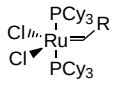
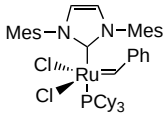
Novel Synthesis of Borane Complexes of Cyclic Phosphanes Using Ruthenium-Catalyzed Olefin Metathesis**

Marc Schuman, Michael Trevitt, Andrew Redd, and Véronique Gouverneur*

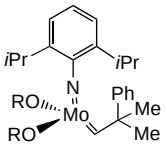
Chiral phosphane ligands are of key importance in catalytic transition metal mediated processes, which have attracted considerable attention in asymmetric synthesis.[1] It is well established that cyclic bisphosphanes and phosphanes, for example 1,2-bis(phospholanyl)benzene (DuPhos), 1,2-bis(phospholanyl)ethane (BPE), and *tert*-butyloxy or benzyloxy-substituted derivatives thereof (RoPhos), have proven to be very efficient ligands in the field of asymmetric catalysis.[2] Owing to the increasing importance of these molecules, there is an ongoing interest in the development of novel methodologies for the preparation of structurally diverse cyclic phosphanes and bisphosphanes along with their metal complexes. A survey of the literature reveals that borane complexes of phosphanes are the most versatile precursors of free phosphanes. These are sensitive to oxidation and prone to racemization if the chiral phosphane bears stereogenic phosphorus atoms.[3] We were recently attracted by the versatility and synthetic applicability of the ring-closing metathesis (RCM) reaction in the construction of functionalized carbocycles and heterocycles[4] using the well-defined ruthenium catalysts **1a**–**c**,[5] molybdenum catalyst **2**,[6] or tungsten catalyst **3**.[7] To date,



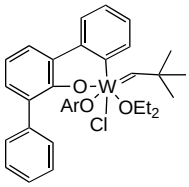
1a R = Ph, **1b** R = CHCPh$_2$



1c Mes = 2,4,6-(CH$_3$)$_3$C$_6$H$_2$



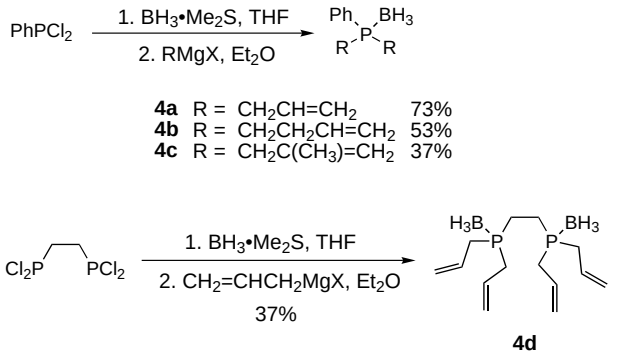
2 R = CMe(CF$_3$)$_2$



3 Ar = 2,6-Ph$_2$C$_6$H$_3$

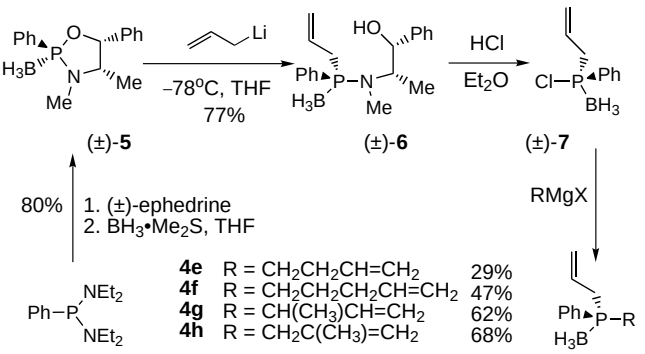
several examples of ring-closing metathesis reactions on phosphorus-containing compounds are known,[8] but only one reaction using a free phosphane as the starting diene:[9] Basset et al. reported that the ring-closing metathesis of diallylphenyl phosphane with 5 mol% of the aryloxide(neopentylidene)tungsten catalyst **3** gave the expected cyclized product in 95% yield. We have found that, on the contrary, the well explored Ru catalyst **1a** (Grubbs catalyst) was ineffective for the ring closure of diallylphenyl phosphane. Based upon these findings, we were intrigued by the possible application of transition metal alkylidene catalyzed ring-closing olefin metathesis to the general problem of constructing borane complexes of cyclic phosphanes. Herein we disclose that five-, six-, and seven-membered borane complexes of alicyclic phosphanes, as well as a bisphosphane are synthesized in good yields by metathesis of the corresponding olefinic phosphane–borane complexes.

