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Synthesis of phosphorus mono- and bicycles by catalytic ring-closing metathesis

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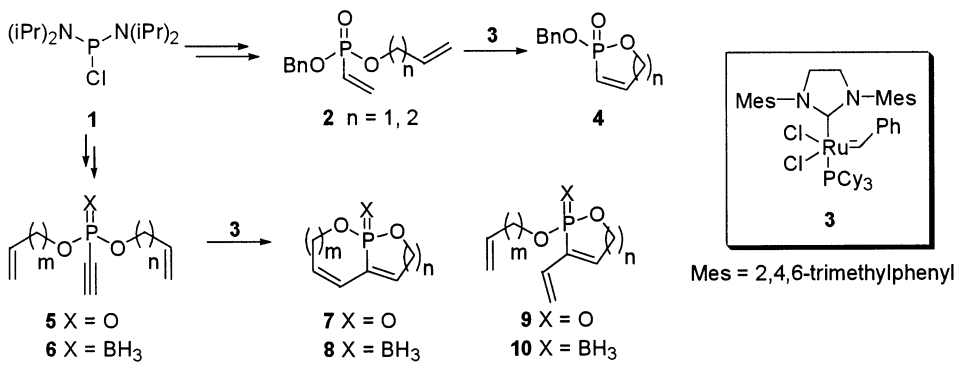
Abstract—A versatile route of synthesis of phosphorus oxide and phosphorus borane templates starting from the bifunctional phosphorylating agent bis(diisopropylamino)ethynylphosphine is presented. Ring-closing enyne metathesis using 4,5-dihydro-imidazol-2-ylidene ruthenium benzylidene complex **3** on these types of substrates led to the formation of mono- and bicyclic phosphorus heterocycles. © 2001 Elsevier Science Ltd. All rights reserved.

Ring-closing diene metathesis (RCM)[1] has emerged as a powerful tool in the construction of structurally diverse heterocyclic compounds containing either a tri- or pentavalent phosphorus atom. For example, a phosphine[2] and some phosphane–borane complexes[3] have been conveniently prepared by executing RCM on appropriate P(III)-diene scaffolds. The outcome of these studies indicated that the RCM approach holds promise in the development of P(III)-chiral ligands in catalytic transition metal-mediated processes and asymmetric synthesis.[4] Moreover, the precedent set by several examples of P(V)-heterocycles displaying interesting biological activities[5] stimulated the preparation of a diverse array of this class of molecules, such as phosphonates,[6] phosphinates,[7] phosphine oxides,[8] phosphonamides,[9] phosphinic acid amides and anhydrides[10] as well as phosphonic acid triesters.[11]

A recent study from our laboratory revealed[12] inter alia that benzylalkenyl vinylphosphonates **2** (Scheme 1), readily accessible from the bifunctional phosphorylating agent **1**, underwent RCM under the influence of ruthenium–alkylidene **3**[13] to give monocyclic phosphonates **4**. With the objective of broadening the scope of this methodology, we here report that RCM of the symmetrical (n=m) and asymmetrical (m≠n) bis(alkenyl) ethynyl-phosphonates **5** under the influence of **3** affords the fused bicyclo [m.n.0] rings **7** as well as the monocyclic derivatives **9**. Moreover, subjection of the symmetrical borane complexes **6** to the same RCM



Scheme 1.

Keywords: regioselectivity; tandem yne-diene metathesis; ethynylphosphonates; phosphane–borane complexes.

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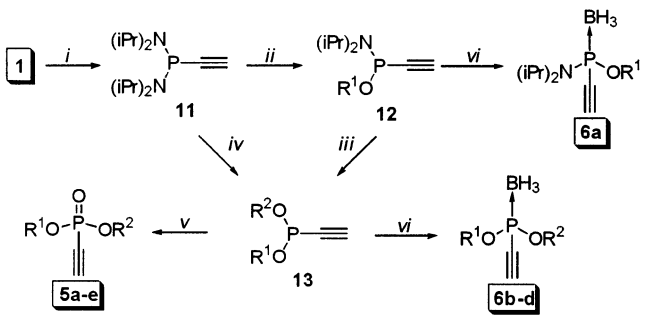
conditions led to an analogous mixture of bi- and monocyclic products **8** and **10**.

