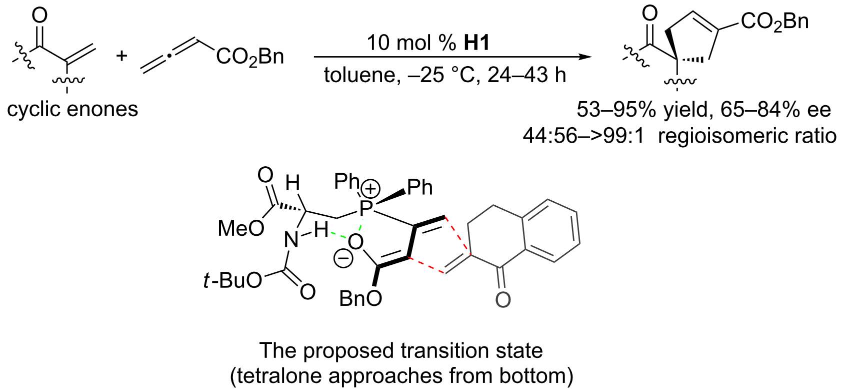


**Scheme 20:** Asymmetric [3 + 2] annulations of α,β-unsaturated ketones with an allenone, catalyzed by the chiral phosphepine **F1**.

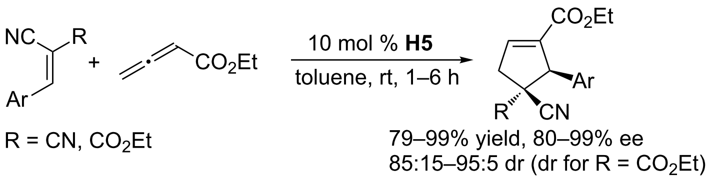
a stoichiometric amount of the catalyst **H1**, giving highly substituted cycloadducts in excellent yields as single regio- and diastereoisomers with 87–93% ee. Although a catalytic amount of **H1** (20 mol %) also afforded 93% ee, the yield deteriorated to 38%. The proposed transition-state model (Scheme 21) illustrates how the dual control of activity and stereoselectivity was achieved: through formation of a zwitterionic intermediate from the allenoate and phosphine moiety and subsequent intramolecular hydrogen bonding between the NH unit and the oxygen atom that was formerly part of the allenoate's carbonyl group.

With the idea of using a natural amino acid as the hydrogen bonding framework, Zhao and co-workers designed the simpler multifunctional chiral *N*-acyl aminophosphine **H5**, which they readily synthesized in four steps from a commercially available Boc-protected amino alcohol [53]. With 10 mol % of catalyst **H5**, various arylidenemalononitriles reacted with an allenoate in toluene at room temperature for 1 h to provide various chiral cyclopentenes in 79–99% yield and 80–99% ee (Scheme 22). In particular, the annulations of 2-cyano-3-arylacrylates, with two different electron-withdrawing functional groups, produced chiral cyclopentenes bearing adjacent quaternary and tertiary stereocenters with exclusive regioselectivity and high diastereoselectivities and enantioselectivities. That study provided a significant advance in phosphine-catalyzed [3 + 2] annulations providing cyclopentenes. Notably, the use of $PPh_3$ as the catalyst led to poor regioselectivities and moderate diastereoselectivities, revealing that the additional functional moiety was critical for accomplishing excellent enantioselectivity as well as regioselectivity and diastereoselectivity. A γ-substituted racemic allenoate also underwent the catalytic annulations smoothly through a dynamic kinetic asymmetric transformation, giving the desired products in high yields and moderate diastereoselectivities, albeit with somewhat decreased ee values. A transition-state model similar to Miller's, mentioned above, was postulated.

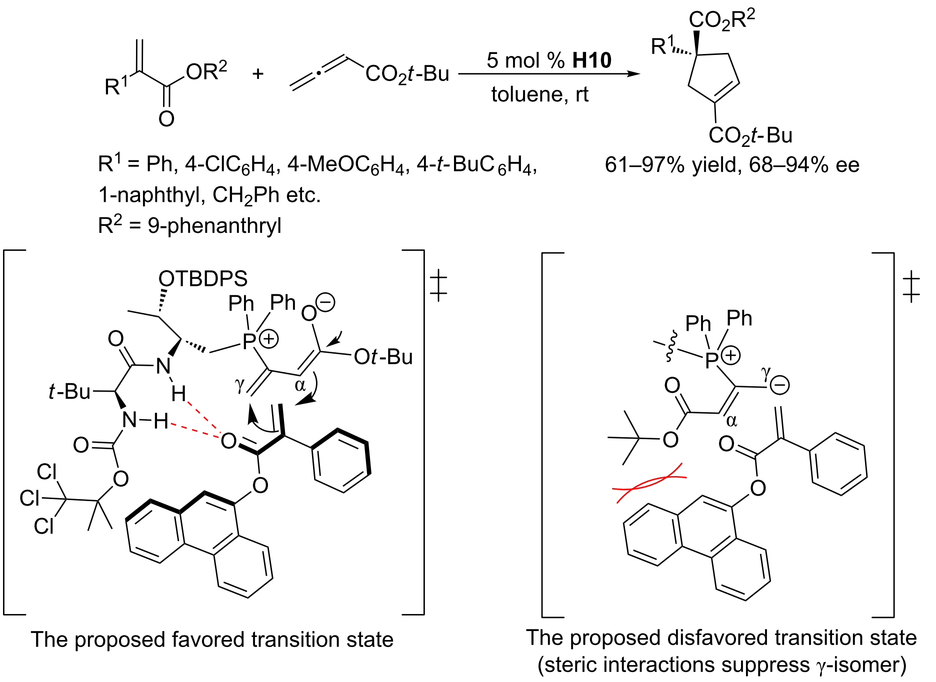
Attracted by the phosphine-catalyzed reactions described above, Lu and co-workers prepared versatile dipeptide-derived phosphines for asymmetric annulations [54]. Their multifunctional catalyst framework comprised a dipeptide moiety and a tertiary phosphine unit. In the presence of 5 mol % of **H10** in toluene at room temperature, the asymmetric [3 + 2] annulations between allenoates and a series of activated olefins yielded exclusively the expected products in good to excellent yields and ee (Scheme 23) [54]. They proposed a transition state model to explain the stereoselectivity; steric hindrance between the *tert*-butyl group of the allenoate and the 9-phenanthryl group of the alkene suppressed the formation of the γ-isomer, affording α-adducts as the major regioselective products, with steric shielding of the *si*-face facilitating production of the major enantiomer (Scheme 23). Shortly after, the Lu group further



**Scheme 21:** Asymmetric [3 + 2] annulations of cyclic enones with allenoates, catalyzed by the chiral α-amino acid-based phosphine **H1**, and the proposed transition state.



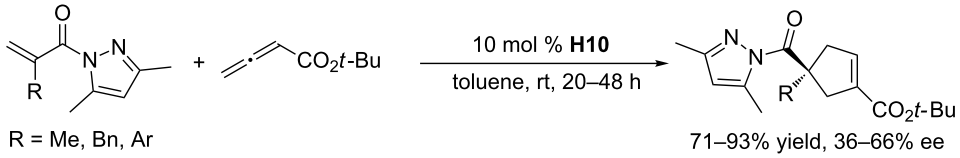
**Scheme 22:** Asymmetric [3 + 2] annulations of arylidenemalononitriles and analogues with an allenoate, catalyzed by the chiral phosphine **H5**.



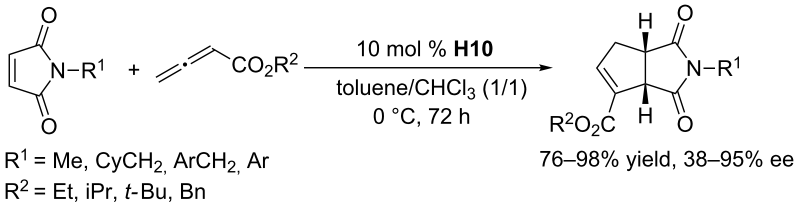
**Scheme 23:** Asymmetric [3 + 2] annulations of α,β-unsaturated esters with an allenoate, catalyzed by the chiral phosphine **H10**, and possible transition states.

expanded the substrate scope of asymmetric [3 + 2] annulations with allenoates to a series of 3,5-dimethyl-1*H*-pyrazole-derived acrylamides (Scheme 24) [55]. The dipeptide-based phosphine **H10** effectively promoted the reaction in good to excellent yields, albeit low to moderate enantioselectivities. In 2012, Lu, Shi, and co-workers found that the dipeptide-based phosphine **H10** was also quite effective as a chiral catalyst for [3 + 2] annulations of various maleimides with allenoates (Scheme 25) [56]. They obtained a wide range of bicyclic cyclopentenes in good to excellent yields. *N*-Alkyl-substituted maleimides were converted to cyclopentenes in high ee, while *N*-aryl-substituted maleimides underwent the reaction with low to moderate enantioselectivity.

Using the multifunctional chiral phosphine **G6**, featuring a binaphthyl skeleton and bearing a thiourea moiety, Shi and



**Scheme 24:** Asymmetric [3 + 2] annulations of 3,5-dimethyl-1*H*-pyrazole-derived acrylamides with an allenoate, catalyzed by the chiral phosphine **H10**.



**Scheme 25:** Asymmetric [3 + 2] annulations of maleimides with allenoates, catalyzed by the chiral phosphine **H10**.

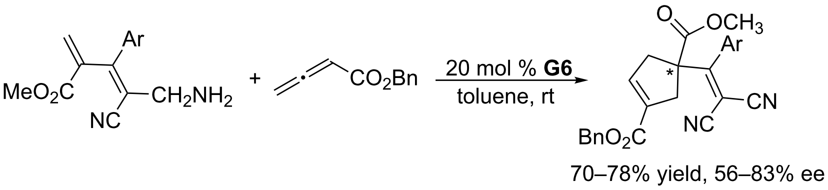
co-workers developed an asymmetric [3 + 2] annulation of α-substituted acrylates with an allenoate (Scheme 26) [57]. The reactions proceeded smoothly in toluene at room temperature to give the corresponding functionalized cyclopentenes in high yields with moderate to good ee. The substrate scope was, however, very limited.

## 2.2 [3 + 2] Annulations of allenes with activated imines

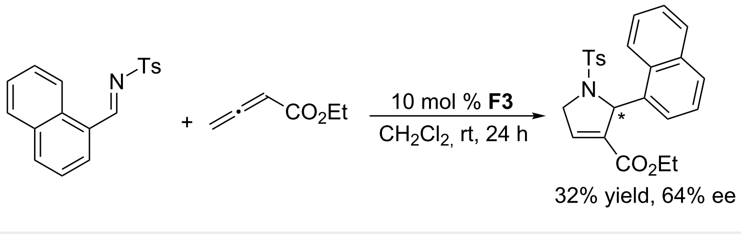
Phosphine-catalyzed [3 + 2] annulation of allenes with activated imines has emerged as an important tool for the synthesis of functionalized pyrrolines, which are valuable heterocyclic compounds for the synthesis of bioactive compounds and natural products. At the end of the century, Lu and co-workers discovered the nucleophilic phosphine-catalyzed [3 + 2] annulation of allenes with electron-deficient imines and established a reasonable reaction mechanism [58-60]. Its asymmetric version, however, did not receive any attention for almost 10 years.

In 2006, Marinetti and co-workers reported the first asymmetric [3 + 2] annulations of imines with allenoates [61]. In this initial exploration, they screened various cyclic and acyclic chiral phosphines, finding that 10 mol % of the acyclic chiral phosphine (*S*)-PHANEPHOS **F3** provided the corresponding pyrroline (Scheme 27) in comparatively high ee (64%), albeit in low yield (32%). Other cyclic and acyclic chiral phosphines provided generally low enantioselectivities. In the same year, Gladysz and Scherer investigated the behavior of an interesting chiral rhenium-containing phosphine **F4** in the asymmetric [3 + 2] annulation of allenoates with *N*-tosylimines (Scheme 28) [62]. Gratifyingly, this acyclic chiral phosphine could efficiently catalyze this transformation, providing pyrroline derivatives in excellent yields (90–93%), albeit after long reaction times (8 days) and with moderate ee (51–60%).

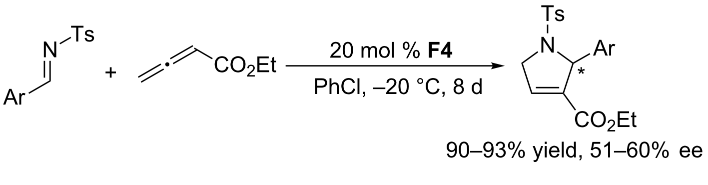
Marinetti et al. employed the binaphthyl-based chiral cyclic phosphine **B2** to improve the enantioselectivities of the [3 + 2] annulation of allenoates with *N*-tosylimines. Compared with the performance of acyclic chiral phosphines, the results were indeed improved, obtaining pyrroline products in 41–80% ee, although the enantioselectivities remained unsatisfactory (Scheme 29) [63]. In subsequent investigations of asymmetric [3 + 2] annulations performed with *N*-diphenylphosphinoylimines (Scheme 30) and allenylphosphonates (Scheme 31) as substrates [64,65], the former reactions generated pyrrolines with good ee (73–88%), albeit with moderate yields (25–74%)



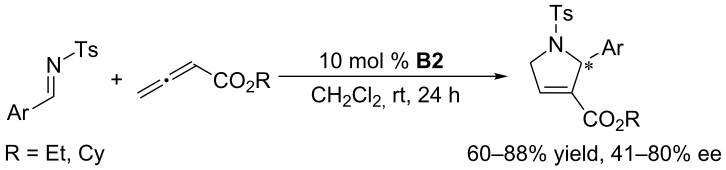
**Scheme 26:** Asymmetric [3 + 2] annulations of α-substituted acrylates with allenoate, catalyzed by the chiral phosphine **G6**.