A series of dienes **4a**–**h** was prepared by using two different strategies. The most obvious chemical problem posed in the synthesis of **4a**–**h** is the presence of double bonds that are sensitive to hydroboration. The symmetrical dienes **4a**–**c** were prepared in two steps from dichloro(phenyl)phosphane. The dichloro(phenyl)phosphane was protected by using $BH_3 \cdot Me_2S$/THF and subsequently the desired dienes were obtained in 37–73% yield by double substitution with the appropriate Grignard reagent (Scheme 1). Similarly,



Scheme 1. Synthesis of the symmetrical bis(alkenyl)phosphane–boranes **4a**–**d**.

the tetraene **4d** was prepared from commercially available 1,2-bis(dichlorophosphanyl)ethane with an overall yield of 37% after column chromatography (Scheme 1). The nonsymmetrical dienes **4e**–**h** were synthesized according to the approach of Genêt and Jugé from the known oxazaphospholidine–borane (±)-**5** (Scheme 2).[10] The diastereomerically



Scheme 2. Synthesis of nonsymmetrical bis(alkenyl)phosphane–boranes **4e**–**h**.

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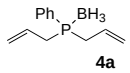
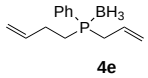
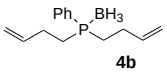
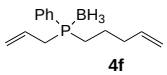
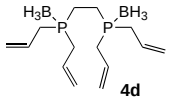
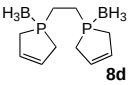
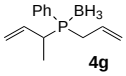
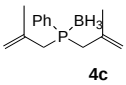
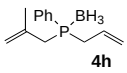
pure complex (±)-**5** was obtained in one step from bis(diethylamino)phenylphosphane, (±)-ephedrine, and $BH_3 \cdot Me_2S$, and was easily isolated as a crystalline product with a chemical yield of 80%. Allyllithium [11] cleanly reacted regioselectively with (±)-**5** at low temperature in THF to give the corresponding aminophosphane–borane (±)-**6** by P–O bond cleavage with a diastereomeric ratio of 80:20 and a chemical yield of 77%. The acidic cleavage of the air-stable aminophosphane–borane (±)-**6** with HCl gas in diethyl ether led to the corresponding chlorophosphane–borane (±)-**7** which is a valuable precursor for the synthesis of a range of nonsymmetrical bis(alkene)phosphane–boranes. The final C–P bond formation was effected smoothly by addition of the appropriate organomagnesium reagent to the crude (±)-**7** to afford the expected nonsymmetrical dienes (±)-**4e–h** in moderate to satisfactory yields (29–68%; Scheme 2) after purification.