The preparation of the phosphonates **5a**,**b** ($R^1=R^2$) and **5c**–**e** ($R^1\neq R^2$) could be readily effected following a similar approach developed, as mentioned before, for the construction of the corresponding vinylphosphonates **2**. Accordingly, alkylation of bis(diisopropylamino)–chlorophosphine (**1**) with sodium acetylide (Scheme 2) gave homogeneous ethynylphosphordiamidite **11** (δ_P 28.3 ppm). The symmetrical dienynes **5a**,**b** were obtained by condensation of **11** with excess allyl or butenyl alcohol in the presence of 1*H*-tetrazole (2 equiv.) and subsequent in situ oxidation of the intermediate phosphines **13** ($R^1=R^2$) with *tert*-butyl hydroperoxide. The asymmetrical ethynylphosphonates **5c**–**e** were prepared by the following three-step sequence. For example, 1*H*-tetrazole catalyzed condensation of **11** with 3-butenol (1 equiv.) gave after purification the phosphoramidite **12** (R^1 = but-3-enyl, δ_P 96 ppm). Reaction of the latter compound with allyl alcohol (1 equiv.) and excess 1*H*-tetrazole led, after in situ oxidation of **13** (R^1 = but-3-enyl, R^2 = allyl, δ_P 130 ppm), to the isolation of homogeneous **5c** (δ_P −7.6 ppm).

It turned out that the requisite phosphine–borane complexes **6a**–**d** could be attained in excellent yields by protecting the purified phosphines **12** and **13** by using BH_3·THF. Thus, no hydroboration was observed by performing the protection step in acetonitrile and using an equimolar amount of BH_3·THF.

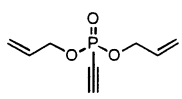
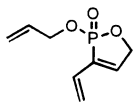
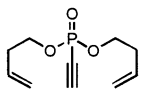
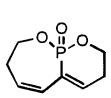
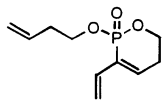
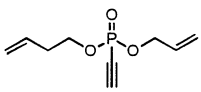
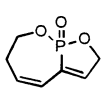
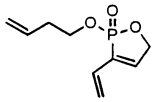
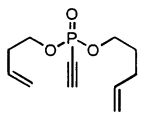
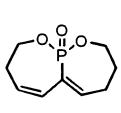
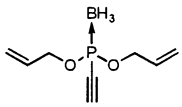
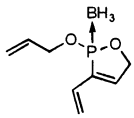
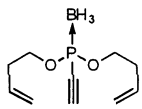
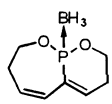
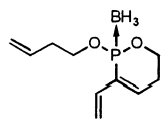
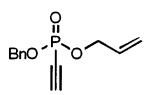
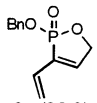
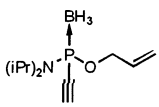
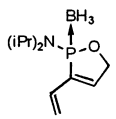
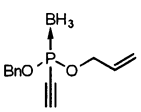
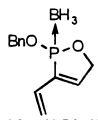
The results of the precatalyst **3** (1 mol%) mediated metathesis of templates **5a**–**e** and **6a**–**d** (0.02 M in refluxing dichloromethane) are recorded in Table 1.



5a	$R^1 = R^2$ = allyl	88% from **11**
b	$R^1 = R^2$ = 3-buten-1-yl	94% from **11**
c	R^1 = 3-buten-1-yl, R^2 = allyl	88% from **11**
d	R^1 = 3-buten-1-yl, R^2 = 4-penten-1-yl	85% from **11**
e	R^1 = benzyl, R^2 = allyl	71% from **11**
6a	R^1 = allyl	96% from **11**
b	$R^1 = R^2$ = allyl	88% from **11**
c	$R^1 = R^2$ = 3-buten-2-yl	94% from **11**
d	R^1 = benzyl, R^2 = allyl	71% from **11**

Scheme 2. *Reagents and conditions*: (i) NaC≡CH, THF (80%); (ii) R^1OH (1 equiv.), 1*H*-tetrazole (0.1 equiv.), MeCN; (iii) R^2OH (1 equiv.), 1*H*-tetrazole (2 equiv.), MeCN; (iv) allyl- or 3-buten-1-yl alcohol (2.2 equiv.), 1*H*-tetrazole (2 equiv.), MeCN; (v) *t*-BuOOH, MeCN, 5 min; (vi) BH_3·THF, MeCN, 5 min.

Table 1. RCM on substrates **5** and **6**[a]

Entry	Substrate (δ_P in ppm)	Products[14] (δ_P in ppm), isolated yield	Combined yield (time)
1	 **5a** (-7.4)	 **7a**, 0%	 **9a** (38.2), 98%	98% (4 h)
2	 **5b** (-7.7)	 **7b** (14.6), 76%	 **9b** (11.2), 18%	94% (0.5 h)
3	 **5c** (-7.6)	 **7c** (7.3), 66%	 **9c** (37.9), 23%	89% (3 h)
4	 **5d** (-7.7)	 **7d** (22.0)		83% (3 h)
5	 **6b** (108.8)	 **10b** (150.1)		99% (16 h)
6	 **6c** (107.6)	 **8c** (119.3), 74%	 **10c** (116.2), 23%	97% (16 h)
7	 **5e** (-7.4)	 **9e** (38.3)		98% (1.5 h)
8	 **6d** (88.9)	 **10d** (126.0)		99% (20 h)
9	 **6a** (108.5)	 **10a** (150.1)		95% (48 h)

[a] *Reagents and conditions*: substrate (0.02 M), **3** (1 mol%), CH_2Cl_2, reflux.

