Stereoselective Synthesis of 3,6-Disubstituted 1,2-Diaminocyclohexanes through Ring-Closing Metathesis of 4,5-Diamino-1,7-octadiene Derivatives

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Abstract: 3,6-Disubstituted 4,5-di[(*S*)-1-phenylethylamino]-1,7-octadienes with different configurations at the carbon stereocenters were protected as dihydrochlorides or cyclic phosphorous diamides and then converted into (1*R*,2*R*)-3,6-disubstituted 1,2-diaminocyclohexanes through ruthenium-catalyzed ring-closing metathesis and subsequent hydrogenolysis–hydrogenation steps.

Key words: catalysis, cyclization, diamines, metathesis, ruthenium

The ring-closing metathesis (RCM) of 1,n-dienes has been widely applied for the construction of nitrogen-containing compounds, for example, natural alkaloids containing the pyrrolidine or piperidine ring[1] and amino-substituted cycloalkenes.[2] We have recently reported[3a] that the dihydrochloride of (4*R*,5*R*)-4,5-diamino-1,7-octadiene derivative **1a** was converted into the N,N′-disubstituted 1,2-diaminocyclohex-4-ene **2a** by a RCM reaction using the first generation Grubbs ruthenium carbene complex **5** as the catalyst (Scheme 1). On the other hand, the cyclization of the vinyl-substituted diaminodiene **1b** was obtained with moderate diastereoselectivity through formation of the formaldehyde aminal **3**, which was then directly converted into diaminocyclohexene **2b** in the presence of trifluoroacetic acid in refluxing toluene.[3b] In contrast, we could not find suitable conditions to achieve the cyclization of the phenyl-substituted substrate **1c**, even using the second generation ruthenium carbene complex **6**.

The importance of compounds **2** stems from their potential as intermediates, due to the possible transformation of the alkene function, e.g., hydrogenation to saturated compounds, or other addition reactions, e.g., epoxidation and dihydroxylation, providing access to ring-substituted derivatives of the prototypical chiral ligand 1,2-diaminocyclohexane.[4] The new compounds can find application as novel chiral N,N-ligands for metal species. In fact, the effect of substituents on the reactivity and stereoselectivity of salen complexes featuring a substituted cyclohexane ring has become object of investigation.[5] Moreover, polyhydroxylated diaminocyclohexenes (diaminoconduritols) and -cyclohexanes are potentially active as glycosidase inhibitors[6] and can form cytostatic platinum complexes.[7]

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In this paper, we describe the results of our efforts to achieve the RCM reaction of other 3,6-disubstituted-4,5-diamino-1,7-octadienes **1c–e** with defined configurations of the stereocenters C3 and C6. Configurationally pure compounds **1** are available through double addition of γ-substituted allylzinc reagents to the optically pure diimine, derived from glyoxal and (*S*)-1-phenylethylamine.[8] In these reactions, the configuration of the α-amino stereocenters (C4, C5) in products **1** is controlled by the chiral auxiliary, whereas the relative stereochemistry of the stereocenters C3 and C6 depends on the *E*/*Z* configuration of the C=C bond in the allylic organozinc reagent. The configuration of all stereocenters in **1** is maintained in the cyclization, leading to stereochemically defined products **2**. Obviously, compounds *ent*-**2** are available starting from (*R*)-1-phenylethylamine.

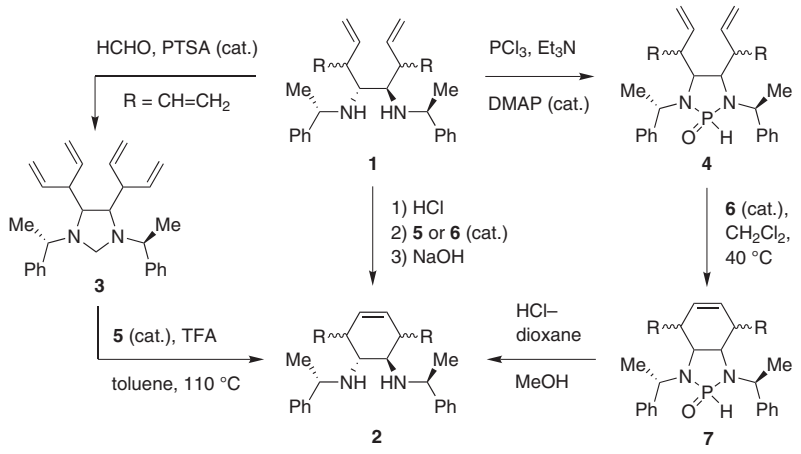
In particular, we describe a novel procedure for the cyclization of diaminodienes **1**, which involves the preliminary preparation of cyclic phosphorous diamides **4** by reaction with phosphorus trichloride.[9,10] The RCM reaction of these intermediates leads to bicyclic phosphorous diamides **7**,[11] which are hydrolyzed to give the required diaminocyclohexenes **2**, avoiding their purification by treatment with a HCl/MeOH solution.

It is noteworthy that the RCM route is an alternative to the zirconium-promoted and -catalyzed reductive cyclizations of **1**,[12] which in our study could not be applied to compound **1e** with hydroxy substituents in the allylic positions.

Since it was apparent from the previous results that the RCM reaction of compounds **1** was strongly affected by the steric effects of the allylic substituents R, we continued the investigation on several 3,6-disubstituted compounds **1,** aiming to find out suitable protocols for their cyclization. The results of the RCM reactions carried out on the dihydrochlorides of diaminodienes **1** or the phosphorous diamides **4** are summarized in Table 1.

Compound **1d** was prepared as a mixture of the two main diastereomers (55:45 ratio, not separated), which differed in the configuration of one allylic stereocenter.