Initially, it was necessary to determine if the ruthenium alkylidene compound **1a** was active for the ring-closing metathesis of dienes containing a phosphane–borane group (Table 1). When diene **4a** was refluxed with 2% mol of catalyst **1a** for 12 h, compound **8a** was isolated in 81% yield with no side product detected in the crude mixture (entry 1, Table 1). Analogously, the reaction allowed access to the six-membered ring **8e** in very good yield (entry 2, Table 1, 95%). Formation of the seven-membered ring **8b** required 12 mol% (added sequentially in 2 mol% portions) of the catalyst **1a** and extended reaction time to achieve a 63% yield (entry 3, Table 1). Interestingly, the isomeric seven-membered ring **8f** was prepared in 94% yield after 9 h and in the presence of only 4 mol% of the catalyst **1a** (entry 4, Table 1). Mechanistically, several products were conceivable from the cyclization of substrate **4d**: A single ring-closing metathesis could lead to borane complexes of the five-membered or eight-membered cyclic phosphanes, and two ring-closing metathesis reactions could yield the desired bisphosphane–borane **8d** or a [4.4.2]bicyclo derivative. After 90 h at reflux in dichloromethane, ring-closing metathesis with 14 mol% of the catalyst **1a** afforded after purification the desired bisphosphane–borane **8d** in 55% yield along with 6% yield of a product resulting from a single ring-closing metathesis, which could be cleanly separated from **8d** by column chromatography. No eight-membered ring, bicyclic product, or dimer could be detected in the crude reaction mixture (entry 5, Table 1). The ring-closing metathesis can be extended to include borane complexes of α-substituted phosphanes, however at the expense of reduced reactivity. Indeed, the cyclization of the methyl α-substituted diene **4g** with **1a** yielded the expected five-membered cyclic compound **8g** in 61% yield (entry 6, Table 1). In contrast, alkylidene **1a** did not react with the β,β'-disubstituted diene **4c**, supporting the hypothesis that alkylidene **1a** is sensitive to steric effects (entry 7, Table 1). Moreover, the data for diene **4h** suggested that the steric influence on reactivity was equally important for borane complexes of β-monosubstituted phosphanes. Indeed, it was found that **1a** did not cyclize substrate **4h** into the corresponding β-substituted heterocycle **8h** (entry 8, Table 1).

Table 1. Ring-closing metathesis of the dienes **4a–h.**

Entry	Substrates	Amount of **1a**[a] [mol%]	t [h]	Products	Yield[b] [%]
1	 **4a**	2	14	 **8a**	81
2	 **4e**	4	9	 **8e**	95
3	 **4b**	12	49	 **8b**	63
4	 **4f**	4	9	 **8f**	94
5	 **4d**	14	90	 **8d**	55[c]
6	 **4g**	4	24	 **8g**	61[d]
7	 **4c**	8	24	 **8c**	–[e]
8	 **4h**	6	24	 **8h**	–[e]

[a] The catalyst **1a** was added sequentially by 2 % mol portions. [b] Yield after column chromatography. [c] This product is formed along with 6% of the product resulting from a single ring-closing metathesis. [d] Diastereomeric ratio 67:33. [e] Recovered starting material.

In summary, the reported synthesis of new cyclic phosphanes represents the first examples of ring-closing metathesis on bis(alkenyl)phosphane–boranes. The synthetic application of this class of compounds is well established and, by employing ring-closing metathesis, the preparation of a large variety of new cyclic phosphanes or bisphosphanes is now possible. In addition, the presence of a double bond in the products could be used for further functionalization.

Experimental Section

Typical ring-closing metathesis: The catalyst **1a** (10 mg, 4 mol%) was added to a solution of diene **4e** (70 mg) in dry and degassed CH_2Cl_2 (16 mL). The mixture was refluxed for 9 h. The solvent was then evaporated and the crude product purified by chromatography on silica gel (toluene/hexane 3/2) to yield product **8e** (59 mg; 95%) as a colorless oil; ^{1}H NMR(500 MHz,$CDCl_3$): $\delta = 7.75$ (m, 2H), 7.50 (m, 3H), 5.88 (m, 2H), 2.62 (m, 2H), 2.49 (m, 1H), 2.03 (m, 2H), 0.77 (br q, $J_{B,H} = 94.5$ Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 131.8$ (d, $J_{P,C} = 8.7$ Hz), 131.7 (d, $J_{P,C} = 3.3$ Hz), 129.7 (d, $J_{P,C} = 53.7$ Hz), 129.6, (d, $J_{P,C} = 12.2$ Hz), 129.2 (d, $J_{P,C} = 9.4$ Hz), 121.4 (d, $J_{P,C} = 7.8$ Hz), 21.2 (d, $J_{P,C} = 4.8$ Hz), 21.1 (d, $J_{P,C} = 36.5$ Hz), 19.8 (d, $J_{P,C} = 35.7$ Hz); ^{31}P NMR (200.4 MHz, $CDCl_3$): $\delta = -1.7$ (d, $J_{P,B} = 60.7$ Hz); ^{11}B NMR (80.2 MHz, $CDCl_3$): $\delta = -35.9$ (dq, $J_{H,B} = 95.6$, $J_{P,B} = 59.8$ Hz); positive-ion APCI MS: m/z: 177 (100%), 188.4 (50%) (APCI = chemical ionization at atmospheric pressure).