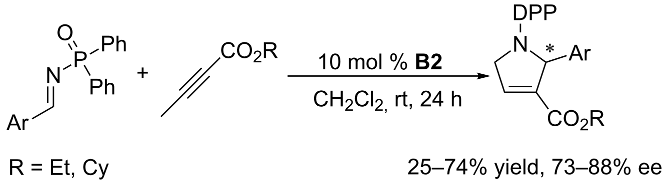
**Scheme 27:** Asymmetric [3 + 2] annulation of an *N*-tosylimine with an allenoate, catalyzed by the chiral phosphine **F3**.



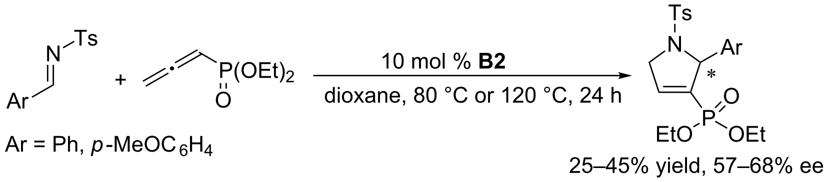
**Scheme 28:** Asymmetric [3 + 2] annulations of *N*-tosylimines with an allenoate, catalyzed by the chiral phosphine **F4**.



**Scheme 29:** Asymmetric [3 + 2] annulations of *N*-tosylimines with an allenoate, catalyzed by the chiral phosphine **B2**.



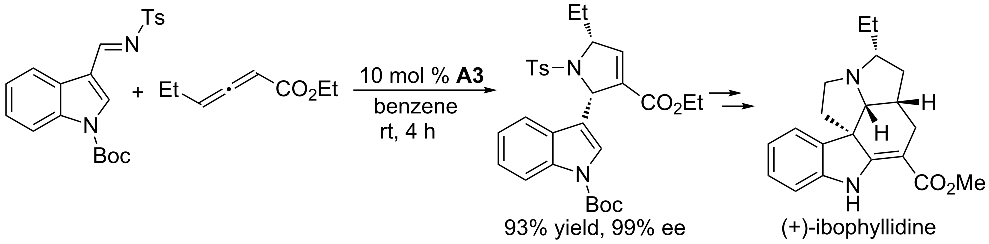
**Scheme 30:** Asymmetric [3 + 2] annulations of *N*-diphenylphosphinoyl aromatic imines with butynoates, catalyzed by the chiral phosphine **B2**.



**Scheme 31:** Asymmetric [3 + 2] annulations of *N*-tosylimines with allenylphosphonates, catalyzed by the chiral phosphine **B2**.

[64]. The relative ease of removal of the diphenylphosphinoyl (DPP) protecting group makes this reaction quite valuable as an organic transformation for the preparation of secondary pyrrolines. The latter reactions (Scheme 31) required harsh conditions, leading to pyrroline derivatives in low yields with moderate ee [65]. In terms of both conversion and enantioselectivity, binaphthyl skeleton-based cyclic chiral phosphines are not ideal catalysts for asymmetric [3 + 2] annulations of electron-deficient imines with allenes.

On the other hand, the rigid bridged [2.2.1] bicyclic chiral phosphine **A3** appears to be an excellent catalyst for allene/imine [3 + 2] annulation. With a chiral phosphine-catalyzed [3 + 2] annulation of an indole-derived imine and an γ-ethylallenoate as the key step, Kwon and Andrews completed the first enantioselective total synthesis of the indole alkaloid (+)-ibophyllidine in 15 steps and 13% overall yield from *N*-Boc-indole-3-aldehyde (Scheme 32) [66]. This approach was the first non-formal total synthesis of a complex natural product employing phosphine-catalyzed asymmetric [3 + 2] annulation. In the key transformation, using 10 mol % of the P-chiral [2.2.1]bicyclic phosphine **A3** derived from *trans*-L-4-hydroxyproline, asymmetric [3 + 2] annulation of 4-ethyl-2,3-butadienoate with an *N*-tosylaldimine (prepared in 90% yield through condensation of *p*-toluenesul-



**Scheme 32:** Asymmetric [3 + 2] annulation of an *N*-tosylimine with an allenoate, catalyzed by the chiral phosphine **A3**, and its application in the total synthesis of (+)-ibophyllidine.

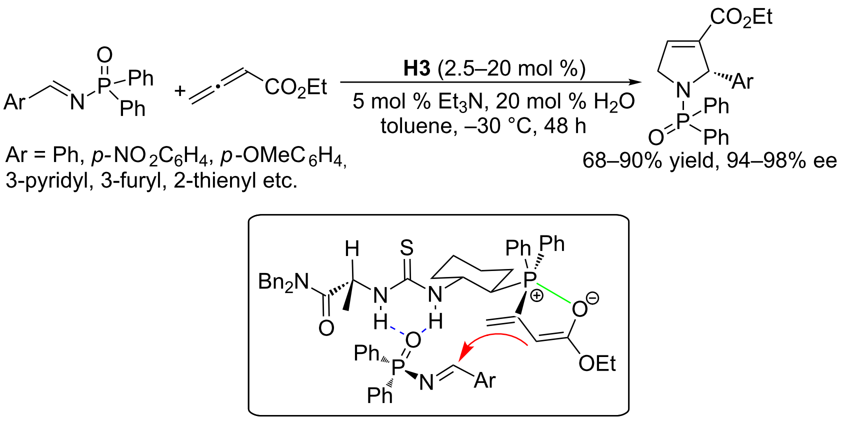
fonamide with *N*-Boc-indole-3-carbaldehyde) for 4 h at room temperature proceeded exceedingly well, giving the desired pyrroline in 93% yield with 99% ee and high diastereoselectivity. In particular, the reaction could be performed on multigram scale to provide the optically pure pyrroline; indeed, in the presence of 10 mol % of the catalyst, the annulation performed on an approximately 30 g scale proceeded in 94% yield and 97% ee.

By using multifunctional chiral phosphines, Jacobsen and Fang obtained a major breakthrough in development of highly enantioselective [3 + 2] annulations of allenoates with imines. Based on thiourea-based catalyst systems, they developed the multifunctional catalyst **H3** containing a phosphine fragment, a thiourea moiety, and an amino acid residue [67]. In the presence of 10 mol % of catalyst **H3**, with the assistance of triethylamine (5 mol %) and water (20 mol %), a wide range of *N*-diphenylphosphinoyl aromatic imines underwent cyclizations (Scheme 33) with an allenoate in toluene at −25 °C for 48 h, affording dihydropyrrole derivatives in 68–90% yield and excellent ee (94–98%). The catalytic amounts of triethylamine and water significantly increased the reaction rates, facilitating proton transfer and catalyst regeneration in the reaction process. In the case of *o*-bromophenylimine, even 2.5 mol % of **H3** could deliver the corresponding product without any loss of enantioselectivity (95% ee), albeit in slightly lower yield. Jacobsen and Fang proposed a possible transition state to explain the high enantioselectivity. In this cooperative system, the phosphine moiety was responsible for activation of the allenoate and the enantioinduction, while the thiourea unit played the dual roles of activating the imine and stereochemically controlling the association of the phosphoryl substituents of the imine. Although the accomplishments with this thiourea-based chiral catalyst were unprecedented, the substrate scope of this reaction is restricted to diphenylphosphinoyl aromatic imines because aliphatic imines decompose under the optimal conditions.

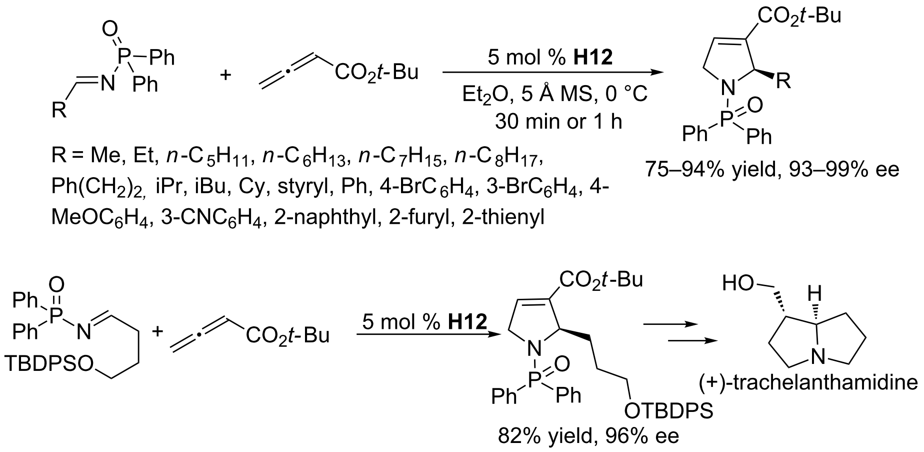
To overcome the limited substrate scope, Lu and co-workers explored imine–allene [3 + 2] annulations catalyzed by a dipeptide-derived phosphine [68]. They identified the phosphine **H12**, a close analogue of **H10**, as the most suitable catalyst. In the presence of 5 mol % of **H12**, a wide range of alkylimines and various arylimines could be employed as reaction partners. The [3 + 2] annulations of allenoates with *N*-diphenylphosphinoylimines proceeded smoothly in ethyl ether in the presence of 5 Å molecular sieves at 0 °C within 30–60 min, providing a variety of pyrroline derivatives in high yields with uniformly excellent enantioselectivities (Scheme 34). Chiral 2-alkyl-substituted 3-pyrrolines are highly valuable building blocks that can be further transformed into various biologically useful molecules. For example, with this reaction as a key step, a concise formal synthesis of (+)-trachelanthamidine was accomplished, highlighting the synthetic value of this methodology (Scheme 34).

## 2.3 [3 + 2] Annulations of allenes with azomethine imines

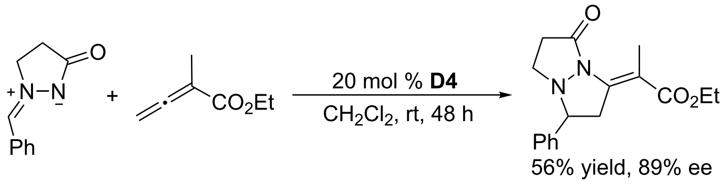
Using the chiral catalyst **D4**, a cyclic phosphine featuring a spiro-skeleton, Guo, Kwon, and co-workers achieved asymmetric [3 + 2] annulation of an allenoate with an azomethine imine (Scheme 35) [69]. The reaction performed in dichloromethane at room temperature for 48 h afforded the product tetrahydropyrazolopyrazolone in 56% yield and 89% ee. Although only a single example was reported, their paper demonstrated that enantioselective [3 + 2] annulations of



**Scheme 33:** Asymmetric [3 + 2] annulations of *N*-diphenylphosphinoyl aromatic imines with allenoates (top), catalyzed by the chiral phosphine **H3**, and a possible transition state (bottom).



**Scheme 34:** Asymmetric [3 + 2] annulation of *N*-diphenylphosphinoylimines with allenoates, catalyzed by the chiral phosphine **H12**, and its application in the formal synthesis of (+)-trachelanthamidine.



**Scheme 35:** Asymmetric [3 + 2] annulation of an azomethine imine with an allenoate, catalyzed by the chiral phosphine **D4**.

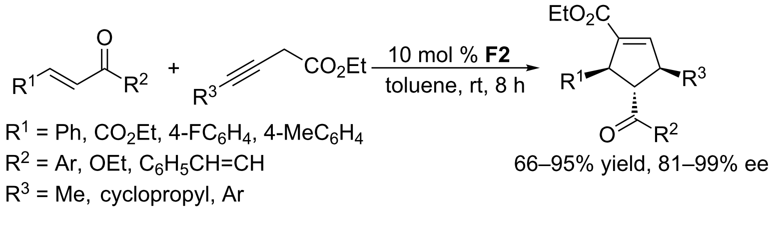
allenoates with azomethine imines could be accomplished when using a suitable chiral catalyst.

## 2.4 [3 + 2] Annulations of alkynes with activated alkenes

In addition to allenoates, alkynes are also compatible substrates for asymmetric [3 + 2] annulations with activated alkenes. Using the commercially available chiral catalyst (*R*,*R*)-DIPAMP **F2**, 3-butynoates underwent [3 + 2] annulations with electron-deficient olefins, providing highly functionalized cyclopentenes in 66–95% yield with 81–99% ee (Scheme 36) [70]. Interestingly, this acyclic catalyst proved to be remarkably efficient at mediating these tandem reactions, despite its structure being less rigid than most of aforementioned cyclic chiral phosphines. Control experiments indicated that under phosphine catalysis conditions, 3-butynoate initially isomerized to the allenoate, which subsequently underwent [3 + 2] annulations with activated alkenes. Notably, only 10 mol % of catalyst **F2** was required, even though it was responsible for promoting the two proposed steps.

## 2.5 [3 + 2] Annulations of MBH carbonates with activated alkenes

MBH carbonates, which are readily accessible from the adducts of MBH reactions, have been used extensively in organocatalysis for the formation of C–C and C–heteroatom bonds [71,72].