The two ruthenium catalysts **5** and **6** displayed different activity in the RCM reaction of **1d**. As a matter of fact, working with catalyst **5** on **1d**·2HCl in refluxing CH_2Cl_2 no reaction was observed after six hours (entry 1). On the other hand, catalyst **6** (5 mol%) under the same conditions



a: R = H; **b**: R = vinyl; **c**: R = Ph; **d**: R = Me; **e**: R = OH; **f**: R = OEt; **g**: R = OPh

Scheme 1

was able to discriminate the two diastereomers of **1d** at a high degree: the C_1-symmetric diastereomer C_1-**1d** was quickly consumed and converted into *cis*-**2d**, i.e. with the *cis* relationship of the two methyl substituents (entry 2). The diaminocyclohexene *cis*-**2d** and unreacted C_2-symmetric **1d** (C_2-**1d**) were separated by column chromatography and obtained in 35% and 37% yield, respectively. Using this route, the separation of the two diastereomers of **1d,** which is tedious and incomplete on a large scale, can be avoided.

Furthermore, we found that protection of the diamine moiety as a cyclic phosphorous diamide is convenient for the RCM reaction, being more easily introduced as well as removed than other common diamides. In fact, we prepared the phosphorous diamide **4d** and then observed a quick cyclization in the presence of 4 mol% of catalyst **6** in CH_2Cl_2 at 40 °C (entry 3). After acidic hydrolysis of the reaction mixture the desired free diamine **2d** was isolated in 92% yield.

The *trans*-dimethyl-substituted diastereomer was similarly prepared in good yield starting from C_2-**1d** (entry 4), that had been recovered from the previous run described in entry 2.

The phosphorous diamide **4b** with pentadienyl substituents was prepared from diamine **1b** in a similar manner. We observed that **4b** did not undergo cyclization in the presence of catalyst **5** in refluxing toluene, as diamine **1b** was almost quantitatively recovered after the hydrolysis step (entry 5). Instead, the RCM reaction of **4b** was moderately successful in the presence of catalyst **6** (7 mol%) in refluxing benzene (3 h), allowing the bicyclic phosphorous amide **7b** to be obtained in ca. 30% yield (NMR analysis) and prevalence of the *cis* isomer after acidic hydrolysis (entry 6). Better reaction conditions were found using CH_2Cl_2 as the solvent at 40 °C. In this case, *cis*-**2b** was isolated in 53% yield after chromatographic separation from minor amounts of the *trans* diastereomer and unreacted **1b** (entry 7).

Unfortunately, phosphorous diamide **4c** prepared from phenyl-substituted diaminodiene **1c** did not undergo cyclization either in CH_2Cl_2 or in benzene at reflux using catalyst **6** (entry 8). In contrast, the presence of hydroxy substituents was not detrimental to the cyclization of **1e** to **2e** (70% yield) catalyzed by complex **6** under the same conditions (entry 10), whereas catalyst **5** was inactive (entry 9). With this regard, it should be underlined that previously described syntheses of oxygen-substituted cyclohexenes via RCM reactions were generally achieved through protection of the hydroxy functions in the starting 1,7-dienes, and required high loadings of the catalyst **5** (up to 30 mol%), high temperatures and long reaction times.[13] Moreover, isomerization of the allylic alcohol to methyl ketone was a competitive pathway in reactions catalyzed by **5**.[13,14]

Either the dihydrochloride or the phosphorous diamide **4f** of the diethoxy-substituted substrate **1f** (75:25 mixture of diastereomers, the prevalent one had C_1-symmetry) were submitted to RCM reactions in refluxing CH_2Cl_2 (entries 11, 12). Only the phosphorous diamide **4f** could be converted in moderate yield into the desired cyclohexene *cis*-**2f**. No successful conversion was achieved in the RCM reactions of the C_2-symmetric phenoxy-substituted compounds **1g**·2HCl and **4g** by using catalyst **6** either in CH_2Cl_2 at 40 °C or in toluene at 110 °C (entries 13, 14).

Table 1 Ring-Closing Metathesis of Diaminodiene Derivatives

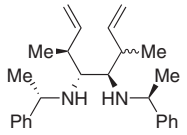
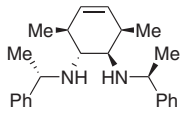
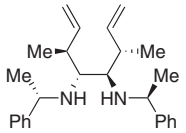
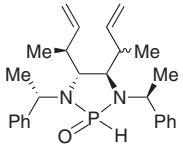
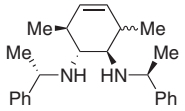
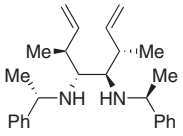
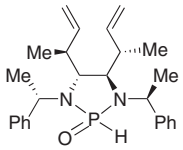
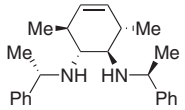
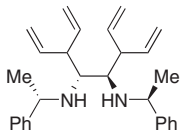
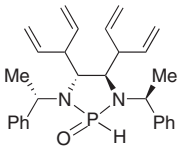
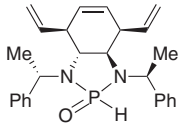
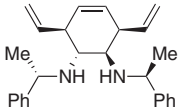
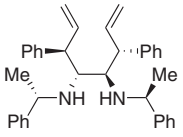
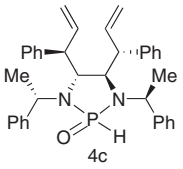
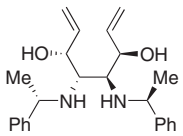
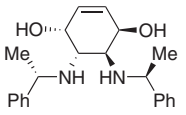
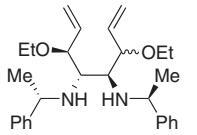
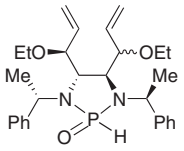
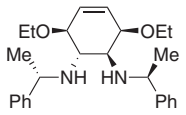
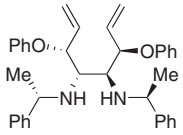
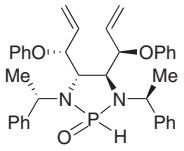
Entry	Diaminodiene	Yield of intermediate (%)	RCM catalyst, solvent, temp., time	Yield of product (%)[a]
1	 **1d** (dr ca. 55:45)	**1d**·2HCl (100)	**5** (5 mol%), CH_2Cl_2, 40 °C, 6 h	**1d**[b]
2		**1d**·2HCl	**6** (5 mol%), CH_2Cl_2, 40 °C, 3 h	 *cis*-**2d** (35)  C_2–**1d** (37)
3	**1d** (dr = 55:45)	 **4d** (87)	**6** (4 mol%), CH_2Cl_2, 40 °C, 4 h; then HCl–MeOH	 **2d** (92, *cis*/*trans* = 55:45)
4	 C_2-**1d**	 C_2-**4d** (93)	**6** (4 mol%), CH_2Cl_2, 40 °C, 3 h; then HCl–MeOH	 *trans*-**2d** (74)
5	 **1b**	 **4b** (92)	**5** (7 mol%), toluene, 110 °C, 6 h; then HCl–MeOH	**1b**[b]
6		**4b**	**6** (7 mol%), benzene, 80 °C, 3 h	 **7b** (30, *cis*-**7b** prevalent)[c]
7		**4b**	**6** (7 mol%), CH_2Cl_2, 40 °C, 3 h; then HCl–MeOH	 *cis*-**2b** (53)[d]
8	 **1c**	 **4c** (94%)	**5** (10 mol%), benzene, 80 °C, 6 h; or **6** (10 mol%), CH_2Cl_2, 40 °C, 6 h; then HCl–MeOH	**1c**[b]
9	 **1e**	**1e**·2HCl (100)	**5** (5 mol%), CH_2Cl_2, 40 °C, 3 h	**1e**[b]

