Formation of macrocyclic ring systems by carboxylation of trifunctional P/B/B frustrated Lewis pairs†

Long Wang, a Shunxi Dong, a Constantin G. Daniliuc, a Lei Liu, b Stefan Grimme, b Robert Knitsch, c Hellmut Eckert, c, d Michael Ryan Hansen, c Gerald Kehr c and Gerhard Erker c

The trifunctional P/B/B frustrated Lewis pairs 11a–c featuring bulky aryl groups at phosphorus [Dmesp (a), Tipp (b), Mes* (c)] react with H₂ by heterolytic hydrogen splitting followed by cleavage of HB(C₆F₅)₂ to give the zwitterionic six-membered heterocyclic PH phosphonium/borate products 14a–c. Compounds 11a,b react with carbon monoxide by means of a Lewis acid induced CO insertion/rearrangement sequence that eventually results in the formation of the macrocyclic dimers 17a,b. The respective carboxylation reaction of the Mes*P/B/B FLP gives the macrocyclic trimer 18c. The new products were characterized spectroscopically and by X-ray diffraction and the reaction mechanism was analyzed by DFT calculations.

Introduction

Macrocyclic compounds have very interesting structural features.1,2 Many such systems play significant roles in medicine and biology3–7 and many serve as important chemical reagents.8–12 Macrocyclic ring closure is often difficult to achieve selectively since ring closure principally competes with entropically favoured formation of the linear oligomers. Chemical synthesis of macrocycles, therefore, has relied on a variety of specific measures in order to achieve the required chemoselectivity; high dilution is one important and often used principle13–15 as is template directed synthesis. Conformational features as well as electrostatic effects may play a role.16–19 There are some reactions that seem to bear a “natural” tendency for macrocyclic ring formation.20–28

We have now found that Lewis pair formation might favor intermolecular cyclooligomerization in cases where the direct internal interaction of the Lewis acid and base functionalities is effectively precluded by specific geometric restrictions. We have found that this may selectively lead to cyclodimeric and even cyclotrimetric ring systems in a rather simple experimental procedure. First examples will be presented and discussed in this account.

Results and discussion

Alkyl boranes are important building blocks in organic synthesis. Many such systems are readily available by convenient hydroboration routes.29–31 Many alkyl boranes insert carbon monoxide into the boron–carbon bond. This reaction type has been used for the preparation of CO derived ketones, aldehydes or alcohols.32 Hydroboration of alkenes with Piers’ borane [HB(C₆F₅)₂] (2) occurs readily.33,34 The resulting products, such as the respective styrene (1) hydroboration compound PhCH₂CH₂B(C₆F₅)₂ (3), however, do not readily insert CO at ambient conditions (r.t., 1.5 bar CO pressure, see Scheme 1, see the ESI† for details). CO insertion was not observed even in the presence of additional B(C₆F₅)₃. The difference is even more pronounced with vicinal P/B frustrated

![Scheme 1](image-url)
Lewis pairs (FLPs), such as compound 6, which readily reacts with CO, but does not form the CO insertion product into the \([B]^{-}\text{CH}_2\) linkage but rather undergoes cooperative 1,1-P/B addition to the carbon atom of carbon monoxide to yield the CO-bridged product 7. A number of related P/B FLPs show a similar behavior.\(^{25-40}\)

We reasoned that this behavior might originate from the very special properties of the strong B(C\(_6\)F\(_5\))\(_2\) Lewis acid unit making the alkyl migration step to carbon monoxide unfavorable. Introduction of a second B(C\(_6\)F\(_5\))\(_2\) group into the system might potentially provide a way out of this behavior: specifically located it could function as an activator for the P/B bonded carbonyl unit and thus initiate the otherwise unfavorable CO insertion reaction in such systems. This turned out to be a successful concept and, in addition, it opened an easy pathway to several rather unusually structured macrocyclic ring systems. Three such examples with some of their remarkable characteristic features will be reported in this account.