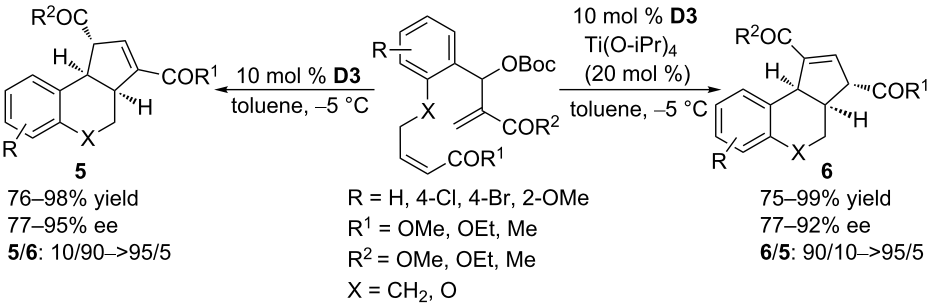


**Scheme 36:** Asymmetric [3 + 2] annulations between α,β-unsaturated esters/ketones and 3-butynoates, catalyzed by the chiral phosphine **F2**.

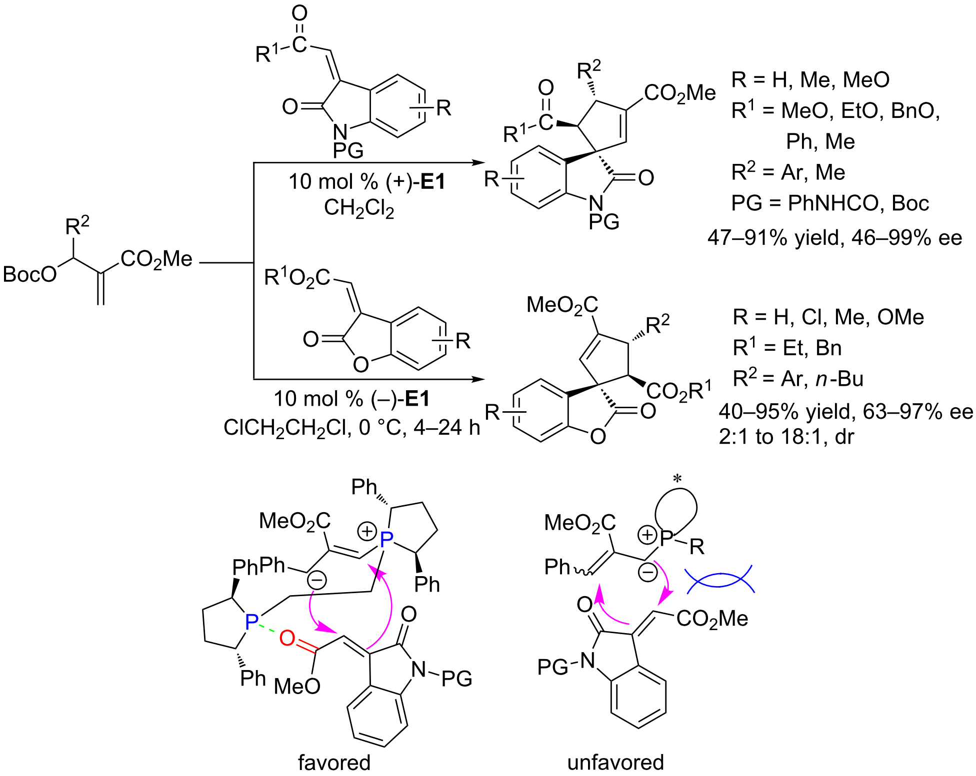
In addition to activated allenes and alkynes, MBH carbonates are often employed as versatile substrates for the phosphine-catalyzed annulations.

In 2010, using the cyclic phosphine (*S*)-DMM-SITCP **D3**, Tang and Zhou developed an intramolecular asymmetric [3 + 2] annulation by combining MBH carbonates and electron-deficient alkenes into a single molecule (Scheme 37) [73]. In the presence of 10 mol % of **D3**, a variety of α,β-unsaturated carbonyl compounds were transformed efficiently in toluene at −5 °C to give optically active benzobicyclo[4.3.0] compounds **5** in excellent yields with high enantioselectivities (77–95% ee). Interestingly, the addition of 20 mol % of Ti(O-iPr)$_4$, under otherwise identical conditions, inhibited the isomerization process, causing the benzobicyclo[4.3.0] compounds **6** to be obtained as major products in excellent yields with high enantioselectivities (77–92% ee).

In 2011, using the chiral phosphine (+)-Ph-BPE **E1** as the catalyst, Barbas and co-workers achieved asymmetric [3 + 2] annulations of MBH carbonates with methyleneindolinones (Scheme 38) [74]. In the presence of 10 mol % of this catalyst,



**Scheme 37:** Asymmetric intramolecular [3 + 2] annulations of electron-deficient alkenes and MBH carbonates, catalyzed by the chiral phosphine **D3**.



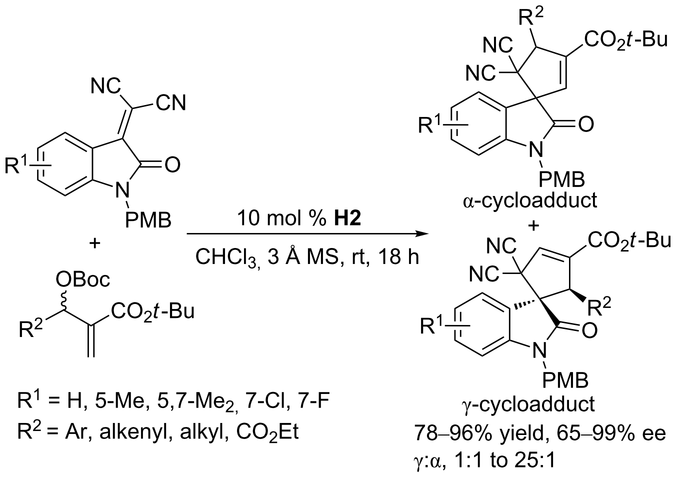
**Scheme 38:** Asymmetric [3 + 2] annulations of methyleneindolinone and methylenebenzofuranone derivatives with MHB carbonates, catalyzed by the chiral phosphines (+)-**E1** and (–)-**E1**, and possible transition states.

the reaction proceeded well in dichloromethane to furnish a wide range of spirocyclopenteneoxindoles in moderate to excellent yields and ee's (Scheme 38). The yields and stereoselectivities were significantly influenced not by electronic effects but by aromatic interactions. Aryl-substituted MBH carbonates reacted smoothly to afford polyfunctionalized spirocyclopenteneoxindoles in good yields (63–85%) and with excellent enantioselectivities (91–99% ee). In contrast, the ee was fairly low (46%) when using a methyl-substituted MHB carbonate at the allylic site. It was rationalized that the aromatic π–π interactions between the catalyst and the substrates favored the formation of the products. Based on control experiments and aforementioned results, Barbas and co-workers proposed a plausible mechanism and suggested that the high stereoselectivity resulted from steric interactions between the bulky substituent of the phosphonium ylide from the MBH carbonate and the carboxylic ester of methyleneindolinone shielding one possible attacking face during the nucleophilic attack (Scheme 38). In 2013, using the same catalytic system, Barbas and co-workers further developed highly stereoselective phosphine-catalyzed [3 + 2] annulations of MBH carbonates with methylenebenzofuranone derivatives, constructing a variety of complex polysubstituted spirocyclopentenebenzofuranones in high yields with good to excellent enantioselectivities [75].

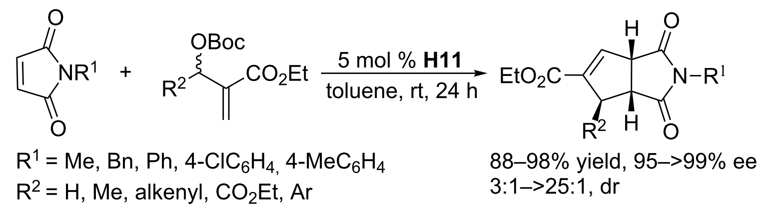
Using the amino acid-derived chiral phosphine **H2**, Lu and co-workers explored asymmetric [3 + 2] cycloadditions between MBH carbonates and activated isatin-based alkenes (Scheme 39) [76]. The reactions, performed in chloroform in the presence of molecular sieves at room temperature, provided biologically important 3-spirocyclopentene-2-oxindoles with two contiguous quaternary centers in very high yields and with good enantioselectivities; they tolerated a wide range of MBH carbonates featuring different electronic properties for their aromatic and heteroaromatic moieties at the allylic position (e.g., phenyl, 4-cyanophenyl, 4-methylphenyl, 2-naphthyl, 3-furyl) as well as diverse isatin-derived alkenes having substituents on their phenyl rings. Of particular interest, even the relatively inert MBH adduct presenting an alkyl unit at the allylic position was applicable to the reactions, furnishing the corresponding product in good yield and enantioselectivity, albeit lower regioselectivity (1:2). After studying the substrate scope and limitations, Lu and co-workers proved that these reactions could be performed in a convenient one-pot manner. For example, the one-pot reactions of isatins, malononitriles (precursors of activated alkene), and MBH adducts produced corresponding spirooxindoles with the same enantioselectivity as that between activated alkenes and MBH adducts, albeit in slightly diminished yields. Shi and co-workers also studied this reaction, but using the chiral bifunctional thiourea-phosphine catalyst **G7**. The [3 + 2] annulation of MBH carbonate with an activated isatin-based alkene in toluene at room temperature gave the corresponding γ-cycloadduct as the major product in 92% yield, with 9:1 dr and 74% ee [77].

Using the amino acid-derived chiral phosphine catalyst **H11**, Lu and co-workers performed asymmetric [3 + 2] annulations between MBH carbonates and maleimides, obtaining access to a wide range of bicyclic imides in excellent yields and enantioselectivities and high diastereoselectivities (Scheme 40) [78]. This methodology worked very well even when operated on gram-scale.

In 2012, using multifunctional chiral phosphines as catalysts, Shi and co-workers investigated a range of asymmetric [3 + 2] annulations of MBH carbonates with various activated alkenes



**Scheme 39:** Asymmetric [3 + 2] annulations of activated isatin-based alkenes with MBH carbonates, catalyzed by the chiral phosphine **H2**.

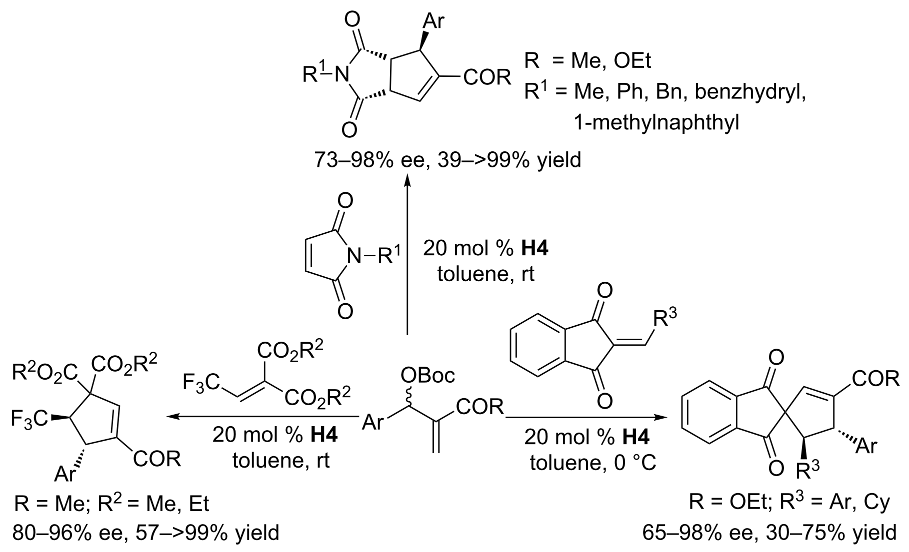


**Scheme 40:** Asymmetric [3 + 2] annulations of maleimides with MBH carbonates, catalyzed by the chiral phosphine **H11**.

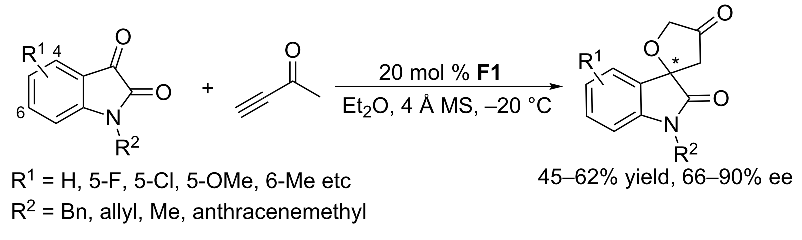
(Scheme 41). They synthesized a range of multifunctional thiourea-phosphines, among which the chiral phosphine **H4** proved to be a versatile and powerful catalyst for these asymmetric [3 + 2] annulations. In the presence of 20 mol % of this chiral phosphine, various activated alkenes, including maleimides [79], trifluoroethylidenemalonate [80], and 2-arylideneindane-1,3-diones [81], were highly compatible for asymmetric [3 + 2] annulation reactions with MBH carbonates, providing moderate to excellent yields, diastereoselectivities, and enantioselectivities (Scheme 41). An array of substituted MBH carbonates bearing neutral, electron-withdrawing, and electron-donating aromatic groups were effectively converted to the corresponding functionalized cyclopentenes. Nevertheless, MBH carbonates having aliphatic substituents, rather than aromatic ones, at the allylic position were not tolerated in these transformations.

## 2.6 [3 + 2] Annulations of an alkyne with isatins

Using the acyclic chiral phosphine (4*S*,5*S*)-DIOP **F1**, Shi and co-workers developed asymmetric [3 + 2] annulations of but-3-yn-2-one with N-protected isatins (Scheme 42) [82]. In the presence of 20 mol % of **F1**, but-3-yn-2-one reacted with a series of



**Scheme 41:** A series of [3 + 2] annulations of various activated alkenes with MBH carbonates, catalyzed by the chiral phosphine **H4**.