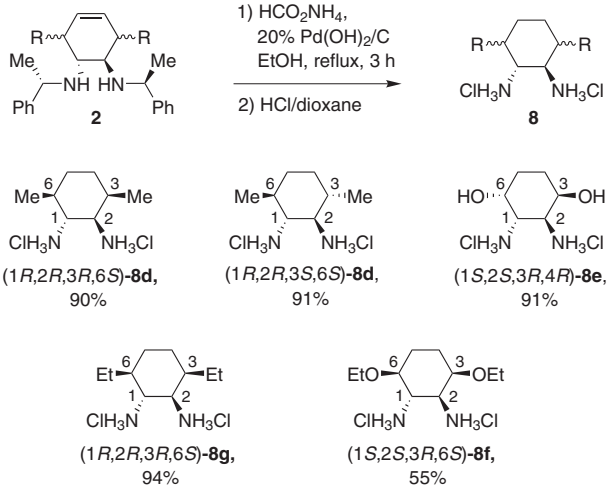
Table 1 Ring-Closing Metathesis of Diaminodiene Derivatives (continued)

Entry	Diaminodiene	Yield of intermediate (%)	RCM catalyst, solvent, temp., time	Yield of product (%)[a]
10		**1e**·2HCl	**6** (7 mol%), CH_2Cl_2, 40 °C, 4 h	 **2e** (70)
11	 **1f** (C_1/C_2 = 75:25)	**1f**·2HCl (100)	**6** (7 mol%), CH_2Cl_2, 40 °C, 4 h	**1f**[a]
12	**1f** (C_1/C_2 = 75:25)	 **4f** (75)[c]	**6** (5 mol%), CH_2Cl_2, 40 °C, 4 h; then HCl–MeOH	 *cis*-**2f** (38) [d]
13	 **1g**	**1g**·2HCl (100)	**6** (10 mol%), CH_2Cl_2, 40 °C, 6 h; or toluene, 110 °C, 3 h	**1g**[b]
14	**1g**	 **4g** (100)	**6** (10 mol%), CH_2Cl_2, 40 °C, 6 h; or **6** (10 mol%), toluene, 110 °C, 4 h; then HCl–MeOH	**1g**[a]

[a] Yield of product isolated by column chromatography.
[b] The unreacted starting material was generally recovered in >95% yield.
[c] Yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[d] Minor amounts of unreacted **1b** or **1f** and *trans*-**2b** or -**2f** were not isolated.

From these results, it appears that the RCM reaction of 3,6-disubstituted 4,5-diamino-1,7-octadienes **1** is preferably accomplished through the cyclic phosphorous diamides **4** by using ruthenium catalyst **6** in CH_2Cl_2 at 40 °C. The reaction is sensitive to steric effects, being affected by the nature of the substituents and the configuration of the inherent stereocenters. Particularly, cyclohexenes are more easily formed when the allylic substituents can assume the relative *cis*-relationship in the six-membered carbon ring. Nevertheless, the C_2-symmetric hydroxy-substituted diaminodiene **1e** can be cyclized to give substituted cyclohexene *trans*-**2e** through the dihydrochloride.

Finally, the N-unsubstituted diaminocyclohexanes (1*R*,2*R*,3*R*,6*S*)-**8d**, (1*R*,2*R*,3*S*,6*S*)-**8d**, (1*S*,2*S*,3*R*,6*R*)-**8e,** (1*R*,2*R*,3*R*,6*S*)-**8g** and (1*S*,2*S*,3*R*,6*S*)-**8f** were prepared from **2d**–**g** by palladium-catalyzed hydrogenation–hydrogenolysis in refluxing ethanol (Scheme 2). Particularly noteworthy is that diethyl-substituted compound **8g** derived from the vinyl-substituted precursor **2b**.



Scheme 2

It can be concluded that the RCM reactions of the proper substrates **1d–g** have allowed to prepare new 1,2-diaminocyclohexane derivatives, where both the amino groups are equatorially oriented and the C3,C6 substituents are in one of the three possible relative orientations: axial-equatorial (**8d–g**), equatorial-equatorial (**8d**) and axial-axial (**8e**). The effect of the relative stereochemistry of the C3,C6 substituents and their size should now be assessed in a number of asymmetric reactions, e.g., those catalyzed by salen complexes.