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Total Synthesis of Luzopeptin E2**

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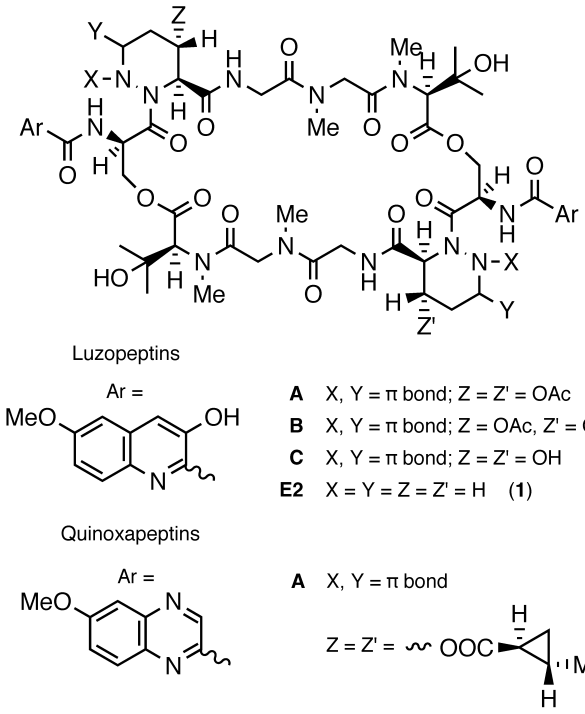
Luzopeptins are symmetric, dimeric macrocyclic depsipeptide antibiotics, which were first described in 1981.[1] Initially, these compounds attracted attention because of their antitumor activity, but the subsequent discovery of their potency as inhibitors of HIV replication in vitro at non cytotoxic doses has stimulated increased interest.[2] The biomolecular target of luzopeptins appears to be reverse transcriptase (RT). This enzyme is found only in retroviruses and it is crucial for their replication. Consequently, it is a prime target for antiretroviral therapy. Anti-HIV activity is even more pronounced in the structurally related quinoxapeptins,[3] which together with luzopeptins constitute what may be referred to as the "peptin" family of natural products. Most known RT inhibitors are nucleoside analogues (e.g, AZT); not so the peptins. This raises a number of questions concerning the mode of action and other details of their bioactivity.

Peptins exhibit an essentially invariant macrocyclic portion that incorporates two unusual components: piperazic acids (piz)[4] and *N*-methyl-3-hydroxyvaline. These delicate subunits complicate the planning of the synthesis, and indeed, peptins have remained elusive goals for a long time. Recently, Boger et al. reported total syntheses of luzopeptins A – C[5] and of the quinoxapeptins.[6, 7] Our own involvement in the peptin area has produced a number of guiding principles for the formulation of a synthetic plan[8] and it has now resulted in the total synthesis of luzopeptin E2 (**1**).[9]



Our strategy is based on the hypothesis that the 32-membered macrocycle of the peptins may self-assemble by spontaneous cyclodimerization of a suitable monomeric precursor.[10] This goal could be accomplished in a macrolactonization (simultaneous formation of both depsi bonds) or a macrolactamization (simultaneous formation of two peptide bonds) mode. Experiment ultimately ruled in favor of the latter approach.

Background work identified pentapetide **10** as our primary subtarget. Oxazolone cleavage[11] of the protected serine – piperazic acid dipeptide **4** obtained from **2**[12] produced the methyl ester **5**, which was converted to the crotyl ester **7** (Scheme 1). This operation was mandated by the sensitivity of later intermediates incorporating an *N*-methyl-3-hydroxyva-

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