**Scheme 42:** Asymmetric [3 + 2] annulations of an alkyne with isatins, catalyzed by the chiral phosphine **F1**.

N-protected isatins in ethyl ether at −20 °C to afford enantioenriched spiro[furan-2,3′-indoline]-2′,4(5*H*)-diones with good to excellent ee's, albeit moderate yields.

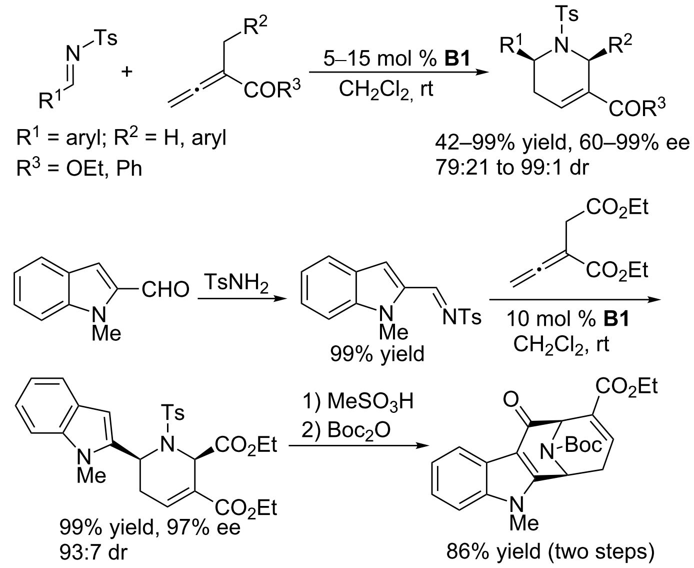
## 2.7 [4 + 2] Annulations of allenes with activated imines

Compared with phosphine-catalyzed asymmetric [3 + 2] annulations, asymmetric [4 + 2] annulations have been less studied, with only limited examples reported. In 2005, based on Kwon's phosphine-catalyzed [4 + 2] annulation of allenoates with *N*-tosylimines [83], Fu and co-workers developed an asymmetric variant using the binaphthyl-based chiral cyclic phosphine **B1** (Scheme 43) [84]. In the presence of 5 mol % of **B1**, asymmetric [4 + 2] annulations of allenoates with a broad range of aromatic *N*-tosylimines worked efficiently in dichloromethane at room temperature to give an array of chiral piperidine derivatives in good to excellent stereoselectivities (up to 99% ee, up to 99:1 dr) and moderate to excellent yields (42–99%). The piperidine products could be transformed conveniently into biologically important heterocyclic compounds. For example, with this asymmetric [4 + 2] annulation as the key step, using indole-2-carboxaldehyde as the starting material, the bridged tetracyclic framework of the *Alstonia* class of indole alkaloids was readily formed in high yield. This asymmetric [4 + 2] annulation was a seminal advance in the area of nucleophilic phosphine catalysis, attracting much attention toward chiral phosphine-catalyzed asymmetric reactions.

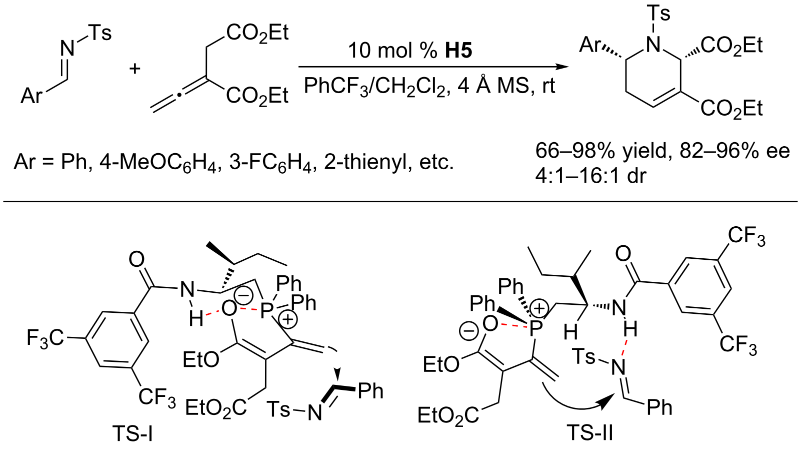
Using the bifunctional *N*-acylaminophosphine **H5**, Zhao and co-workers also achieved enantioselective [4 + 2] annulations of allenoates with *N*-tosylaldimines (Scheme 44) [85]. In the presence of 4 Å molecular sieves and with $PhCF_3$ and $CH_2Cl_2$ as the mixed solvent, **H5**-catalzyed enantioselective [4 + 2] annulations between α-substituted allenoates and *N*-tosylaldimines afforded a wide range of tetrahydropyridines in high yields and with good to excellent enantioselectivities. For some imines, the bifunctional phosphine displayed catalytic capability superior to that of Fu's monophosphine system [84] in terms of yield, ee, or both. Based on previous literature, Zhao and co-workers speculated two possible transition states; in both cases, the dienolate adopts a conformation, featuring hydrogen bonding and O–P electrostatic attraction, that favors *re*-face attack of the imine (Scheme 44).

## 2.8 [4 + 2] Annulations of allenes with activated alkenes

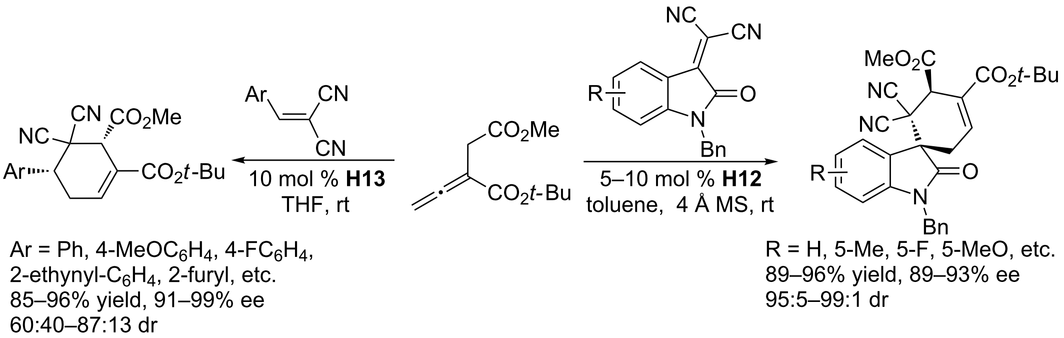
Phosphine-catalyzed [4 + 2] annulation of an allenoate with an activated alkene is a powerful tool for the synthesis of a functionalized cyclohexene [86,87]. To develop an asymmetric version, Lu and co-workers screened 14 bifunctional chiral amino acid-derived phosphines, from which they found that the amido phosphine **H13** was the most efficient catalyst for the [4 + 2] annulations of allenoates with 2-aryl-1,1-dicyanoethylenes (Scheme 45) [88]. In the presence of 10 mol % of **H13** in THF at room temperature, the 1,1-dicyanoethylenes reacted with the α-substituted allenoates to afford an array of functionalized cyclohexenes. A wide range of 2-aryl- and 2-heteroaryl-1,1-dicyanoethylenes were applicable to this transformation, rendering high yields, moderate to good diastereoselectivities, and excellent enantioselectivities. These reaction conditions were not applicable, however, to transformations involving isatin-derived alkenes as substrates, resulting in very poor dia-



**Scheme 43:** Asymmetric [4 + 2] annulations catalyzed by the chiral phosphine **B1**.



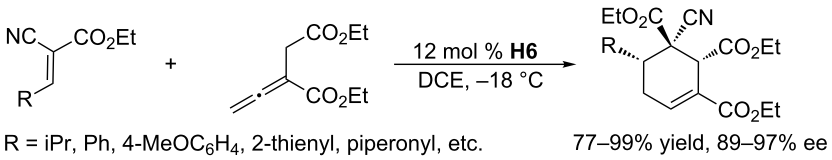
**Scheme 44:** Asymmetric [4 + 2] annulations catalyzed by the chiral phosphine **H5**.



**Scheme 45:** Asymmetric [4 + 2] annulations catalyzed by the chiral phosphines **H13** and **H12**.

stereoselectivities and enantioselectivities. For these oxindole derivatives, the use of the chiral dipeptide-derived phosphine **H12** in toluene at room temperature provided the corresponding [4 + 2] cycloadducts, 3-spirocyclohexene-2-oxindoles, in high yields with excellent ee and dr. These asymmetric [4 + 2] annulations of allenoates with activated alkenes significantly offset the limitations of Diels–Alder reactions when synthesizing enantioenriched multisubstituted cyclohexenes.

At about the same time, Zhao and co-workers also examined the application of bifunctional chiral phosphines in asymmetric [4 + 2] annulations between activated alkenes and α-substituted allenoates (Scheme 46) [89]. They found that the chiral *N*-acyl aminophosphine **H6** in 1,2-dichloroethane at −18 °C mediated a smooth reaction to produce various optically active cyclohexenes containing three neighboring carbon stereocenters in high yields and with excellent ee. Notably, not only arylidenecyanoacetates but also alkylidenecyanoacetates (e.g., isobutyli-



**Scheme 46:** Asymmetric [4 + 2] annulations catalyzed by the chiral phosphine **H6**.

denecyanoacetate) were applicable to the reaction, being converted to their desired products in excellent yields and ee.

## 2.9 [2 + 2] Annulations of ketenes with imines

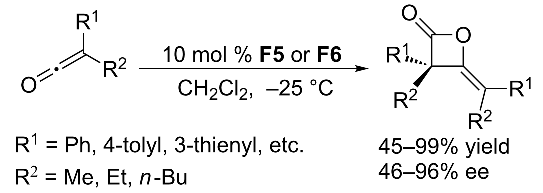
Various ketenes, another class of cumulenes that are analogues of allenes, are also suitable substrates for phosphine-catalyzed asymmetric annulations. Unlike allenes, which act as three- and four-carbon synthons, ketenes typically serve as binary synthons in their annulations. Recently, using the cyclic chiral phosphine (*R*)-BINAPHANE **B7**, the Kerrigan group developed phosphine-catalyzed asymmetric [2 + 2] annulations of ketenes with imines (Scheme 47) [90]. In the presence of 10 mol % of **B7** in dichloromethane or tetrahydrofuran, the reaction of disubstituted ketenes and *N*-tosyl arylimines provided corresponding *trans*-β-lactams in moderate to excellent ee (up to 98%), diastereoselectivities (up to 99:1 dr), and yields (up to >99%). Of particular interest, this methodology facilitates the formation of diverse *trans*-β-lactams that are complimentary to the related *cis*-lactams.

## 2.10 [4 + 1] Annulations of MBH carbonates with dienes

Phosphine-catalyzed asymmetric [4 + 1] annulations between MBH carbonates and activated dienes could be achieved when using the bifunctional phosphine **G6** as the catalyst (Scheme 48) [91]. The reaction worked efficiently in the presence of 4 Å molecular sieves in toluene at room temperature to furnish a variety of functionalized cyclopentenes bearing quaternary carbon stereocenters in 29–92% yield with 66–98% ee. Unfortunately, the reaction times were long (up to 7 days), and substrates with bulky substituents were not well tolerated, giving low yields or ee. Notably, the reactions proved that MBH carbonates can serve as one-carbon synthons for the annulations and expanded the utility of MBH carbonates in synthetic chemistry.

## 2.11 Annulations through homodimerization of ketoketenes

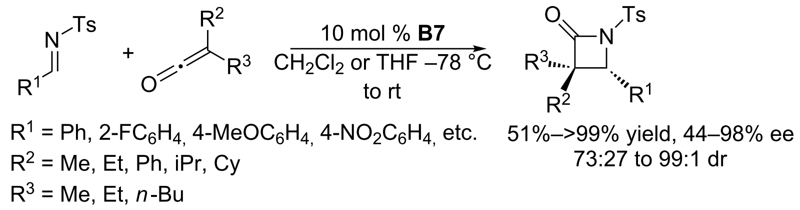
Using the chiral catalysts (*S*,*R*p)-Josiphos **F5** and **F6**, the Kerrigan group developed the asymmetric homodimerization of ketenes (Scheme 49) [92]. This self-condensation of ketoketenes proceeded in dichloromethane at –25 °C to give chiral β-lactones in high yields (up to 99%) with good to excellent ee (up to 96%). In subsequent transformations, the β-lactone products underwent various ring opening reactions to provide very useful derivatives, such as 1,3-diketones and enol esters, with good diastereoselectivity.



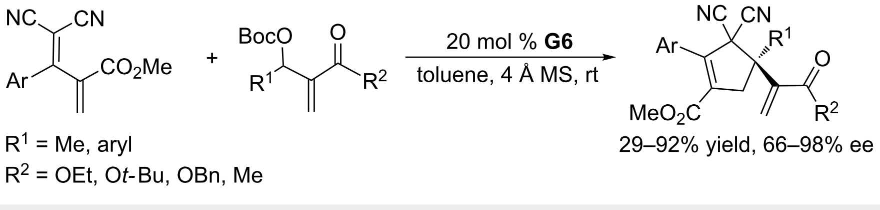
**Scheme 49:** Asymmetric homodimerization of ketenes, catalyzed by the chiral phosphine **F5** and **F6**.