Melting points are uncorrected. Solvents were distilled over the appropriate drying agent under N_2 atmosphere before use: THF (sodium benzophenone ketyl, then $LiAlH_4$), CH_2Cl_2 (P_2O_5). Optical rotations were measured on a digital polarimeter in a 1 dm cell and $[\alpha]_D$ values are given in 10^{-1} deg·cm^3·g^{-1}. ^{1}H NMR spectra were recorded on a Varian Gemini instrument at 300 MHz or 200 MHz for samples in $CDCl_3$, which was stored over Mg: ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to $CHCl_3$, $\delta_H = 7.27$, $\delta_C = 77.0$) and *J* values are given in Hz. ^{31}P NMR spectra were recorded on a Varian Mercury 400 spectrometer at 161.90 MHz; chemical shifts are referenced to external standard 85% H_3PO_4. MS spectra were taken at an ionizing voltage of 70 eV on a Hewlett-Packard 5970 or 5890 spectrometer with GLC injection. Chromatographic separations were performed on columns of SiO_2 (Merck, 230–400 mesh) at medium pressure. The ruthenium catalysts **5** and **6** were purchased from Aldrich. The metathesis reactions were carried out in a flame-dried apparatus under a static atmosphere of dry Ar.

RCM Reactions of Diaminodienes 1 through their Dihydrochlorides; General Procedure

To the stirred solution of diaminodiene **1** (2 mmol) in MeOH (5 mL) was added HCl (4 M in dioxane, 1 mL). Then the solvent was removed at reduced pressure to leave an off-white solid. This solid was dissolved in CH_2Cl_2 (6 mL), complex **6** (5–7 mol%) was added while Ar was bubbled through the solution (0.5 min), and the solution was stirred at 40 °C until (almost) complete conversion (TLC analysis). The cooled reaction mixture was treated with 2 M NaOH (5 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 5 mL). The collected organic layers were dried ($CaCl_2$) and concentrated at reduced pressure to leave a greyish solid. Pure diaminocyclohexenes were obtained by column chromatography (SiO_2, cyclohexane–EtOAc).

(1*R*,2*R*,3*R*,6*S*)-3,6-Dimethyl-*N*,*N*′-bis[(1*S*)-1-phenylethyl]cyclohex-4-ene-1,2-diamine (*cis*-2d)

This compound was obtained as an oil starting from the (6*R*,6*S*)-mixture of **1d**·2HCl through chromatographic separation of unreacted C_2-**1d**.

$[\alpha]_D^{25}$ –61.5 (*c* 0.22, $CHCl_3$).

IR (neat): 3340, 3295, 3062, 3023, 1602, 1370 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.63 and 1.11 (2 d, 6 H, *J* = 6.9 Hz), 1.22 and 1.48 (2 d, 6 H, *J* = 6.6 Hz), 1.27 (s, 1 H) 2.0 (m, 2 H), 2.07 (dd, 1 H, *J* = 9.9, 8.7 Hz), 2.36 (dd, 1 H, *J* = 15.3, 5.1 Hz), 2.40 (m, 1 H), 3.68 and 3.81 (2 q, 2 H, *J* = 6.6 Hz), 5.21 (ddd, 1 H, *J* = 9.9, 1.8, 1.5 Hz), 5.46 (ddd, 1 H, *J* = 9.9, 4.8, 2.4 Hz), 7.1–7.4 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 20.2, 24.1, 25.6, 31.1, 41.0, 53.5, 55.7, 56.7, 58.4, 126.7, 127.2, 128.1, 128.3, 130.3, 131.5.

GC-MS: *m/z* (%) = 105 (100), 214 (65), 110 (51), 120 (17), 348 (2, M^+).

Anal. Calcd for $C_{24}H_{32}N_2$: C, 82.71; H, 9.25; N, 8.04. Found: C, 82.46; H, 9.29; N, 8.07.

(1*R*,4*R*,5*S*,6*S*)-5,6-Bis{[(1*S*)-1-phenylethyl]amino}cyclohex-2-ene-1,4-diol (2e)

White powder; mp 120–122 °C.

$[\alpha]_D^{25}$ –11.4 (*c* 0.63, $CHCl_3$).

IR (KBr): 3318, 3027, 1600, 1324, 1259 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 (d, 6 H, *J* = 6.6 Hz), 1.9–2.9 (broad, 4 H), 2.45 (m, 2 H), 3.81 (q, 2 H, *J* = 6.6 Hz), 4.06 (m, 2 H), 5.97 (dd, 2 H, *J* = 1.4, 2.8 Hz), 7.2–7.4 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 52.5, 55.1, 62.3, 126.6, 127.2, 128.6, 130.5, 145.1.

Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.67; H, 8.04; N, 7.92.

Phosphorous Diamides 4; General Procedure

To a stirred solution of diaminodiene **1** (2 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (2.02 g, 20 mmol) and DMAP (10 mg). Freshly distilled PCl_3 (0.55 g, 4 mmol) was added at 0 °C and the mixture was stirred for 3 h at reflux. After cooling at 0 °C, H_2O (10 mL) was slowly added (**Caution!**), CH_2Cl_2 was removed at reduced pressure, and the organic materials were extracted with Et_2O (3 × 10 mL). The ethereal layers were collected, then Na_2SO_4 and SiO_2 (1 g) were added, the mixture was stirred for 30 min, then filtered through a small pad of Celite, and the organic solution was concentrated at reduced pressure. The products were used without further purification.

(4*R*,5*R*)-1,3-Bis[(1*S*)-1-phenylethyl]-4,5-bis(1-vinylprop-2-en-1-yl)-1,3,2-diazaphospholidine 2-Oxide (4b)

Whitish oil.

$[\alpha]_D^{25}$ +21.6 (*c* 0.44, $CHCl_3$).