Metathesis of the symmetrical diolefinic substrate **5a** (entry 1) led to the exclusive formation of the enyne ring closure product **9a**. Attempts to convert **9a** into the

expected [4.3.0] ring product **7a**, using 5 mol% of precatalyst and prolonged reaction times, was abortive. In contrast, the analogous dibutenylic substrate **5b** provided (entry 2) approximately a 1:4 ratio, as gauged by ^{31}P NMR, of the monocyclic product **9b** and the bicyclo [5.4.0] ring **7c**, resulting from a tandem yne-diene transformation. The same ratio of products was also obtained by subjecting pure **9b**, isolated after silica gel chromatography of the original mixture, to precatalyst **3** (1 mol%) in refluxing CH_2Cl_2 for 24 h. On the other hand, a near quantitative and rapid conversion of **5b** into the double ring-closure product **7b** occurred with 5 mol% of **3** in CH_2Cl_2 under reflux. Analysis of the reaction mixture resulting from the metathesis of the unsymmetrical substrate **5c** revealed the presence (entry 3) of **9c** and **7c** (ratio 1:3), and no trace of the corresponding six-membered and bicyclo [4.4.0] ring products, indicating that the metathesis is a regioselective process. Also, in this case, exclusive formation of the bicyclo [5.3.0] product **7c** occurred in the metathesis of **5c** with 5 mol% of **3**. The high regioselectivity as observed in entry 3 is further illustrated in the exclusive and high yielding conversion of the asymmetrical substrate **5d** into the bicyclo [5.5.0] product **7d**.

At this stage, it was gratifying to establish that the bis(alkenyloxy)phosphine–boranes **6b**,**c** followed a metathesis course of events which did not substantially deviate from the ring-closures observed earlier for the corresponding symmetrical phosphonates **5a**,**b**. Thus, **6b** led to the formation (entry 5) of the borano–oxaphosphole **10b**. Similarly, **6c** yielded the respective mono- and bicyclic products **10c** and **8c** in a ratio of 1:3 (entry 6). Interestingly, however, the rate of formation of these ring-closure products was in both cases much slower than for the corresponding phosphonates **5a**,**b**. The latter aspect was also corroborated independently by the experiments recorded in entries 7–9. Perusal of these entries clearly indicates that the rate of the enyne metathesis on substrates **5e**, **6d** and **6a**, to give the corresponding monocyclic products **9e**, **10d** and **10a**, decreased substantially.

In conclusion, the results thus far obtained show that bis(alkenyl) ethynylphosphonates **5c**,**d** undergoes a regioselective ring-closure metathesis under the influence of precatalyst **3** to afford fused bi- and(or) monocyclic products. Moreover, the exclusive formation of the bicyclo [m.n.0] rings not only depends on the length of the alkenyl tethers, but also on the quantity of catalyst used. Apart from this, it was also found that a similar course of events took place, although with a much slower rate, in the RCM of the symmetrical phosphine–borane complexes **6b**,**c**. We believe that the above mentioned aspects may be of great importance in the future design and synthesis of biologically interesting P(V)-heterocycles and P(III)-ligands.

Acknowledgements

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14. All compounds were fully characterized by ^{1}H, ^{13}C and ^{31}P NMR. Relevant examples: 3,4,8,9-tetrahydro-2*H*-1,10-dioxa-10a-phospha-heptalene 10a-oxide (**7d**), ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.51 (dt, J 45.9 Hz, J 6.5 Hz, 1H), 6.13 (dd, J 29.0 Hz, J 11.9 Hz, 1H), 5.68 (m, 1H), 4.29 (m, 4H), 2.69 (m, 2H), 2.63 (m, 2H), 2.06 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 145.6 (d, J 9.4 Hz), 129.7 (d, J 14.0 Hz), 126.7, 67.4 (d, J 3.7 Hz), 65.6 (d, J 3.4 Hz), 29.8, 27.3 (d, J 6.0 Hz), 27.0. ^{31}P NMR (243 MHz, $CDCl_3$): δ 22.0. MS: 201.0 [M+H$^+$]. 2,3,7,8-Tetrahydro-1,9-dioxa-9a-phospha-benzocycloheptene–borane complex (**8c**), ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.72 (m, 1H), 6.27 (m, 1H), 5.76 (m, 1H), 4.39 (m, 2H), 4.12 (m, 2H), 2.63 (m, 2H), 2.54 (m, 2H), 0.59 (dq, J_P 18 Hz, J_B 95 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 142.4, 130.7, 124.7 (d, J 13.7 Hz), 67.7 (d, J 10.7 Hz), 62.8 (d, J 9.2 Hz), 33.0, 26.8 (d, J 6.1 Hz). ^{31}P NMR (243 MHz, $CDCl_3$): δ 119.0 (q, J 95 Hz).