## 2.12 Annulations through domino aza-MBH/Michael reactions

Because organocatalytic asymmetric domino reactions allow the rapid construction of structurally complex molecules from readily available starting materials in two or more steps in a single operation, they have attracted much attention. Bifunc-



**Scheme 47:** Kerrigan's [2 + 2] annulations of ketenes with imines, catalyzed by the chiral phosphine **B7**.



**Scheme 48:** Asymmetric [4 + 1] annulations, catalyzed by the chiral phosphine **G6**.

tional chiral phosphines are ideal chiral catalysts for tandem reactions. In 2010, using the bifunctional chiral phosphine **G1**, bearing both Brønsted acid and Lewis base units, as the catalyst, asymmetric domino aza-MBH/aza-Michael reactions of activated alkenes and *N*-tosylimines with Michael acceptor moieties at their ortho positions were accomplished to give chiral 1,3-disubstituted isoindolines (Scheme 50) [93]. Good to excellent yields were obtained with excellent ee. A wide range of activated alkenes containing acyl, alkoxycarbonyl, and formyl groups and a series of *N*-tosylarylimines with alkyl- and halo-substituted benzene rings were compatible with the reaction conditions. The obtained products could be transformed smoothly into many complex and potentially useful compounds, through diverse derivatization, without significant losses of enantiomeric excesses.

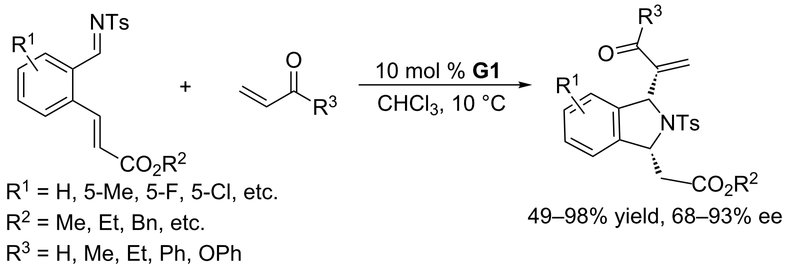
## 2.13 Annulations through tandem RC/Michael reactions

In 2012, using the chiral threonine-derived phosphine **H14**, Zhong and Loh developed asymmetric [4 + 2] annulations of activated *N*-sulfonyl-1-aza-1,3-dienes and alkenes through tandem RC/Michael reactions (Scheme 51) [94]. In the presence of 10 mol % of **H14**, various 1-aza-1,3-dienes smoothly underwent [4 + 2] annulations with enones in chloroform at room temperature, affording a broad spectrum of densely functionalized tetrahydropyridine derivatives, with exclusive 4,5-*trans* diastereoselectivity, excellent enantioselectivity, and good to excellent yields. The transformations tolerated a wide range of *N*-sulfonyl-1-aza-1,3-dienes with different C4-substituents, both aryl and alkyl. The addition of a Brønsted acid to the reaction system slightly improved the yields and diastereocontrol. In addition, the resulting tetrahydropyridines could be transformed to more complex dihydroxylated piperidine derivatives.

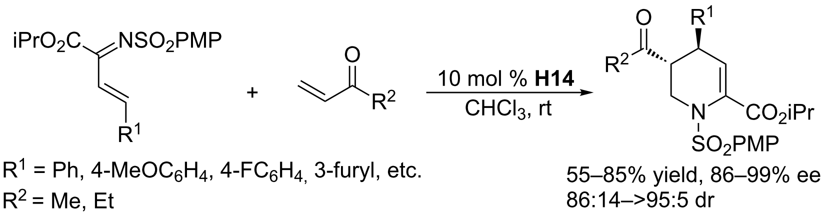
At almost the same time, an intramolecular variant of this [4 + 2] annulation was developed, employing the chiral bifunctional phosphine **H15** as the catalyst (Scheme 52) [95]. The substrates were constructed by installing an acrylate moiety and an α,β-unsaturated imine moiety on the aryl scaffold. In the presence of 5 mol % of **H15**, the functionalized substrates underwent the intramolecular [4 + 2] annulation in toluene at room temperature for 24 h to provide highly functionalized tetrahydropyridines in moderate to excellent yields with exceptionally high diastereo- and enantioselectivities. The optically pure products, containing multiple functional groups, could undergo further transformations, such as Diels–Alder reactions, reduction, and hydrolysis, to afford nitrogen-containing heterocyclic compounds. In contrast to the intermolecular aza-RC reaction/Michael addition sequence described above, the mechanism was assumed to involve an initial aza-RC reaction between the α,β-unsaturated imine and the enolate, followed by an $S_N2$ reaction.

## 2.14 Annulations through double-Michael additions

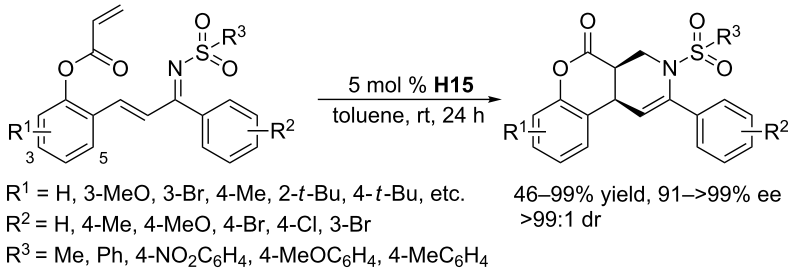
The bisphosphine-catalyzed double-Michael addition of dinucleophiles to electron-deficient alkynes provides an efficient approach for the synthesis of biologically significant nitrogen-containing heterocycles. To develop its asymmetric



**Scheme 50:** Aza-MBH/Michael reactions, catalyzed by the chiral phosphine **G1**.



**Scheme 51:** Tandem RC/Michael additions, catalyzed by the chiral phosphine **H14**.

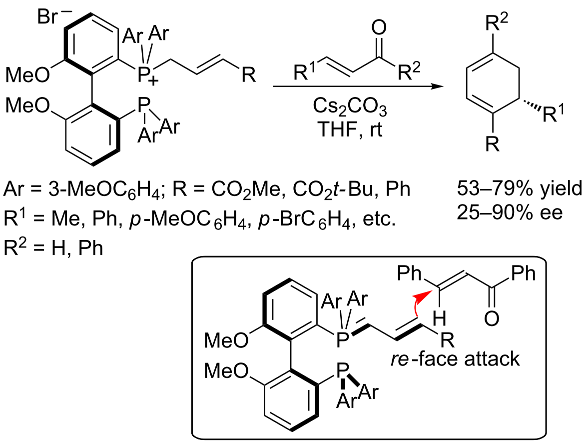


**Scheme 52:** Intramolecular tandem RC/Michael addition, catalyzed by the chiral phosphine **H15**.

variant, Kwon and co-workers examined several common and commercially available chiral bisphosphines, as well as a series of newly prepared chiral aminophosphines [96]. Unfortunately, these phosphines displayed no or very poor enantioselectivity. In a relatively successful example, the chiral aminophosphine **G9** catalyzed the asymmetric double-Michael reaction between *o*-tosylamidophenyl malonate and 3-butyn-2-one to give the indoline derivative in 69% yield and up to 10% ee (Scheme 53).

## 2.15 Annulation through tandem Michael addition/ Wittig olefination

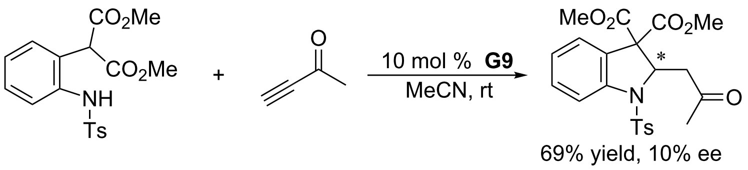
In 2009, Tang and Zhou developed an annulation through tandem Michael addition/Wittig olefination, mediated by the chiral phosphine BIPHEP, for the synthesis of optically active cyclohexa-1,3-diene derivatives (Scheme 54) [97]. Although this reaction required a stoichiometric amount of chiral phosphine, it is quite interesting and deserves mention. In the presence of cesium carbonate, chiral BIPHEP-derived phosphonium ylides reacted with various α,β-unsaturated aryl/alkylketones in THF at room temperature to afford corresponding cyclohexadienes in good yields and with up to 90% ee. It was proposed that the major enantiomer formed through *re*-face attack of the ylide onto the Michael acceptor, rather than attack from the sterically hindered *si*-face.



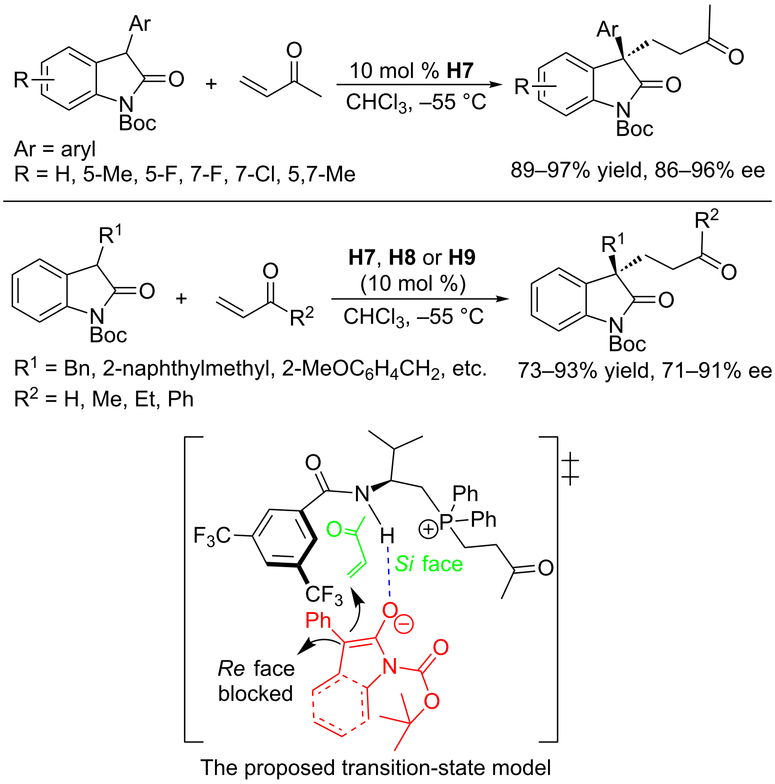
**Scheme 54:** Tandem Michael addition/Wittig olefinations, mediated by the chiral phosphine BIPHEP.

## 2.16 Michael additions

Asymmetric Michael addition is one of the most studied enantioselective processes in organic synthesis, with many successful examples having been reported. Michael reactions employing nucleophilic phosphines are believed, however, to proceed through a mechanism involving phosphine-initiated general base catalysis; consequently, they do not involve covalent linkage of the phosphine to the reactants [98]. Accordingly, the development of chiral phosphine–assisted asymmetric Michael reactions has lagged behind other phosphine-catalyzed reactions. Recently, using bifunctional chiral amino acid–derived phosphines, Lu and co-workers developed asymmetric Michael additions of oxindoles to α,β-unsaturated carbonyl compounds (Scheme 55) [99]. They identified the chiral phosphine **H7** as the best catalyst, providing the corresponding Michael adducts in excellent yields and enantioselectivities. Notably, the less studied and relatively inert 3-alkyl-substituted



**Scheme 53:** Double-Michael addition, catalyzed by the chiral aminophosphine **G9**.



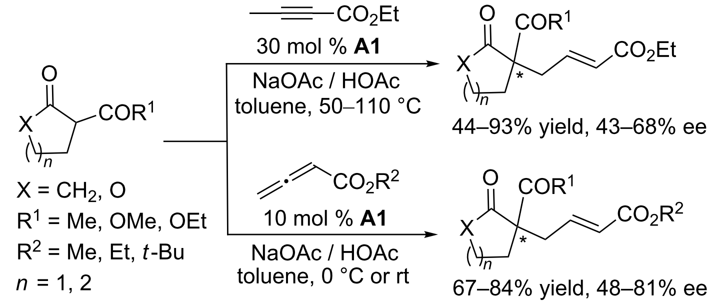
**Scheme 55:** Asymmetric Michael additions, catalyzed by the chiral phosphines **H7**, **H8**, and **H9**.

oxindoles were also applicable to the reaction in the presence various chiral phosphines. When exposed to appropriate catalysts (**H7**, **H8**, or **H9**), 3-alkyl-substituted oxindoles reacted smoothly with Michael acceptors for an extended period of time, giving an array of corresponding products in good to excellent yields and enantioselectivities. In the proposed transition state, a hydrogen bond between the amide NH proton and the enolate oxygen atom assisted the Michael addition from the *si*-face of the enolate. The alternative *re*-face attack was blocked by the 3,5-bistrifluoromethylphenyl group (Scheme 55).

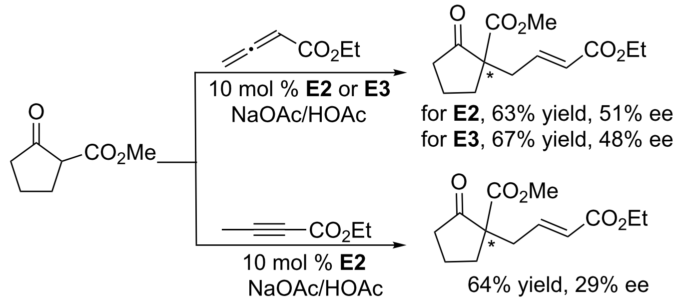
## 2.17 γ-Umpolung additions of allenes or alkynes

In the phosphine-catalyzed annulations of allenoates and activated alkenes, the first C–C bond forms through nucleophilic addition of the β-phosphonium dienolate intermediate to the activated alkene at its α- or γ-carbon atoms. Conversely, when allenoates are mixed with pronucleophiles that contain acidic protons in the presence of a phosphine, the β-phosphonium dienolate zwitterion becomes protonated at its α-carbon atom, resulting in the formation of vinylphosphonium species and anionic nucleophiles. The nucleophile anion then undergoes γ-umpolung addition to the γ-carbon atom of the vinylphosphonium species, producing a phosphonium ylide intermediate. Subsequent proton transfer and β-elimination of the phosphine catalyst results in a γ-functionalized α,β-unsaturated enoate. The reaction, known as γ-umpolung addition, was reported by Trost [100] and Lu [101] in 1994 and 1995, respectively. Trost employed butynoates, which are converted to β-phosphonium dienolates under the conditions of phosphine catalysis.