IR (neat): 3428, 3077, 2360 (PH), 1635, 1226 (P=O), 1129, 1037, 998, 918, 773, 704 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (d, 3 H, *J* = 7.3 Hz), 1.78 (d, 3 H, *J* = 7.3 Hz), 2.55–2.75 (m, 3 H), 2.85–2.95 (m, 1 H), 4.10–4.20 (m, 1 H), 4.25–4.55 (m, 3 H), 4.75–5.25 (m, 7 H), 5.30–5.50 (m, 1 H), 5.50–5.70 (m, 2 H), 7.25–7.45 (m, 8 H), 7.55–7.65 (m, 2 H), 8.04 (d, 1 H, $^1J_{P,H}$ = 609 Hz, PH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.42 (d, $^3J_{C,P}$ = 3.6 Hz, CH_3), 21.4 (d, $^3J_{C,P}$ = 3.6 Hz, CH_3), 51.2 (*C*HCH=CH_2), 51.6 (*C*HCH=CH_2), 55.85 (d, $^2J_{C,P}$ = 7.2 Hz, *C*HCH$_3$), 56.2 (d, $^2J_{C,P}$ = 6.1 Hz, *C*HCH$_3$), 59.7 (d, $^2J_{C,P}$ = 9.0 Hz, CH*C*HN), 62.6 (d, $^2J_{C,P}$ = 7.8 Hz, CH*C*HN), 116.6 (CH_2=), 116.9 (CH_2=), 117.6 (CH_2=), 117.8 (CH_2=), 127.4, 127.5, 127.85, 128.0, 128.35, 128.6 (6 lines for arom. CH), 136.1 (CH=), 136.2 (CH=), 136.9 (CH=), 137.25 (CH=), 142.8 (arom. C), 143.1 (arom. C).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 8.9 (dm, $^1J_{P,H}$ = 609 Hz).

(4*R*,5*R*)-4,5-Bis[(1*S*)-1-methylprop-2-en-1-yl]-1,3-bis[(1*S*)-1-phenylethyl]-1,3,2-diazaphospholidine 2-Oxide (C_2-4d)

Whitish oil.

$[\alpha]_D^{25}$ –31.2 (*c* 0.73, $CHCl_3$).

IR (neat): 3445, 3065, 3035, 2346 (PH), 1638, 1600, 1228 (P=O), 1130, 1033, 913, 802, 704 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76 (d, 3 H, *J* = 7.1 Hz), 0.79 (d, 3 H, *J* = 7.1 Hz), 1.76 (d, 3 H, *J* = 7.0 Hz), 1.82 (d, 3 H, *J* = 7.0 Hz), 2.20–2.49 (m, 2 H), 2.58–2.90 (m, 2 H), 4.12–4.42 (m, 2 H), 4.52–5.04 (m, 4 H), 5.15–5.34 (m, 1 H), 5.65–5.84 (m, 1 H), 7.23–7.43 (m, 8 H), 7.52–7.60 (m, 2 H), 7.96 (d, 1 H, $^1J_{P,H}$ = 609 Hz, PH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (*C*H_3CHCH=), 15.6 (*C*H_3CHCH=), 21.6 (d, $^3J_{C,P}$ = 4.7 Hz, *C*H_3CHN), 21.7 (d, $^3J_{C,P}$ = 5.2 Hz, *C*H_3CHN), 38.2 (*C*HCH=CH_2), 38.7 (*C*HCH=CH_2), 55.0 (d, $^2J_{C,P}$ = 6.9 Hz, N*C*HCH$_3$), 55.1 (d, $^2J_{C,P}$ = 7.6 Hz, N*C*HCH$_3$), 60.1 (d, $^2J_{C,P}$ = 9.1 Hz, CH*C*HN), 62.55 (d, $^2J_{C,P}$ = 8.2 Hz, CH*C*HN), 115.5 (CH_2=), 116.0 (CH_2=), 127.3, 127.4, 127.7, 127.9, 128.2, 128.4 (6 lines for arom. CH), 138.3 (CH=), 139.3, (CH=), 142.35 (arom. C), 142.8 (arom. C).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 9.9 (dm, $^1J_{P,H}$ = 609 Hz).

(4*R*,5*R*)-1,3-Bis[(1*S*)-1-phenylethyl]-4,5-bis[(1*R*)-1-phenylprop-2-en-1-yl]-1,3,2-diazaphospholidine 2-Oxide (4c)

White solid; mp 210–215 °C (dec.).

$[\alpha]_D^{25}$ +19.2 (*c* 0.39, $CHCl_3$).

IR (KBr): 3429, 3026, 2329 (PH), 1600, 1226 (P=O), 1128, 1035, 988, 933, 900, 770, 701, 635, 542 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, 3 H, *J* = 7.2 Hz), 1.44 (d, 3 H, *J* = 7.2 Hz), 2.58–3.05 (m, 5 H), 3.05–3.20 (m, 1 H), 3.80 (d, 1 H, *J* = 17.3 Hz), 3.95 (d, 1 H, *J* = 17.3 Hz), 4.69 (dd, 1 H, *J* = 10.4, 1.8 Hz), 4.77 (dd, 1 H, *J* = 10.4, 1.8 Hz), 5.50–5.70 (m, 2 H), 7.05–7.20 (m, 4 H), 7.20–7.45 (m, 14 H), 7.50–7.62 (m, 2 H), 8.30 (d, 1 H, $^1J_{P,H}$ = 602 Hz, PH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (d, $^3J_{C,P}$ = 6.0 Hz, CH_3), 21.3 (d, $^3J_{C,P}$ = 5.0 Hz, CH_3), 53.8 (*C*HCH=CH_2), 54.8 (*C*HCH=CH_2), 56.0 (d, $^2J_{C,P}$ = 6.8 Hz, *C*HCH$_3$), 57.0 (d, $^2J_{C,P}$ = 5.0 Hz, *C*HCH$_3$), 61.9 (d, $^2J_{C,P}$ = 9.7 Hz, CH*C*HN), 65.6 (d, $^2J_{C,P}$ = 7.7 Hz, CH*C*HN), 117.6 (CH_2=), 117.9 (CH_2=), 126.75, 126.92, 127.2, 127.4, 127.7, 128.1, 128.35, 128.4, 128.4, 128.6 (10 lines, 2 sign. overl. for arom. CH), 137.2 (CH=), 137.7 (CH=), 141.4 (arom. C), 141.7 (arom. C), 143.9 (arom. C), 143.95 (arom. C).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 7.2 (dm, $^1J_{P,H}$ = 602 Hz).

