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Cyclopentannulation on 3-phospholenes: an expedient route to the 2-phosphabicyclo[3.3.0]octene ring system

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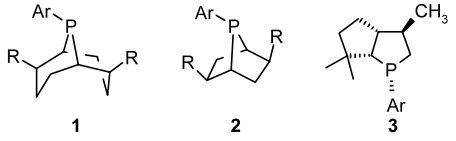
Abstract—Treatment of 1-phenyl-3-phospholene derivatives with 2 equiv. of LDA followed by quenching the metallated intermediates with 1,3-dihaloalkanes affords 2-phosphabicyclo[3.3.0]oct-3-ene derivatives in good yield. The annulation reactions are highly regio- and stereoselective and lead to the formation of *exo*-Ph-P substituted products exclusively. Reduction of the resulting bicyclic phosphine oxides by phenylsilane gives the corresponding phosphines with complete retention of configuration at P. Application of this annulation procedure to acyclic allylic substrates leads to the corresponding monocyclic annulation products.

Phosphines are among the most powerful and versatile ligands for use in catalysis involving transition metals and the development of new classes of chiral phosphines with diversified structural motifs remains critical to the progress of the field.[1,2] Recently, monophosphines **1**–**3** of rigid bicyclic structures containing a phosphorus atom embedded in a five-membered ring have been identified as highly efficient chiral ligands as well as excellent chiral catalysts.[3]

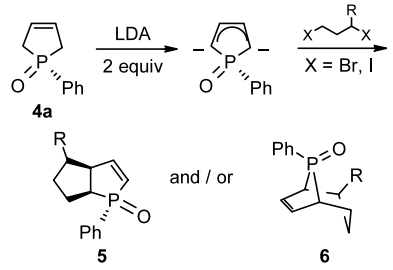


1 **2** **3**

In order to facilitate access to congeners of these valuable bicyclic compounds we decided to study the possibility of approaching their synthesis from an extant monocyclic organophosphorus precursor. The synthetic approach selected starting from readily available 1-phenyl-3-phospholene 1-oxide[4] (**4a**) is delineated in Scheme 1.

As shown in Scheme 1, the process is based on a straightforward deprotonation–alkylation reaction sequence which, due to the mesomeric nature of the potential dianionic intermediate, could in principle lead to the formation of either the fused 2-phosphabicyclo[3.3.0]bicyclooctene **5** or the bridged 8-phosphabicyclo[3.2.1]bicyclooctene **6** bicyclic system. In the event, the process proved viable and highly selective towards the formation of the fused ring system.[5] In this paper we wish to demonstrate that 2-phosphabicyclo[3.3.0]bicyclooctenes of type **5** can be readily constructed in a single synthetic step from 3-phospholene derivatives.

In an exploratory experiment, deprotonation of 1-phenyl-3-phospholene 1-oxide (**4a**) by treatment with 2 equiv. of LDA at −78°C in THF, followed by quenching with 1,3-dibromopropane at the same temperature yielded the bicyclic phosphine oxide **5a** in 49% yield. However, the reaction was found to be capricious and the product obtained was always contaminated with the by-products **6a** and/or **7a**. In contrast, alkylation of **4a** with 1,3-diiodopropane proceeded cleanly and reproducibly and gave **5a** as the sole reaction product in high yield (Scheme 2, Table 1, entries 1 and 2).[6]



Scheme 1.

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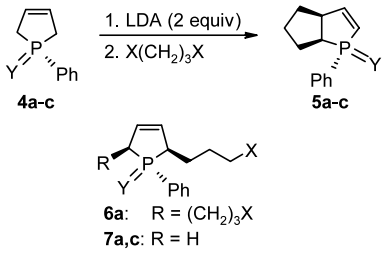
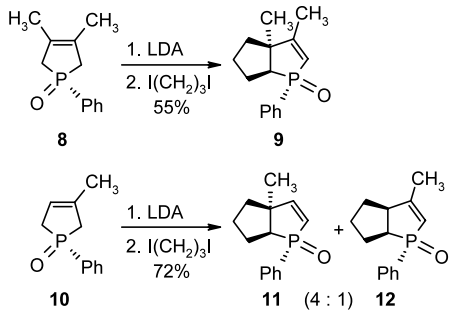
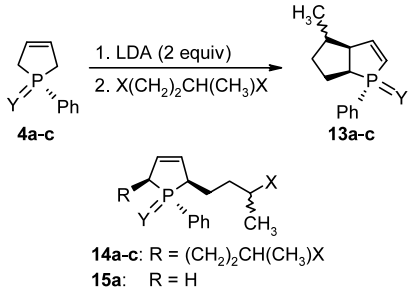


Scheme 2.



Scheme 3.