Early in 1998, the Zhang group explored phosphine-catalyzed asymmetric γ-umpolung addition of 2-butynoates and allenoates (Scheme 56) [102]. Using the cyclic chiral phosphine **A1**, featuring a bridged-ring skeleton, as the catalyst and NaOAc/HOAc as additives, asymmetric γ-addition of cyclic β-dicarbonyl nucleophiles to 2-butynoate occurred in toluene at relatively high temperature to produce γ-adducts with quaternary carbon centers in good to excellent yields (up to 93%) and with moderate ee (up to 68%). Under the same conditions, the allenoates also underwent the γ-addition to give corresponding products in up to 84% yield and with up to 81% ee. In 2004, using the cyclic chiral phosphines **E2** and **E3**, based on a five-membered phospholane ring skeleton, as catalysts, Pietrusiewicz and co-workers reinvestigated these reactions (Scheme 57) [103]. The catalytic activities and enantiocontrol provided by these chiral phosphanes were, however, unsatisfactory, leading to only low to moderate ee.



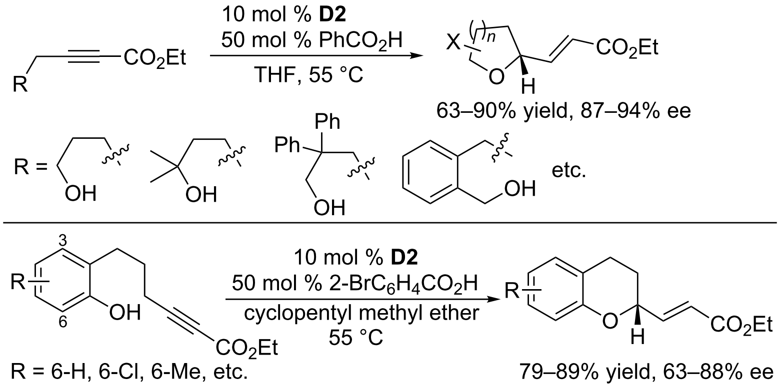
**Scheme 56:** Asymmetric γ-umpolung additions, catalyzed by the chiral phosphine **A1**.



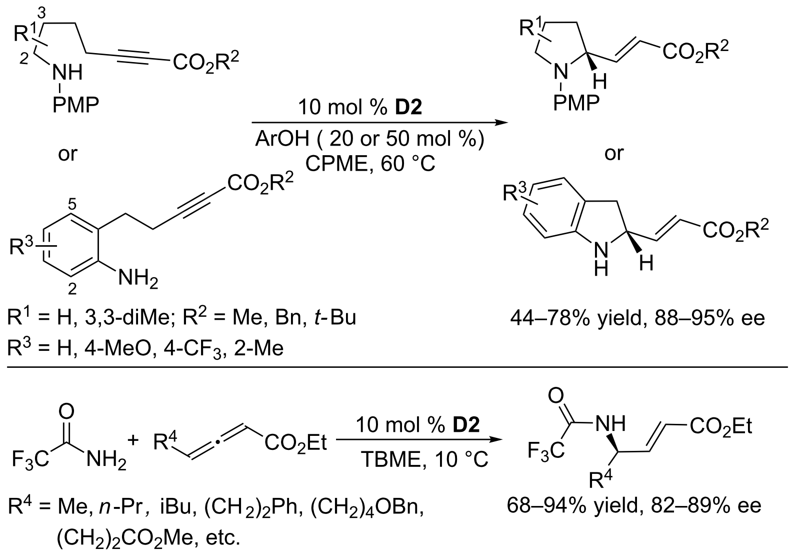
**Scheme 57:** Asymmetric γ-umpolung additions, catalyzed by the chiral phosphines **E2** and **E3**.

Although intermolecular γ-additions of 2-butynoates were quite unsuccessful, Fu and co-workers achieved successful γ-addition-based intramolecular annulations when using cyclic chiral phosphines featuring a spirocyclic skeleton (Scheme 58) [104]. In the presence of 10 mol % of **D2** and 50 mol % of benzoic/4-bromobenzoic acid as additives, γ-additions of a series of hydroxy-2-alkynoates occurred smoothly in THF at 50–55 °C to give substituted tetrahydrofurans, tetrahydropyrans, and dihydrobenzopyrans in good to excellent yields (63–90%) and enantioselectivities (87–94% ee). Both alkanol and phenol derivatives were compatible with this catalytic system.

Building on the successful oxa-umpolung additions, Fu and co-workers further extended the reaction to intramolecular γ-additions of amino 2-alkynoates (Scheme 59) [105]. For this γ-addition of nitrogen nucleophiles, the chiral phosphine **D2** remained the most effective catalyst. In the presence of 10 mol % of **D2** and 2,4-dimethoxyphenol as an additive,



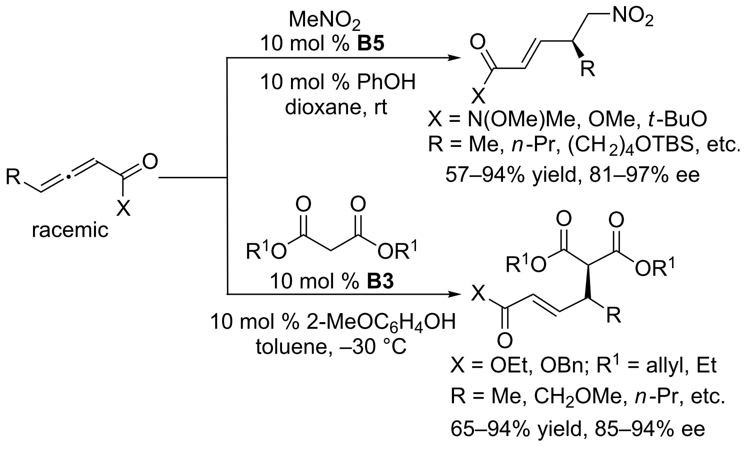
**Scheme 58:** Intramolecular γ-additions of hydroxy-2-alkynoates, catalyzed by the chiral phosphine **D2**.



**Scheme 59:** Intra-/intermolecular γ-additions, catalyzed by the chiral phosphine **D2**.

intramolecular γ-additions of aromatic nitrogen nucleophiles to alkynoates occurred in cyclopentyl methyl ether at 60 °C to give functionalized pyrrolidines in moderate to good yields with excellent enantioselectivities (88–95% ee). A wide range of substrates was well-tolerated. Gratifyingly, intermolecular γ-addition of a nitrogen nucleophile to allenes was also possible; in the presence of 10 mol % of **D2**, the γ-addition reactions of 2,2,2-trifluoroacetamide to a variety of allenoates proceeded smoothly in *tert*-butyl methyl ether at 10 °C, leading to a wide range of α,β-unsaturated γ-amido carbonyl compounds in good to excellent yields and with high ee.

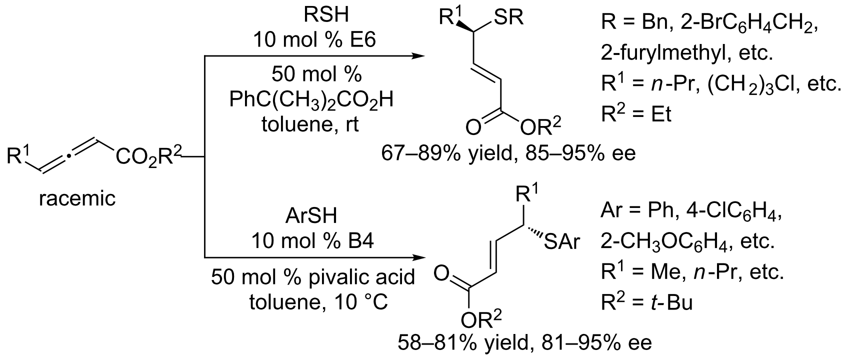
Using cyclic chiral phosphines based on a binaphthyl skeleton, Fu and co-workers also achieved γ-additions of nitromethane to allenoates [106]. In the presence of 10 mol % of **B5** and the assistance of 10 mol % phenol, nitromethane underwent γ-additions to various allenoates in dioxane at room temperature (Scheme 60) to give corresponding α,β-unsaturated δ-nitro carbonyl compounds with good catalytic efficiency (57–94% yields, 81–97% ee). In the further exploration, using 10 mol % of the chiral phosphine **B3** as the catalyst and 10 mol % of 2-methoxyphenol as an additive, the γ-additions of malonate esters to allenoates were also successfully developed [107]. The γ-additions between a wide array of racemic allenoates and malonate esters proceeded well in toluene at –30 °C, furnishing a variety of the corresponding γ-substituted α,β-unsaturated esters in good yields with good to excellent enantioselectivities (Scheme 60). Notably, the α-substituted malonate esters could



**Scheme 60:** Intermolecular γ-additions, catalyzed by the chiral phosphines **B5** and **B3**.

react with the allenoates to provide optically active α,β-unsaturated carbonyl compounds featuring two adjacent carbon stereocenters: a chiral quaternary carbon atom and a chiral tertiary carbon atom.

In subsequent investigations, Fu and co-workers further demonstrated that alkyl and aryl thiols could also act as nucleophiles for asymmetric γ-additions to various allenoates [108,109]. In the presence of 10 mol % of TangPhos **E6** as the catalyst and 50 mol % of 2-methyl-2-phenylpropionic acid as an additive, alkyl thiols underwent γ-additions to various allenoates in toluene at room temperature to give γ-thioesters in 67–89% yields and with 85–95% ee (Scheme 61) [108]. Notably, the enantioselectivities were significantly additive-dependent. For the asymmetric γ-additions of aryl thiols to allenoates, the chiral binaphthyl phosphine **B4** proved to be the best catalyst [109]. In the presence of 10 mol % of **B4** as the catalyst and pivalic acid as an additive, the γ-additions between various aryl thiols and an array of allenoates progressed well in toluene at 10 °C to afford γ-arylthio-α,β-unsaturated esters in 58–81% yields and with 81–95% ee. This reaction provides facile access to various chiral alkyl aryl thioethers under mild conditions.

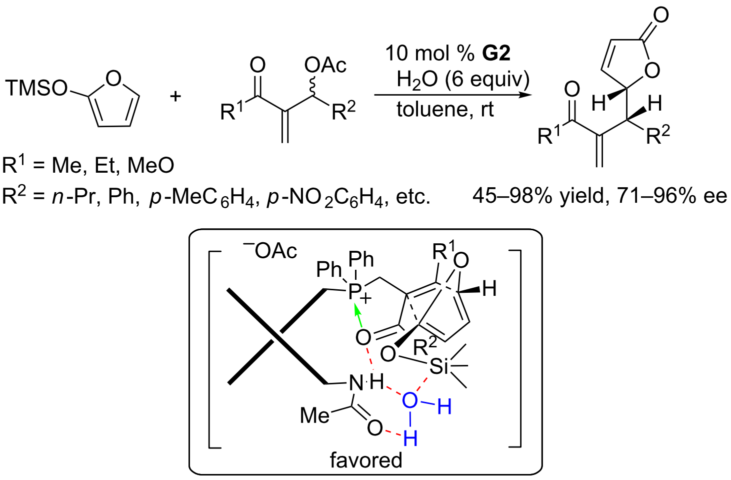


**Scheme 61:** Intermolecular γ-additions, catalyzed by the chiral phosphines **E6** and **B4**.

## 2.18 Allylic substitutions of MBH acetates or carbonates with nucleophiles

In addition to various annulations, allylic substitution is another important class of reaction of MBH acetates or carbonates in nucleophilic phosphine catalysis that can be used to synthesize valuable molecules.