We have prepared the aryldivinylphosphanes 8a-c by treatment of the respective ArP\(_2\)Cl\(_2\) precursors\(^{11a-c}\) with two molar equiv. of vinyl magnesium bromide. We had reported the reaction of compound 8c with one molar equiv. of HB(C\(_6\)F\(_5\))\(_2\) which had given the unique zwitterionic methylene phosphonium/borate product 14a (Ar: Dmesp) and HB(C\(_6\)F\(_5\))\(_2\). The latter was removed from the mixture by the hydroboration reaction with 1-pentene converting it to pentane soluble pentyl-B(C\(_6\)F\(_5\))\(_2\). It was isolated and identified as its pyridine adduct 15py (for details see the ESI†). The heterocycle 14a was eventually isolated as a white solid in 78% yield. Its X-ray crystal structure analysis (see Fig. 1) showed the presence of the chair-shaped 1,4-P/B heterocycle with tetracoordinated boron and the PH(Dmesp) phosphonium unit being part of it. In solution, compound 14a shows a typical borate \(^{11}\)B NMR feature at \(\delta = -14.6\) and a phosphonium \(^{31}\)P NMR signal at \(\delta = 9.0\) (\(J\) \(= 5.56\), \(J_{\text{PF}} = 463.0\) Hz). The \(^{13}\)C NMR spectrum shows signals of the six-membered core unit at \(\delta = 19.0\) (PCH\(_2\), \(J_{\text{PC}} = 43.1\) Hz) and \(\delta = 20.8\) (broad, BCH\(_2\)), respectively (see Scheme 3, also see the ESI† for details).

The P/B/B compounds 11b,c reacted analogously with dihydrogen with formation of the PH/B products 14b,c. We isolated them both in ca. 70% yield; both were characterized by spectroscopy and by X-ray diffraction (see the ESI† for details). We assume a reaction pathway (see Scheme 3) that is initiated by

**Scheme 2** Formation and some previously reported reactions of the P/B/B FLP systems 11.

**Scheme 3** Reaction of the P/B/B FLPs 11 with dihydrogen.
heterolytic splitting of dihydrogen by using a P/B pair\textsuperscript{39-40} of the P/B/B FLP 11 to give the PH\textsuperscript{+}/BH\textsuperscript{-}/B intermediates 13. We assume that the additional \(-\text{B(C}_6\text{F}_5\text{)}_2\) Lewis acid becomes actively involved and forms the six-membered P/B heterocycles 14 by a \(\sigma\)-bond metathesis type reaction\textsuperscript{59-61} with concomitant formation of HB(C\text{F}_3\text{)}\text{B}. The formation of the products 14 and HB(C\text{F}_3\text{)}\text{B} (2) gave us a strong indication of the active role of the additional-B(C\text{F}_3\text{)}\text{B} Lewis acid in the compounds 11. This we used advantageously in the reaction of the P/B/B FLPs 11a-c with carbon monoxide.

We generated the P/B/B system 11b (Ar: Tipp) \textit{in situ} (24 h, r.t., see Scheme 2) and then exposed the solution to a carbon monoxide atmosphere (1.5 bar, r.t.). After 30 min reaction time a white precipitate of the cyclodimeric CO insertion product 17b had formed. It was isolated as a white solid in 54% yield (for details see the ESI†). Compound 17b is thermally quite stable in solution. However, it lost carbon monoxide upon heating for 6 h at 80 °C in benzene-\(d_6\) solution to re-form the starting material 11b.