Scheme 4.

Analogous reactions of 1-phenyl-3-phospholene 1-sulfide (**4b**) afforded the expected bicyclic phosphine sulfide **5b** cleanly and in high yield with either dihalide (Scheme 2, Table 1, entries 3 and 4). 1-Phenyl-3-phospholene-borane (**4c**) also reacted in the same way and provided the annulated phosphine–borane **5c** as the main product although somewhat less cleanly and less efficiently (Scheme 2, Table 1, entries 5 and 6).

Ring-substituted phospholenes could also be successfully annulated. Consecutive treatment of 3,4-dimethyl-1-phenyl-3-phospholene 1-oxide[4] (**8**) with 2 equiv. of LDA and 1,3-diiodopropane as above afforded the bicyclic product **9** (δ_P 54.4) in good yield (Scheme 3). Under the same conditions 3-methyl-1-phenyl-3-phospholene 1-oxide[4] (**10**) gave a mixture of regioisomeric products **11** and **12** in a 4:1 ratio (δ_P 63.3[7] and 60.9, respectively) (Scheme 3). Interestingly, in this case the formation of the angularly substituted product **11** originating from the annulation at the more crowded side of the substrate was found to be markedly preferred.

The use of 1,3-dihalobutanes as alkylating agents in these reactions offered further possibilities for diversification of the substitution pattern of the annulated products (Scheme 4). The results of the alkylations of phospholenes **4a**–**c** with 1,3-dibromobutane and 1,3-diiodobutane are collected in Table 2.

In the reactions with 1,3-dibromobutane the diminished reactivity of the secondary bromide functionality markedly slowed down the cyclization step and in addition to the expected annulated product, considerable amounts of monocyclic alkylated products were also observed (Table 2, entries 1, 3, and 5). As previously, the use of the corresponding diiodide provided the possibility of achieving the formation of bicyclic products in a selective manner, although in this case at the cost of somewhat decreased yields (entries 2 and 4). Reactions of the phosphine–borane **4c** were less clean (entries 5 and 6) and in addition, the bicyclic product could not be purified from the corresponding dialkylated derivatives **14c**.

A similar annulation reaction of 2,4-dimethyl-1-phenyl-3-phospholene 1-oxide (**8**) afforded trisubstituted bicyclooctene **16** (two diastereomers, δ_P 52.1 and 50.1, Scheme 5).

Due to the chiral nature of the 1,3-dihalobutanes used products **13a**–**c** were formed as mixtures of the corresponding C-4 epimers in ratios between 1.2:1 and 2:1. In the reaction of 1,3-diiodobutane with 3,4-dimethyl-3-phospholene **8** the two C-4 epimeric annulation products **16** were formed stereoselectively in a 6:1 ratio indicating stereocontrol by the phospholene methyl group which ends up in the angular position.

Table 1. Annulation of phospholene derivatives **4a**–**c** by 1,3-dihalopropane

Entry	Starting material	Y	X	Isolated yield (%) of **5**	^{31}P NMR (ppm) **5**
1	**4a**	O	Br	39–64[a]	61.2[7]
2	**4a**	O	I	74	
3	**4b**	S	Br	87	73.8[7]
4	**4b**	S	I	74	
5	**4c**	BH_3	Br	53[b]	54.6
6	**4c**	BH_3	I	53[b]	

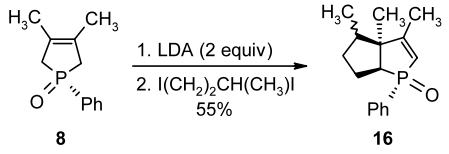
[a] Up to 7% of **6a** and traces of **7a** were present in the crude product mixture as identified by ^{1}H and ^{31}P NMR spectroscopy and mass spectrometry.

[b] Contaminated with traces of **7c** as assigned by ^{1}H and ^{31}P NMR spectroscopy and mass spectrometry.

Table 2. Annulation of phospholene derivatives **4a–c** by 1,3-dihalobutane

Entry	Starting material	Y	X	Isolated yield (%)		^{31}P NMR (ppm) **13**[a]
				13[a]	**14**	
1	**4a**	O	Br	19	41[b]	60.8, 59.2
2	**4a**	O	I	42	–	
3	**4b**	S	Br	74	13	74.2, 71.7
4	**4b**	S	I	53	–	
5	**4c**	BH_3	Br	71	16	56.1, 53.3
6	**4c**	BH_3	I	32	11	

[a] Two diastereomers.
[b] 2-Monoalkylated product **15a** was identified in the product as a contaminant (5%).