For the synthesis of γ-butenolide ring systems, which are very common structural motifs in naturally occurring organic molecules, the Krische group developed $PPh_3$-catalyzed allylic substitutions of MBH acetates with 2-(trimethylsilyloxy)furan [110,111]. Using the bifunctional chiral phosphine **G2**, Shi and co-workers accomplished the asymmetric variant of this reaction (Scheme 62) [112]. In the presence of 10 mol % of **G2** and excess water (6 equiv), which was assumed to function as an



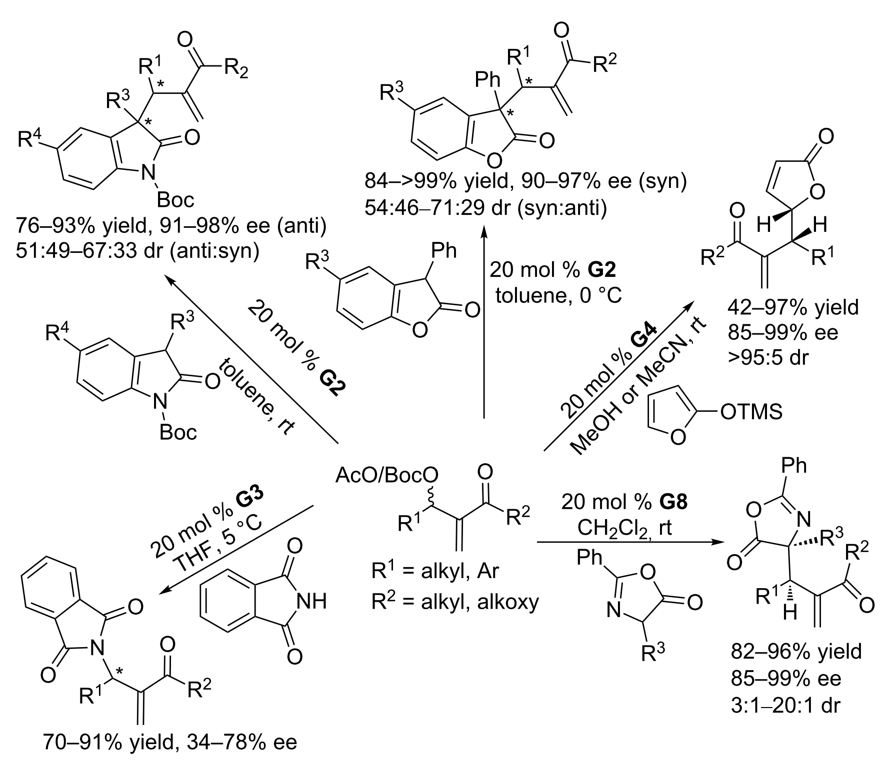
**Scheme 62:** Asymmetric allylic substitution of MBH acetates, catalyzed by the chiral phosphine **G2**.

extra proton source, the allylic substitutions of MBH acetates bearing either aromatic or aliphatic substituents at the allylic position with 2-(trimethylsilyloxy)furan proceeded smoothly in toluene to afford enantioenriched γ-butenolides in moderate to excellent yields and with excellent enantioselectivities. An intermediate arising from *endo*-selective Diels–Alder annulation of the siloxy-furan complex with the enone was believed to play a key role in the enantiocontrol (Scheme 62). In the intermediate, a molecule of water served as a bridge of hydrogen bonds to connect the amide NH proton of the phosphonium ylide to the silicon atom of the trimethylsilyloxy group, which directed the approaching furan moiety to the Michael acceptor in an *endo* manner.

Using multifunctional chiral phosphines based on a binaphthyl skeleton, Shi and co-workers explored the phosphine-catalyzed asymmetric allylic substitutions of MBH acetates or carbonates with various nucleophiles, both experimentally and theoretically. In the presence of chiral phosphines presenting tethered amide or thiourea moieties (**G2**, **G3**, **G4**, **G8**), various activated nucleophiles, including phthalimide [113,114], oxazolones [115], and benzofuran-2(3*H*)-ones and oxindoles [116], could undergo substitution reactions with MBH acetates or carbonates, generating a variety of optically active MBH adducts in good yields and stereoselectivities (Scheme 63). Theoretical calculations were performed to explore the origins of stereoselectivities and to confirm Shi's previously proposed mechanism [117]. The MP2/6-31G(d)//HF/3-21G* level of theory was used to calculate and compare the energies of the transition states. The calculations revealed that the energy of the transition state for *endo*-Diels–Alder [4 + 2] annulation was the lowest among the four possible transition states, presumably arising from the π–π-stacking interactions; these energy gaps likely account for the diastereoselection. Furthermore, the enantioselectivity was ascribed to the energy difference between the transition states for the two possible faces of attack (*re*- and *si*-endo transition states), on the basis of optimized structures. The *si*-endo transition state was disfavored because of additional repulsion between the trimethylsilyloxy unit and the phosphine, as well as the absence of hydrogen bonding between the amide NH proton and the C=O group in the MBH adduct.

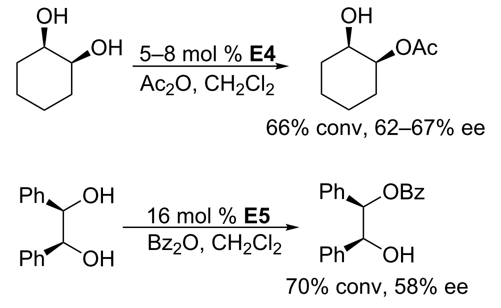
## 2.19 Asymmetric acylations of alcohols

Kinetic resolution of a racemic mixture is a powerful tool for the synthesis of enantioenriched compounds. Among the various methods, including enzyme catalysis, metal catalysis, and organocatalysis, that have been developed for this process, phosphine catalysis is particularly interesting. In 1996, Vedejs and co-workers reported the first example of chiral phosphine-catalyzed enantioselective acylation based on kinetic resolution



**Scheme 63:** Allylic substitutions between MBH acetates or carbonates and an array of nucleophiles, catalyzed by chiral binaphthyl-derived multifunctional phosphines.

(Scheme 64) [19]. They demonstrated that the cyclic chiral phosphines **E4** and **E5** catalyze the acetylation and benzoylation of secondary alcohols effectively in dichloromethane, yielding corresponding esters in moderate to good conversions and with moderate enantioselectivities. For instance, in the presence of 5–8 mol % of **E4**, the desymmetrization reaction of *cis*-1,2-cyclohexanediol with acetic anhydride in dichloromethane at 0–20 °C gave the monoacetate in 66% conversion and with 62–67% ee. Using 16 mol % of **E5**, the reaction of *meso*-hydrobenzoin with benzoic anhydride afforded the monobenzoate in 70% conversion and with 58% ee.



**Scheme 64:** Asymmetric acylation of diols, catalyzed by the chiral phosphines **E4** and **E5**.

In a subsequent study, Vedejs and co-workers developed more efficient and enantioselective chiral phosphines – **E8** and **E9** – for the kinetic resolution (Scheme 65) [20]. In the presence of 2–12 mol % of **E8** or **E9**, racemic secondary alcohols reacted with $(iPrCO)_2O$ in heptane to provide isobutyrates in moderate conversions and with good to excellent enantioselectivities. At the same time, the starting materials were kinetically resolved into corresponding enantioenriched alcohols. Moreover, this kinetic resolution could be performed on the gram-scale.

## Conclusion

This review reveals that, in less than two decades, tremendous progress has been made in the study of asymmetric reactions catalyzed by nucleophilic chiral phosphines. These reactions have emerged as attractive and powerful synthetic tools, allowing the convenient preparation of many enantioenriched and functionalized carbocycles, heterocycles, and acyclic compounds in satisfactory yields. Nevertheless, the range of successful asymmetric reaction types remains relatively limited. Although many chiral phosphines have been prepared, the number of appropriate and available chiral phosphines is small when compared with those that mediate achiral reactions. Because of the lack of suitable chiral catalysts, asymmetric variants of many phosphine-catalyzed reactions remain unsubstantiated. Even for those successful asymmetric reactions, quite a few catalyst systems are substrate-dependent and do not work for slightly different, yet analogous, substrates. Based on these issues, the design and synthesis of novel chiral phosphines, including cyclic phosphines and multifunctional chiral phosphines, remains an interesting challenge. Because of the powerful capabilities of phosphine-catalyzed reactions in the synthesis of biologically active molecules and natural products, there is a need for further research in this area, such that more asymmetric reactions can be anticipated.

## Acknowledgements

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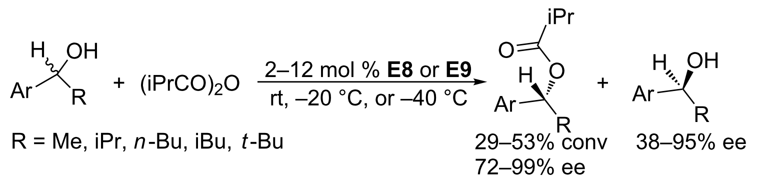

**Scheme 65:** Kinetic resolution of secondary alcohols, catalyzed by the chiral phosphine **E8** and **E9**.

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

# A modular phosphate tether-mediated divergent strategy to complex polyols

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Full Research Paper

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## Abstract

An efficient and divergent synthesis of polyol subunits utilizing a phosphate tether-mediated, one-pot, sequential RCM/CM/reduction process is reported. A modular, 3-component coupling strategy has been developed, in which, simple “order of addition” of a pair of olefinic-alcohol components to a pseudo-$C_2$-symmetric phosphoryl chloride, coupled with the RCM/CM/reduction protocol, yields five polyol fragments. Each of the product polyols bears a central 1,3-*anti*-diol subunit with differential olefinic geometries at the periphery.

## Introduction

1,3-*anti*-Diol subunits are a central component in several potent biologically active polyketides [1-4]. This prevalence has led to the development of various synthetic methods for their construction [5]. In particular, divergent strategies are ideal for analog generation [6-11], which in turn, can enhance the quality of screening decks in early phase drug discovery. One aim of divergent synthetic strategies is to produce multiple scaffolds from a single set of starting materials [12]. In this regard, one-pot, sequential processes [13-16] are well suited to address this challenge by forming multiple bonds and stereocenters, while invoking step- [17], atom- [18-21], green- [22,23], and pot economy [24-26]. We have previously reported phosphate tether-mediated strategies to streamline the synthesis of 1,3-*anti*-diol containing natural products, including recent reports employing one-pot, sequential protocols [27-32]. Herein, we report a modular, divergent approach to construct advanced polyol intermediates **10**–**14** and **17**–**21** in one- or two-pot sequences utilizing the innate properties of a phosphate tether. Taken collectively, this modular, divergent 3-component coupling strategy generates five polyol fragments, bearing differential *Z*- and *E*-olefins, from a pair of olefinic-alcohol components **A** and **B** and a pseudo-$C_2$-symmetric phosphoryl chloride (*S*,*S*)-**1**. Moreover, the method relies on simple "order of addition" of components for the phosphoryl coupling, ring-closing metathesis (RCM) and cross metathesis (CM) steps of the process as outlined in Scheme 1. This protocol further highlights the utility of phosphate tether mediated desymmetrization of $C_2$-symmetric 1,3-*anti*-diene-diol subunit to generate polyol scaffolds which would otherwise be difficult to produce via (*Z*)-and (*E*)-selective CM of 1,3-*anti*-diene-diol subunits with olefinic-alcohol components.

## Results and Discussion

The titled divergent strategy was initiated during efforts to further explore the utility of phosphate tethers. Previous reports emphasized the utilization of phosphate tethers in chemo- and diastereoselective reactions including one-pot, sequential RCM/CM/$H_2$ protocols and their applications in total synthesis of various natural products [27-32]. In addition, the scope of phosphate-tethered methods was further expanded via extensive RCM studies of different triene subunits utilizing stereochemically divergent olefin partners [33]. Recently, the potential of phosphate tethered facilitated processes were highlighted in the pot-economical and efficient total synthesis of the antifungal agent strictifolione, whereby two consecutive phosphate tether-mediated, one-pot, sequential protocols were employed [34].

The requisite trienes **5–7** for this study were generated via our previously reported coupling of the pseudo-$C_2$-symmetric phosphoryl chloride (*S,S*)-**1** with the olefinic alcohol components **2–4** [27-32]. The alcohol substrates are carefully chosen to incorporate exo-allylic methyl groups since previous RCM studies [33] showed that the productive RCM for 8-membered ring formation was observed only for the *S,S*- configured trienes in the presence of an exo-methyl group at the allylic position (Figure 1).

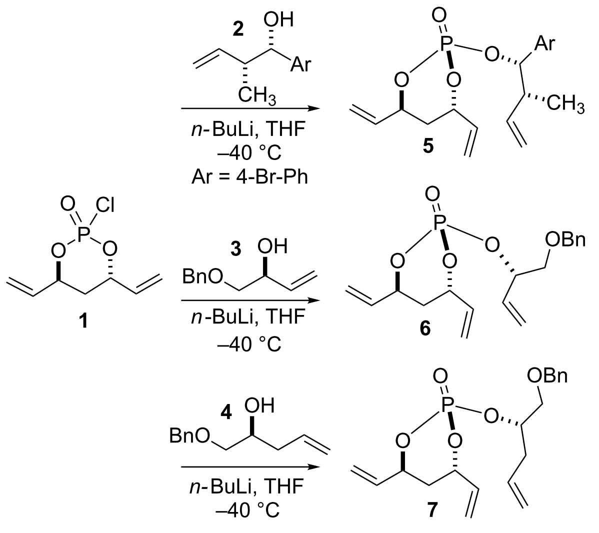
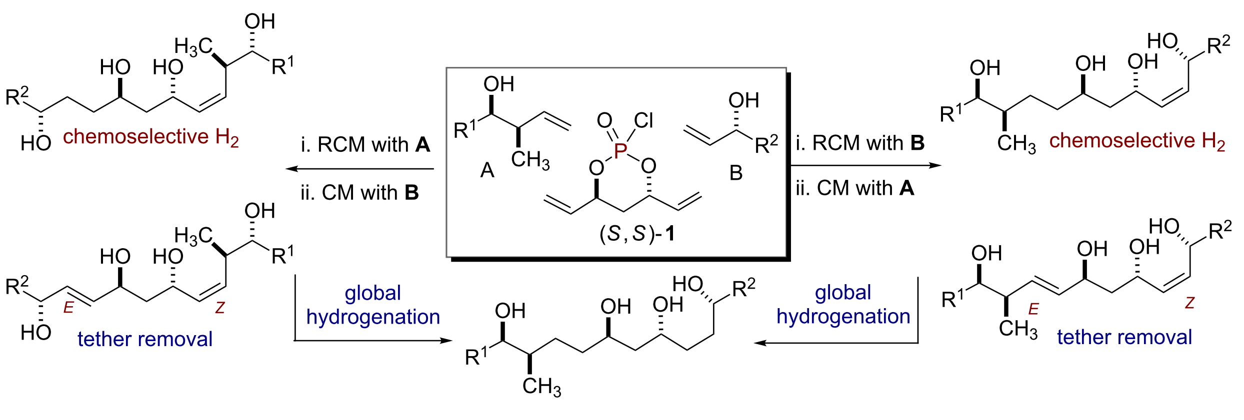