We assume a reaction pathway as it is depicted in Scheme 4, which was supported by the results of DFT calculations\textsuperscript{69} (for details see the ESI†). All structures were optimized with a composite DFT method PBEh-3c,\textsuperscript{69} followed by single point energy calculations at the PW6B95-D3 level of theory\textsuperscript{65,67,68} with a Gaussian AO def2-TZVP basis set.\textsuperscript{64,66} The COSMO-RS (conductor-like screening model for real solvents) solvation model\textsuperscript{69,71} with toluene as the solvent was used to compute solvation free energies. Endergonic opening of the P-B linkage of 11b yields the reactive P/B/B intermediate 11open, which may undergo the typical 1,1-P/B FLP addition reaction to carbon monoxide.\textsuperscript{53,54} Carbonyl activation by the remaining pendant –B(C\text{F}_3\text{)}\text{B} functionality\textsuperscript{70-72} via 16A might initiate the kinetically facile and thermodynamically feasible formation of the CO insertion product\textsuperscript{13} 16B. Isomerization forms the P/B Lewis pair. In 16C the direct internal interaction of the carbonyl oxygen with the pendent borane Lewis acid is geometrically precluded; the system may serve as an active C=O/B frustrated Lewis pair. This leads to dimerization giving the observed macrocyclic reaction product 17b.

The X-ray crystal structure analysis confirmed the sixteen-membered cyclodimeric heterocyclic ring structure. The monomeric units are connected by a pair of carbonyl C=O···borane interactions. The remaining boron atoms form Lewis pair interactions with their adjacent phosphane Lewis bases. In this situation two diastereoisomers are possible due to the phosphorus chirality\textsuperscript{72,73}; we found the near to \(C_2\)-symmetric rac-structure in the crystal (see Fig. 2, also see the ESI† for details).

In solution, compound 17b shows the NMR features of the symmetry-equivalent monomeric subunits. We monitored eight separate \(^{1}H\) NMR sp\(^3\)-CH signals of the methylene groups, the \(^{19}F\) NMR signals of four different C\text{F}_3\text{B} substituents at boron and a single \(^{31}P\) NMR signal at \(\delta\) 21.0. From a \(^{13}C\) labelled sample we located the \(^{13}C\) NMR carbonyl resonance at \(\delta\) 269.0,\textsuperscript{70,71} Compound 17b shows a \(v(\text{CO})\) = 1588 cm\(^{-1}\) \([\tilde{v}(^{13}\text{CO}) = 1547 \text{ cm}^{-1}\] ) carbonyl stretching band.

The Dmesp substituted P/B/B system 11a reacts analogously with CO. We isolated the \(C_2\)-symmetrical dimer 17a in 61% yield and characterized it by C,H-elemental analysis, by \(\text{C}_{\text{H}}\)-elemental analysis, by NMR (\(^{19}F\) NMR signals of four different C\text{F}_3\text{B} substituents at boron and a single \(^{31}P\) NMR signal at \(\delta\) 21.0. From a \(^{13}C\) labelled sample we located the \(^{13}C\) NMR carbonyl resonance at \(\delta\) 269.0,\textsuperscript{70,71} Compound 17a lost CO upon heating to 50 °C (12 h) in dichloromethane solution to give the starting material 11a.

The carbonylation reaction of the Mes\(^{+}\)P/B/B system 11c took a slightly different course. Exposure of the \textit{in situ} generated Mes\(^{+}\)P/B/B system 11c to CO (1.5 bar, r.t. 30 min) gave compound 18c (81% isolated) (see Scheme 5, for details see the ESI†). The compound was stable in the solid state but lost carbon monoxide with re-formation of the starting material 11c.

![Scheme 4](https://example.com/scheme4.png)

Scheme 4 Carboxylation reaction of the P/B/B FLPs 11a, with computed reaction Gibbs free energies at PW6B95-D3/def2-TZVP (COSMO-RS, toluene)//PBEh-3c level of the theory. The energy of 11b + CO is selected as the reference and all values are given in kcal mol\(^{-1}\) at 298 K. The value of the dimer 17b refers to the monomeric subunit for the purpose of comparability.
Scheme 5  Formation of the cyclotrimeric carbonylation product 18c.