(4*S*,5*S*)-4-[(1*R*)-1-Ethoxyprop-2-en-1-yl]-5-[(1*S*)-1-ethoxyprop-2-en-1-yl)-1,3-bis[(1*S*)-1-phenylethyl]-1,3,2-diazaphospholidine 2-Oxide and (4*S*,5*S*)-4,5-Bis[(1*S*)-1-ethoxyprop-2-en-1-yl)-1,3-bis[(1*S*)-1-phenylethyl]-1,3,2-diazaphospholidine 2-Oxide (4f)

Yellowish oil; dr = 70:30.

$[\alpha]_D^{25}$ –7.0 (*c* 0.68, $CHCl_3$).

IR (neat): 3433, 3062, 3028, 2346 (PH), 1640, 1226 (P=O), 1131, 929, 772, 703 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 7.0 Hz), 0.95 (t, 3 H, *J* = 7.0 Hz), 1.01 (t, 3 H, *J* = 7.0 Hz), 1.07 (t, 3 H, *J* = 7.0 Hz), 1.11 (t, 3 H, *J* = 7.0 Hz), 1.14 (t, 3 H, *J* = 7.2 Hz), 1.69 (d, 3 H, *J* = 7.3 Hz) 1.70 (d, 3 H, *J* = 7.0 Hz), 1.71 (d, 3 H, *J* = 7.1 Hz), 1.72 (d, 3 H, *J* = 7.2 Hz), 1.76 (d, 3 H, *J* = 7.0 Hz), 1.78 (d, 3 H, *J* = 6.5 Hz), 2.40–3.60 (m, 24 H), 4.10–5.90 (m, 24 H), 7.20–7.50 (m, 24 H), 7.50–7.65 (m, 6 H), 7.96 (d, 2 H, $^1J_{P,H}$ = 609 Hz, PH), 8.07 (d, 1 H, $^1J_{P,H}$ = 604 Hz, PH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9 (*C*H_3CH$_2$OCH=), 15.0 (*C*H_3CH$_2$OCH=), 15.1 (*C*H_3CH$_2$OCH=), 15.2 (*C*H_3CH$_2$OCH=), 15.2 (*C*H_3CH$_2$OCH=), 15.3 (*C*H_3CH$_2$OCH=), 21.2 (d, $^3J_{C,P}$ = 3.4 Hz, CH_3), 21.2 (d, $^3J_{C,P}$ = 3.2 Hz, CH_3), 21.3 (d, $^3J_{C,P}$ = 4.3 Hz, CH_3), 21.4 (d, $^3J_{C,P}$ = 3.7 Hz, CH_3), 21.5 (d, $^3J_{C,P}$ = 5.5 Hz, CH_3), 21.7 (d, $^3J_{C,P}$ = 4.9 Hz, CH_3), 55.2 (d, $^2J_{C,P}$ = 6.0 Hz, *C*HCH$_3$), 55.6 (d, $^2J_{C,P}$ = 7.1 Hz, *C*HCH$_3$), 55.8 (d, $^2J_{C,P}$ = 7.5 Hz, *C*HCH$_3$), 55.9 (d, $^2J_{C,P}$ = 6.1 Hz, *C*HCH$_3$), 56.25 (d, $^2J_{C,P}$ = 7.0 Hz, *C*HCH$_3$), 56.9 (d, $^2J_{C,P}$ = 5.7 Hz, *C*HCH$_3$), 57.3 (d, $^2J_{C,P}$ = 8.7 Hz, CH*C*HN), 56.2 (d, $^2J_{C,P}$ = 9.6 Hz, CH*C*HN), 58.8 (d, $^2J_{C,P}$ = 9.6 Hz, CH*C*HN), 60.8 (d, $^2J_{C,P}$ = 8.2 Hz, CH*C*HN), 61.35 (d, $^2J_{C,P}$ = 7.8 Hz, CH*C*HN), 61.6 (d, $^2J_{C,P}$ = 8.4 Hz, CH*C*HN), 63.95 (OCH_2), 64.0 (OCH_2), 64.15 (OCH_2), 64.3 (OCH_2), 64.5 (OCH_2), 64.5 (OCH_2), 81.1 (*C*HCH=CH_2), 81.6 (*C*HCH=CH_2), 82.7 (*C*HCH=CH_2), 82.9 (*C*HCH=CH_2), 83.2 (*C*HCH=CH_2), 83.5 (*C*HCH=CH_2), 117.9 (CH_2=), 118.0 (CH_2=), 118.9 (CH_2=, 3 sign. overl.), 119.7 (CH_2=), 127.15, 127.2, 127.27, 127.3, 127.3, 127.4, 127.5, 127.5, 127.6, 127.8, 127.9, 128.0, 128.2, 128.2, 128.2, 128.3, 128.23 128.5 (18 lines for arom. CH), 134.6 (CH=), 135.0 (CH=), 135.1 (CH=), 135.38 (CH=), 135.58 (CH=), 135.69 (CH=), 143.10 (arom. C), 143.35 (arom. C), 143.4 (arom. C), 143.4 (arom. C), 143.55 (arom. C), 143.8 (arom. C).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 12.1 (dm, $^1J_{P,H}$ = 609 Hz), 11.1 (dm, $^1J_{P,H}$ = 609 Hz), 8.3 (dm, $^1J_{P,H}$ = 604 Hz).

(4*S*,5*S*)-4,5-Bis[(1*R*)-1-phenoxyprop-2-en-1-yl]-1,3-bis[(1*S*)-1-phenylethyl]-1,3,2-diazaphospholidine 2-Oxide (4g)

White solid; mp 125–134 °C (dec.).