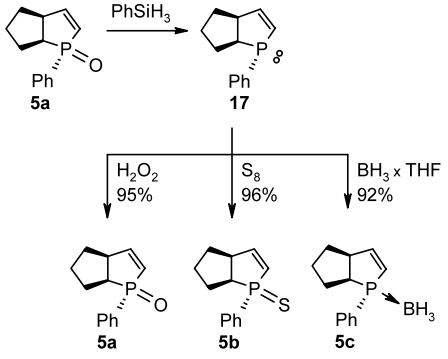


Scheme 5.

Stereochemical assignments for the annulation products were made on the basis of their ^{1}H, ^{13}C and ^{31}P NMR spectra, including NOE experiments.[7] As indicated in all cases the annulations took place on the P=O bearing side of the phospholene ring and resulted in the formation of the *cis* fused ring system exclusively. This is in accord with the literature data demonstrating that α-lithiation of 3-phospholene oxide occurs preferentially *cis* to the coordinating phosphoryl oxygen and that subsequent alkylation of the lithiated species is stereoretentive.[8]

Reduction of **5a** with phenylsilane in a toluene solution at 100°C gave the corresponding bicyclic phosphine **17** (δ_P 25.4 in C_6D_6) quantitatively, with complete retention of configuration at phosphorus,[9] without affecting the double bond functionality (Scheme 6).

The expected retention of configuration at phosphorus in the reduction step was confirmed through oxidation of the resulting phosphine back to the starting phosphine oxide by treatment with hydrogen peroxide, a reagent known to oxidize phosphines with 100% retention.[10] The oxide **5a** obtained was found to be identical



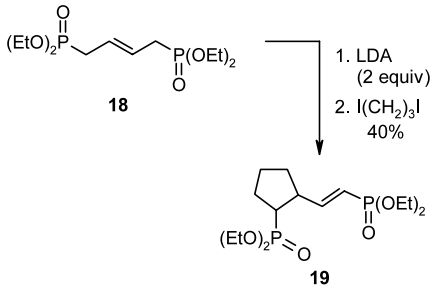
Scheme 6.

in every respect with the starting material. Treatment of phosphine **17** with elemental sulfur or with BH_3×THF also cleanly provided the phosphine sulfide **5b** and phosphine-borane **5c**, respectively, which were again found to be identical with those obtained previously by direct annulation. In fact, this route could be recommended as the method of choice for the preparation of **5c** which, in the direct annulation process, is only produced in moderate yield and is difficult to purify from monoalkylation side products.

This annulation procedure could also be extended to acyclic allylic systems similarly activated by adjacent phosphorus substituents. This was demonstrated with 2-butene-1,4-bis(phosphonate) **18** which on sequential treatment with 2 equiv. of LDA and 1,3-diiodopropane at −78°C gave the five-membered ring annulation product **19** as a 95:5 mixture of two diastereoisomers [δ_P 33.5, 19.1 (major) and 32.7, 17.3 (minor)] in 40% yield (Scheme 7). The *trans* stereochemistry of the ring substitution and of the double bond was assumed for the major diastereoisomer of **19**, but this still needs to be unequivocally confirmed.

In summary, we have demonstrated that readily available 3-phospholene derivatives can be expeditiously converted into 2-phosphabicyclo[3,3,0]oct-3-ene derivatives in a straightforward annulation process utilizing 1,3-dihaloalkanes as the annulating agents.

The annulation process is highly regio- and stereoselective and easily accommodates substituents in either of the substrates. When applied to acyclic allylic substrates it also offers rapid access to cyclopentanes functionalized vicinally with two differentiated organophosphorus



Scheme 7.

functionalities. It has also been demonstrated that 2-phosphabicyclo[3,3,0]oct-3-ene oxides can be reduced stereoselectively to the corresponding bicyclic unsaturated phosphines without loss of configurational integrity at phosphorus.

Work is in progress to secure access to selected 2-phosphabicyclo[3.3.0]oct-3-enes in enantiomerically pure form.

Acknowledgements

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6. *General procedure for the annulation reaction*: To a solution of freshly prepared LDA (2.1 mM) in THF (6 mL) cooled to −78°C was added a solution of 1-phenyl-3-phospholene 1-oxide (**4a**, 178 mg, 1.0 mM) in THF (2 mL). The resulting deep red solution was stirred at −78°C for 10 min and a solution of 1,3-diiodopropane (235 mg, 1.1 mM) in THF (2 mL) was then added in one portion. Stirring was continued for 1 h at −78°C and the reaction was quenched by addition of a few drops of water at −78°C and then allowed to attain room temperature. Solvents were evaporated. Column chromatography of the residue (hexane–ethyl acetate–methanol, 5:3:1 as eluent) gave pure **5a** (161 mg, 74%). All products were characterized by ^{1}H, ^{13}C and ^{31}P NMR and HR-MS.
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