in solution (CD$_2$Cl$_2$). Therefore, the solution NMR data were monitored using in situ generated samples at low temperature (for details see the ESI†). Single crystals of compound 18c for the X-ray crystal structure analysis were obtained from a toluene solution in a carbon monoxide atmosphere at −5 °C. Compound 18c shows a macrocyclic twenty-four-membered core structure. It is composed of three monomeric subunits that were probably formed by a CO insertion/rearrangement sequence analogous to the one described in Scheme 4; this was supported by DFT calculations (for details see the ESI†). The presence of the three phosphorus chirality centers would principally allow for two diastereoisomers, an all-α-phosphorus chirality centers would principally allow for two (for details see the ESI†).

Ar–R---[B]

Scheme 5  Formation of the cyclotrimeric carbonylation product 18c.

Ar–R---[B]: B(C$_6$F$_5$)$_2$

Fig. 3  A view of the core structure of the macrocyclic P/B/B carbonylation trimer 18c (the substituents at boron and phosphorus are omitted for clarity; thermal ellipsoids are shown with 15% probability). Selected bond lengths (Å) and angles (°): P1–B1 2.096(5), C3A–O1 1.253(5), O1–B6 1.590(6), P3–B5 2.110(5), C3C–O3 1.245(5), O3–B4 1.603(5), P2–B3 2.094(5), C3B–O2 1.239(5), O2–B2 1.625(6), B1–C3A–O1 117.7(4), C3A–O1–B6 133.7(3), B5–C3C–O3 119.6(4), C3C–O3–B4 133.4(3), B3–C3B–O2 113.8(4), C3B–O2–B2 131.9(4).

Fig. 4  Side view of a 2,4,6-tri-$^t$Buphenyl-P (i.e. Mes*-P) unit of the macrocyclic trimer 18c. The P1–C11–C14 angle of this unit amounts to 144.1°.

We note an almost co-linear arrangement for the pair of Tipp-P units in the dimer 17b. The respective P1–C11–C14 angles for the pair of crystallographically independent Tipp-P subunits were found at 174.4° and 173.1°. We find a slightly bent structure for the more bulky Dmesp-P groups in compound 17a with P1–C11–C14 angles of 171.0° and 166.2°, respectively, but we note a rather extreme bending of the Mes*-P moiety. In the Mes*-P,Cl$_2$ reagent the P1–C11–C14 type angle amounts to 156°.46 In the three Mes*-P subunits in our trimer 18c we find this distortion of the (aryl)C–P moieties being increased further by ca. 10° to P1–C11–C14 values of 144.1°, 147.9°, and 146.1°, respectively. Fig. 4 shows a side-on projection of one out of the three Mes*-P moieties of compound 18c, which visualizes this strong distortional effect. This might actually have created an overall conformational situation that may have contributed to determining the observed chemistry of this system to a considerable extent, especially the specific association behaviour of the monomeric subunits forming the observed cyclotrimer 18c.

The solid-state $^{31}$P MAS NMR spectra confirmed the asymmetric (C$_1$) structure of the cyclotrimer 18c containing three different phosphorus atoms. Consequently, three $^{31}$P NMR signals at 12, 13 and 15 ppm were observed which are broadened and additionally split by the indirect $^{31}$P–$^{11}$B spin–spin coupling ($J$(31P–$^{11}$B) ~ 80 Hz). As illustrated in Fig. 5(a), simultaneous $^{11}$B and $^1$H decoupling enhances the resolution (see Fig. 5, left, for further details including the $^{11}$B–$^{31}$P REDOR and 2D-INEPT experiments see the ESI†). Compound 18c also showed three equal intensity $^{31}$P NMR resonances in solution (Fig. 5, right). It showed 22 different $^1$H NMR signals (two with relative intensity two, all others with intensity one at 243 K) of the 12 pairs of diastereotopic CH$_2$ hydrogen atoms as well as 12 methylene $^{13}$C NMR signals of the core ring carbons. There are nine separate $^1$H NMR t-Bu singlets and the $^{31}$P NMR signals of 12 C$_6$F$_5$ groups at the boron atoms of compound 18c. The $^{13}$CO derived isotopologue showed three $^{13}$C NMR carbonyl signals [δ 273.3 (d, $^2$J$_{PC}$ = 23.6 Hz), 272.0 (d, $^2$J$_{PC}$ = 29.9 Hz) and 271.9 (d, $^2$J$_{PC}$ = 29.9 Hz)] (for details see the ESI†).
Conclusions