$[\alpha]_D^{25}$ +1.7 (*c* 1.8, $CHCl_3$).

IR (KBr): 3406, 3070, 3042, 2365 (PH), 1646, 1597, 1228 (P=O), 1118, 1031, 928, 803, 753, 700, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (d, 3 H, *J* = 7.0 Hz), 1.79 (d, 3 H, *J* = 7.0 Hz), 3.28–3.41 (m, 1 H), 3.41–3.55 (m, 1 H), 4.16–4.34 (m, 2 H), 4.38–4.60 (m, 2 H), 4.98–5.30 (m, 4 H), 5.40–5.57 (m, 1 H), 5.60–5.78 (m, 1 H), 6.65 (d, 2 H, *J* = 8.1 Hz), 6.74 (d, 2 H, *J* = 8.1 Hz), 6.88–7.00 (m, 2 H), 7.10–7.30 (m, 10 H), 7.34–7.53 (m, 4 H), 8.06 (d, 1 H, $^1J_{P,H}$ = 613 Hz, PH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.83 (d, $^3J_{C,P}$ = 4.2 Hz, CH_3), 21.3 (d, $^3J_{C,P}$ = 4.2 Hz, CH_3), 54.6 (d, $^2J_{C,P}$ = 6.5 Hz, *C*HCH$_3$), 55.0 (d, $^2J_{C,P}$ = 8.0 Hz, *C*HCH$_3$), 57.7 (d, $^2J_{C,P}$ = 8.9 Hz, CH*C*HN), 60.14 (d, $^2J_{C,P}$ = 8.1 Hz, CH*C*HN), 78.4 (*C*HCH=CH_2), 79.4 (*C*HCH=CH_2), 115.7 (arom. CH), 116.3 (arom. CH), 118.6 (CH_2=), 119.0 (CH_2=), 121.10, 121.15, 127.3, 127.4, 127.5, 127.5, 128.4, 128.5, 129.2, 129.3 (10 lines for arom. CH), 133.65 (CH=), 134.5 (CH=), 142.35 (arom. C), 142.4 (arom. C), 142.7 (arom. C), 142.7 (arom. C).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 13.4 (dm, $^1J_{P,H}$ = 613 Hz).

RCM Reactions of Phosphorous Acid Diamides 4; General Procedure

Preparation of Diaminocyclohexenes 2 through 8

Complex **6** (43 mg, 0.05 mmol) was added to the stirred solution of phosphorous diamide **4** (2 mmol) in CH_2Cl_2 (6 mL) while Ar was bubbled through the solution (0.5 min) at 40 °C. An equal amount of complex **6** was added after 1.5 h and the mixture was further stirred at 40 °C for 1.5–2 h. The solvent was removed under reduced pressure and the residue was dissolved in MeOH (8 mL), then HCl (4 M in 2 mL dioxane) was added and the mixture was stirred overnight. The solvent was removed at reduced pressure and the residue was treated with Et_2O (10 mL), H_2O (10 mL) and solid NaOH until pH 11. The organic phase was separated and the aqueous layer was further extracted with Et_2O (3 × 5 mL). The collected organic layers were dried (Na_2SO_4) and concentrated at reduced pressure to leave a yellowish oil. Pure diaminocyclohexene was obtained through column chromatography (SiO_2, cyclohexane–EtOAc).

Compound **2b** was previously described.[3b]

(1*R*,2*R*,3*S*,6*S*)-3,6-Dimethyl-*N*,*N*′-bis[(1*S*)-1-phenylethyl]cyclohex-4-ene-1,2-diamine (*trans*-2d)

Yellowish oil.

$[\alpha]_D^{25}$ +64.2 (*c* 1.74, $CHCl_3$).

IR (neat): 3317, 3082, 3060, 3011, 1602, 1368 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (d, 6 H, *J* = 5.7 Hz), 1.28 (d, 6 H, *J* = 6.6 Hz), 1.68 (br m, 2 H), 2.04 (m, 4 H), 3.89 (q, 2 H, *J* = 6.6 Hz), 5.21 (s, 2 H), 7.1–7.4 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.5, 24.8, 40.6, 58.1, 62.3, 126.8, 127.1, 128.3, 131.4, 145.8.

GC-MS: *m*/*z* (%) = 105 (100), 214 (63), 110 (50), 120 (17), 348 (3, M^+).

Anal. Calcd for $C_{24}H_{32}N_2$: C, 82.71; H, 9.25; N, 8.04. Found: C, 82.41; H, 9.29; N, 8.01.

(1*S*,2*S*,3*R*,6*S*)-3,6-Diethoxy-*N*,*N*′-bis[(1*S*)-1-phenylethyl]cyclohex-4-ene-1,2-diamine (*cis*-2f)
Yellowish oil.

$[\alpha]_D^{25}$ –82.7 (*c* 0.7, $CHCl_3$).

IR (neat): 3301, 3027, 1602, 1369, 1326, 1270, 1088 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.09 and 1.26 (2 t, 6 H, *J* = 7.0 Hz), 1.32 and 1.44 (2 d, 6 H, *J* = 6.2 Hz), 2.24 (dd, 2 H, *J* = 11.4, 3.2 Hz), 2.55 (dd, 2 H, *J* = 11.4, 8.0 Hz), 3.43 (dq, 1 H, *J* = 1.8, 8.0 Hz), 3.5–3.75 (m, 4 H), 3.75–3.95 (m, 2 H), 4.17 (q, 1 H, *J* = 6.6 Hz), 5.79 (dd, 1 H, *J* = 1.8, 10.4 Hz), 5.90 (ddd, 1 H, *J* = 1.2, 4.8, 10.4 Hz), 7.1–7.5 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.55, 15.8, 24.9, 25.8, 26.9, 54.0, 54.2, 55.4, 57.1, 64.1, 64.2, 68.5, 125.8, 126.3, 126.9, 127.0, 127.0, 128.1, 128.5, 131.6, 145.3, 146.5.