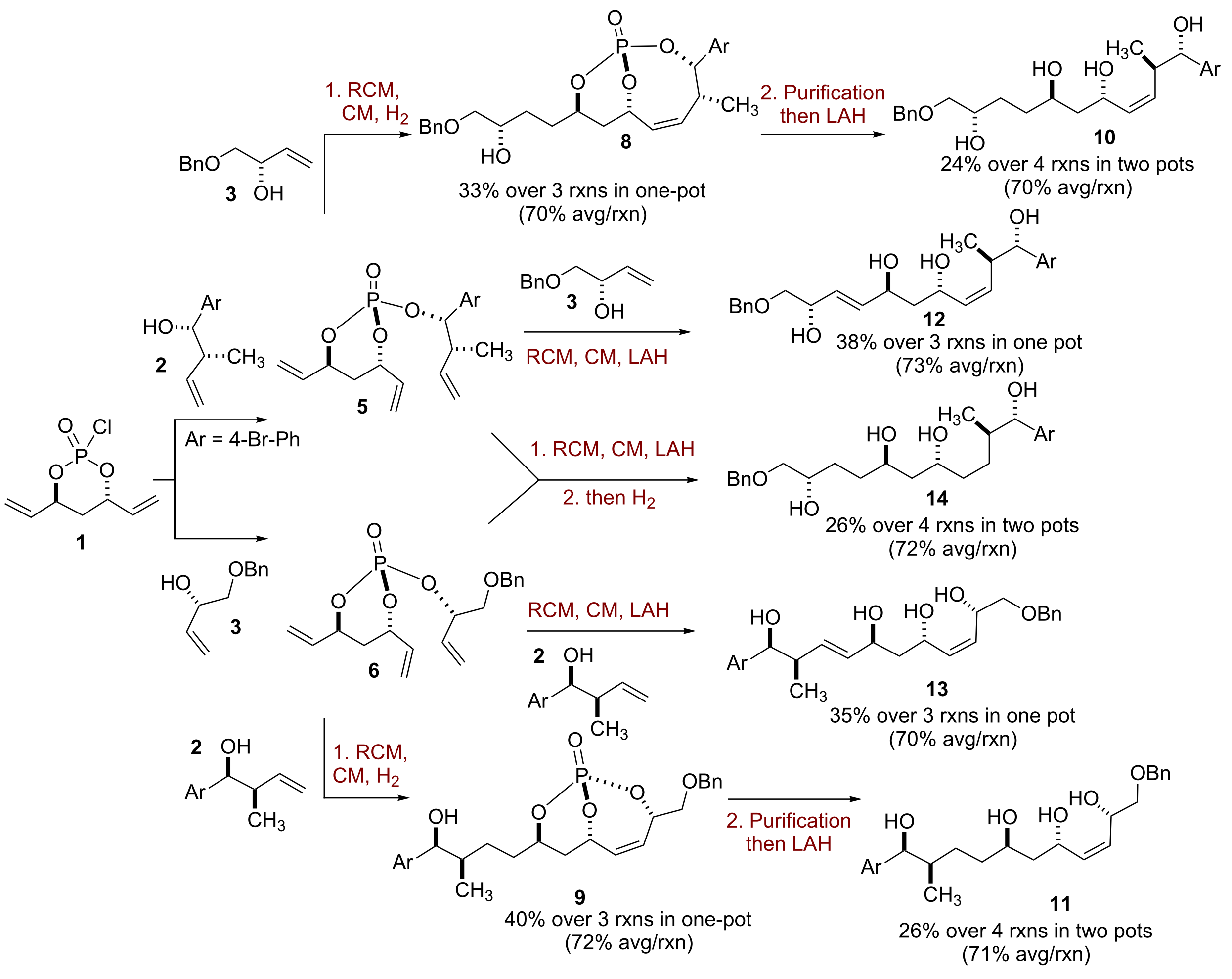
**Figure 1:** Synthesis of trienes **5–7**.

Initial attempts were focused on generating the first set of five polyols starting from trienes **5** and **6** in a two-pot operation (Scheme 2). The first operation entailed a one-pot, sequential RCM/CM/chemoselective hydrogenation protocol [32], yielding two bicyclo[*n*.3.1]phosphate intermediates **8** and **9**, and a second pot $LiAlH_4$ reduction to provide the *Z*-configured tetraol subunits **10** and **11**. Trienes **5** and **6** were generated via coupling with alcohol partners **2** and **3**, respectively, and the divergent aspect of the method was introduced by simple switching of the olefinic partners in the subsequent CM reaction to afford five differentiated polyols starting from three coupling partners.

In this regard, triene **5** was first subjected to RCM in the presence of the Hoveyda–Grubbs II (**HG-II**) catalyst [35-37] in refluxing $CH_2Cl_2$, followed by solvent concentration and CM with allylic alcohol **3** in refluxing $CH_2Cl_2$ for two hours. It was observed that the use of $CH_2Cl_2$ was critical for the successful



**Scheme 1:** The 3-component coupling strategy.



**Scheme 2:** Synthesis of polyols **10–14** in one-, two-pot sequential protocols.

CM reactions in order to avoid the formation of isomerized ketone byproducts. Subsequent chemoselective diimide reduction with *o*-nitrobenzenesulfonylhydrazine (*o*-NBSH) [38-40] in $CH_2Cl_2$ at room temperature afforded bicyclo[5.3.1]phosphate **8** in 33% overall yield, representing a 70% average yield/reaction in the one-pot, sequential protocol (Scheme 2). Subsequent treatment of **8** with $LiAlH_4$ furnished the tetraol **10** in 24% overall yield over the course of four reaction steps carried out in two pots, representing a 70% average yield per reaction.

Similarly, starting with the triene **6**, a one-pot RCM/CM/chemoselective $H_2$ was performed to obtain the bicyclo[4.3.1]-phosphate **9** in 40% yield over 3 reaction steps in a one-pot operation (72% avg/rxn). In this example, the RCM reaction was performed in dicholoroethane (DCE) at 70 °C for 2 h, since lower reactivity was observed in $CH_2Cl_2$. Subsequently, phosphate **9** was treated with $LiAlH_4$ to generate tetraol **11** in 26% overall yield in the four reactions carried out in two pots, representing a 71% average yield per reaction.

Next, a one-pot RCM/CM/LAH protocol was established to obtain two additional tetraol subunits possessing both *E*- and *Z*-olefin geometries. Triene **5**, was subjected to an RCM reaction, followed by a CM reaction with allylic alcohol **3**. After removing the solvent, the CM product was treated with $LiAlH_4$ to produce tetraol **12** in 38% yield over three reaction steps in the one-pot, sequential process (73% avg/rxn) (Scheme 2). Similarly, triene **6** was subjected to an RCM reaction, followed by CM with homoallylic alcohol **2**, and subsequent treatment with $LiAlH_4$ to afford tetraol **13** in 35% yield over the three reaction steps, representing a 70% avg/rxn in the one-pot, sequential method.

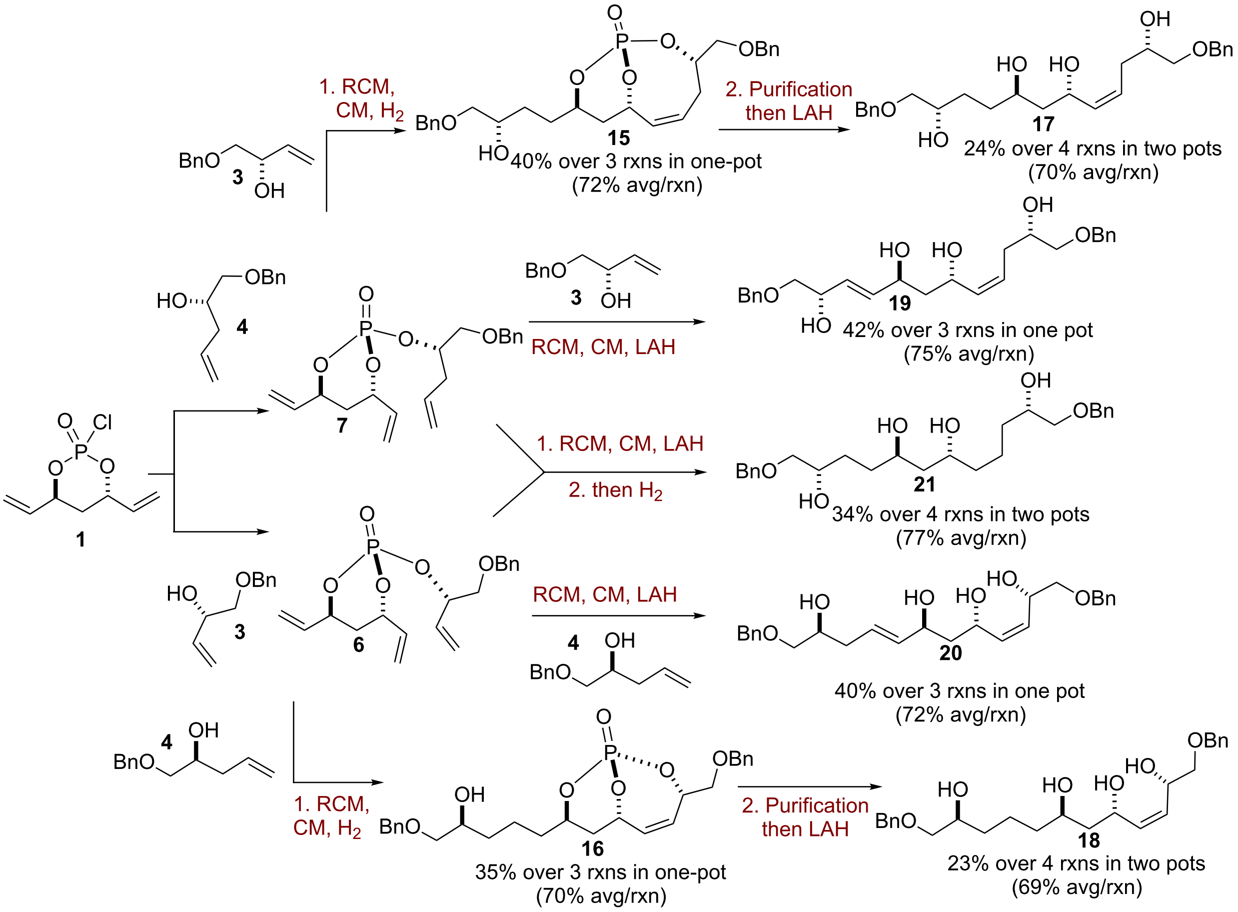
This RCM/CM/LAH procedure was further merged with global hydrogenation, whereby the resulting tetraols **12** and **13**, after one-pot, sequential RCM/CM/LAH protocol, were separately treated with *o*-NBSH to obtain tetraol **14** in 26% yield over the four reaction steps in a two-pot operation starting from triene **5** (72% avg/rxn). Utilizing this two-pot sequential protocol, the same tetraol **14** was obtained starting from two different trienes (**5** and **6**) and reacting with two different CM partners. It should be noted, that after phosphate tether removal, treatment of tetraol with *o*-NBSH (20 equiv), resulted in the global reduction of both *E*- and *Z*-olefins in very good yields, while in contrast, diimide reduction in the presence of phosphate intermediates did not hydrogenate the endocyclic olefin even when large excesses of diimide reagent were employed (30 equiv). This empirical result further substantiates the protecting group ability of the phosphate tether for the endocyclic *Z*-olefin.

Next, our attempts were focused on generating the second set of five polyols starting from trienes **6** and **7**. Utilizing the aforementioned strategy detailed in Scheme 2, triene **7** was subjected to the one-pot, sequential RCM/CM/chemoselective $H_2$ procedure and subsequent $LiAlH_4$ reduction to generate tetraol **17** in 24% yield over 4 reaction steps in a two-pot operation (70% avg/rxn) (Scheme 3). Further, starting with the same triene **6**, which was previously used in Scheme 2, but utilizing a different cross-metathesis partner (homoallylic alcohol **4**), a different tetraol **18** was generated in 23% yield over the four reaction steps in a two-pot operation (69% avg/rxn) (Scheme 3).

In a similar manner, starting with triene **7**, RCM and subsequent CM with allylic alcohol **3**, followed by tether removal with $LiAlH_4$, were performed to obtain tetraol **19** in 42% yield over three reaction steps in the one-pot, sequential operation (75% avg/rxn). Triene **6** was next subjected to RCM, followed by CM with homoallylic alcohol **4** and $LiAlH_4$ reduction to furnish tetraol **20** in an overall 40% yield over three reaction steps in a one-pot operation (72% avg/rxn). Tetraols **19** and **20** were separately subjected to a global hydrogenation using *o*-NBSH to afford tetraol **21** in 34% yield over four reaction steps in a two-pot operation starting from triene **6** (77% avg/rxn).

## Conclusion

In conclusion, we have reported one- or two-pot sequential methods mediated by a phosphate tether to generate a diverse array of polyol molecules utilizing readily prepared trienes **5**, **6**



**Scheme 3:** Synthesis of polyols **17–21** in one-, two-pot sequential protocols.

and **7** and CM partners **2**, **3**, and **4**. This divergent method was established by taking advantage of the innate properties of phosphate tethers to provide efficient syntheses of the stereochemically-rich polyol subunits **10–14** and **17–21**.

## Supporting Information

### Supporting Information File 1

Experimental section.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-242-S1.pdf]

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