It seems that the presence of the additional B(C6F5)2 Lewis acid function influences the reaction of the internal ethylenediamine-bridged P/B FLP functionality of the compounds 11 to two decisive ways: activation of the carbonyl group at the stage of the conventional cooperative P/B CO addition intermediate 16A8-10 by the reactive boron Lewis acid probably makes the CO insertion reaction into the adjacent \(-\text{CH}_2\)-B(C6F5)2 group feasible. Our DFT analysis of the CO insertion step of the Mes*P/B/B system revealed an exergonic ($\Delta G$ ca. $-4 \text{ kcal mol}^{-1}$) formation of the intermediate 16Bc (the intermediate analogous to 16Bb in the Tipp system shown in Scheme 4). In contrast the hypothetical CO insertion reaction from compound 7 (see Scheme 1) was computed by the DFT calculations as markedly endergonic ($\Delta G$ ca. $+9 \text{ kcal mol}^{-1}$, rel. $\Delta G(7) = 0$). Once the carbonyl compound is formed by C–C bond formation it is prone to rearrangement generating a monomeric intermediate 16C featuring both an organic carbonyl function and a remote free –B(C6F5)2 Lewis acid, a combination which paves the way to formation of the unique macrocyclic oligomers 17 and 18 by Lewis adduct formation between these pairs of functional groups.

Why are the macrocyclic dimers and even a cyclotrimer formed in our examples instead of the alternative linear oligomers? Actually, we do not know for sure, but we may speculate that this has to do with the special properties encountered in phosphine/borane frustrated Lewis pair chemistry. This chemistry is governed by van der Waals interactions between the bulky protagonists and it becomes increasingly apparent that conformational features strongly determine frustrated Lewis pair behavior.8,9,10 In our case it might be a combination of both factors that serves to tip the balance toward cyclooligomer formation. The conformational influence is probably indicated by the different behavior of the (Dmesp)P and (Tipp)P containing FLP pairs 11a,b vs. the Mes*P derived system 11c in the carbonylation/cyclooligomerization reaction. The former systems feature rather normal steric features of the bulky aryl-P linkage, whereas the latter shows the special conformational feature of the uncommon strongly bent P-aryl moiety. Our DFT analysis points to an energetic difference in the formation of the observed dimer (17b) in the Tipp substituted system vs. the cyclotrimer (18c) in the case of the Mes* containing system: in the Tipp containing system we find an energetic preference of the formation of the cyclodimer of ca. 5 kcal mol$^{-1}$ over the trimer, whereas in the case of the more bulky Mes* system this becomes reversed and the cyclotrimer is favored by ca. 10 kcal mol$^{-1}$ over the dimer (see the ESI† for details). The favored formation of the unusual macrocyclic trimer 18c might indeed point to a marked influence of specific conformational features introduced by the very bulky aryl Mes* substitutent into this chemistry.

The formation of the macrocyclic dimers and trimers from our carbonylated P/B/B FLP systems may place some frustrated Lewis pair reactions into the group of macrocyclic ring closure procedures that show a “natural” tendency of favoring the internal bond formation in cases of a suitable general design.8-10 This unique behavior of the carbonylation chemistry of the P/B/B systems 11 emphasizes the potential that frustrated Lewis pair chemistry has for discovering surprisingly facile pathways to unusual products formed under mild reaction conditions.

Conflicts of interest

There are no conflicts to declare.

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