GC-MS: *m*/*z* (%) = 105 (100), 57 (33), 77 (22), 161 (20), 106 (12), 266 (10), 120 (6).

Anal. Calcd for $C_{26}H_{36}N_2O_2$: C, 76.43; H, 8.88; N, 6.86. Found: C, 76,74; H, 8.91; N, 6.84.

Preparation of 1,2-Diaminocyclohexanes Dihydrochlorides 8; General Procedure
A mixture of 1,2-diaminocyclohexene **2** (1 mmol), HCO_2NH_4 (0.800 g, 12.5 mmol), 20% $Pd(OH)_2$/C (0.100 g) in EtOH (10 mL) was heated at reflux temperature for 3 h. The cooled mixture was filtered through a small pad of celite and the organic solution was treated with HCl (0.5 mL; 4 M in dioxane). The solvents were removed under reduced pressure to leave the diamine dihydrochloride as a white solid (>95% pure by ^1H NMR).

(1*R*,2*R*,3*R*,6*S*)-3,6-Dimethylcyclohexane-1,2-diaminium Dichloride (*cis*-8d)
Mp 200–210 °C (dec.).

$[\alpha]_D^{25}$ –8.4 (*c* 0.5, MeOH).

IR (KBr): 3420, 2500–3500 (br), 1594, 1566, 1498 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 1.13 (d, 3 H, *J* = 7.2 Hz), 1.20 (d, 3 H, *J* = 6.6 Hz), 1.50 (dt, 1 H, *J* = 2.7, 12.9 Hz), 1.60–1.90 (m, 4 H), 2.50 (m, 1 H), 3.39 (dd, 1 H, *J* = 10.5, 11.1 Hz), 3.66 (dd, 1 H, *J* = 4.8, 10.5 Hz).

^{13}C NMR (75 MHz, CD_3OD): δ = 12.9, 18.8, 28.3, 30.9, 33.1, 37.3, 56.2, 56.4.

Anal. Calcd for $C_8H_{20}Cl_2N_2$: C, 44.66; H, 9.37; N, 13.02. Found: C, 44.47; H, 9.40; N, 12.97.

(1*R*,2*R*,3*S*,6*S*)-3,6-Dimethylcyclohexane-1,2-diaminium Dichloride (*trans*-8d)
Mp 230–240 °C (dec.).

$[\alpha]_D^{25}$ +7.2 (*c* 1.3, MeOH).

IR (KBr): 3425, 2500–3400 (br), 1594, 1520 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 1.18 (d, 6 H, *J* = 6.0 Hz), 1.34 (m, 2 H), 1.82 (d, 4 H, *J* = 7.5 Hz), 3.2 (d, 2 H, *J* = 7.8 Hz).

^{13}C NMR (75 MHz, CD_3OD): δ = 19.0, 33.4, 37.1, 59.8.

Anal. Calcd for $C_8H_{20}Cl_2N_2$: C, 44.66; H, 9.37; N, 13.02. Found: C, 44.48; H, 9.41; N, 12.98.

(1*S*,2*S*,3*R*,6*R*)-3,6-Dihydroxycyclohexane-1,2-diaminium Dichloride (8e)
Mp 200–210 °C (dec.).

$[\alpha]_D^{25}$ –73.2 (*c* 0.17, MeOH).

IR (KBr): 3364, 2600–3200 (br), 1549, 1205 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 1.60 (dd, 2 H, *J* = 9.8, 4.2 Hz), 1.89 (dd, 2 H, *J* = 9.8, 1.2 Hz), 3.53 (m, 2 H), 4.07 (m, 2 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 26.2, 53.3, 67.1.

Anal. Calcd for $C_6H_{16}Cl_2N_2O_2$: C, 32.89; H, 7.36; N, 12.79. Found: C, 32.75; H, 7.39; N, 12.75.

(1*S*,2*S*,3*R*,6*S*)-3,6-Diethoxycyclohexane-1,2-diaminium Dichloride (8f)
The crude compound was isolated as a yellowish solid in 87% yield, then washed with Et_2O–MeOH (8:1) to give a white solid in 55% yield.

Mp 175–185 °C (dec.).

$[\alpha]_D^{25}$ –14.1 (*c* 0.27, MeOH).

IR (KBr): 3413, 3143, 2200–2500 (br), 1626, 1107 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 1.27 and 1.29 (2 t, 6 H, *J* = 6.9 Hz), 1.55 (m, 2 H), 2.12 (m, 1 H), 2.25 (m, 1 H), 3.40–3.65 (m, 4 H), 3.65–3.90 (m, 3 H), 3.93 (s, 1 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 15.85, 15.9, 23.7, 24.1, 54.7, 55.5, 65.6, 66.0, 74.4, 77.7.

Anal. Calcd for $C_{10}H_{24}Cl_2N_2O_2$: C, 43.64; H, 8.79; N, 10.00. Found: C, 43 51; H, 8.82; N, 10.15.

(1*R*,2*R*,3*R*,6*S*)-3,6-Diethylcyclohexane-1,2-diaminium Dichloride (8g)
Mp 170–180 °C (dec.).

$[\alpha]_D^{25}$ –3.8 (*c* 0.44, MeOH).

IR (KBr): 3436, 2500–3400 (br), 1594, 1503 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 0.88 (t, 6 H, *J* = 7.0 Hz), 1.1–1.7 (m, 8 H), 1.7–1.8 (m, 1 H), 1.9–2.1 (m, 1 H), 3.26 (dd, 1 H, *J* = 9.6, 8.0 Hz), 3.49 (dd, 1 H, *J* = 9.6, 4.8 Hz).

^{13}C NMR (75 MHz, CD_3OD): δ = 11.0, 11.9, 19.2, 23.6, 25.1, 25.3, 39.6, 42.6, 54.7, 56.6.

Anal. Calcd for $C_{10}H_{24}Cl_2N_2$: C, 49.38; H, 9.95; N, 11.52. Found: C, 49.58; H, 9.99; N, 11.48.

Acknowledgment

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