Frustrated Lewis Pairs

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Formation of Thermally Robust Frustrated Lewis Pairs by Electrocyclic Ring Closure Reactions

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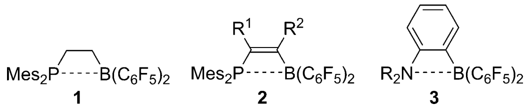
Dedicated to Professor Siegfried Hünig on the occasion of his 95th birthday

Abstract: *The phosphorus/boron-substituted hexatriene systems **6** undergo thermally induced electrocyclic ring closure to yield the cyclohexadiene-derived P/B frustrated Lewis pairs (FLPs) **7**. Subsequent TEMPO oxidation gives the phenylene-bridged FLPs **8**. Both systems activate dihydrogen and the thermally robust FLPs undergo carbon–carbon coupling reactions at a mesityl group upon treatment with dimethyl acetylenedicarboxylate at elevated temperatures.*

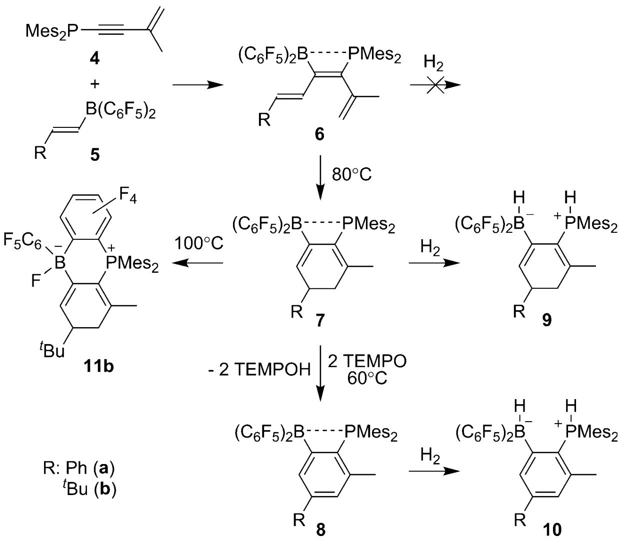
Frustrated Lewis pairs (FLPs) show a high potential of finding new reactions in a metal-free situation.[1] Cooperative heterolytic cleavage of dihydrogen and use as efficient metal-free hydrogenation catalysts is a most prominent feature of FLP chemistry.[2] In addition, FLPs have been shown to add a great variety of molecules including CO_2, SO_2, CO, and nitrogen oxides.[3] A number of new reactions have been developed that specifically take place at FLP templates or in the FLP regime, such as for example, [B]H borane reduction of carbon monoxide[4] or the phospha-Stork reaction.[5]

Intramolecular vicinal FLPs have played a significant role in these developments. However, their stabilities and reactivities were found to strongly depend on the nature of the bridging units. The saturated P/B FLP **1** and its derivatives are very reactive in most of the reactions mentioned above; the parent compound **1** has been one of the most active metal-free dihydrogen activators so far.[4,6] In contrast, the unsaturated otherwise closely related systems **2** are close to inactive in most of these reactions.[7] The phenylene-bridged N/B FLPs **3** can show high H_2 splitting activities, but that is strongly dependent on the substituents at the nitrogen atom (see Scheme 1).[8]



Scheme 1. Intramolecular vicinal frustrated Lewis pairs.

We have now developed a convenient entry to the new phenylene-bridged phosphane/borane FLPs **8** and their cyclohexadiene-derived precursors **7** (see Scheme 2) and found that these systems represent a class of thermally very robust frustrated Lewis pairs that allowed a much wider temperature range for the development of new FLP reactions. This will be described and discussed in this account with some selected examples.



Scheme 2. Synthesis of the new active frustrated Lewis pair systems **7** and **8** that split dihydrogen under mild conditions.

The synthesis of the new FLP systems was achieved in the following way. The unsaturated vicinal P/B FLPs **6a**,**b** were prepared by 1,1-carboboration[9] of the dimesitylphosphino-substituted conjugated enyne **4** with the readily available alkenylboranes **5a**,**b**, as we had previously described.[10] Subsequent thermolysis (80 °C, 3 d) resulted in a clean electrocyclic ring closure reaction of the P/B-substituted hexatriene derivatives **6a**,**b** to yield the P/B cyclohexadiene products **7a**,**b** which were isolated in 91 and 74% yield, respectively (see Scheme 2). Both compounds were characterized by C,H-elemental analysis, NMR spectroscopy, and single-crystal X-ray diffraction. Figure 1 shows a projection of the molecular structure of compound **7a** (R: Ph) (for further details of the characterization see the Supporting Information).

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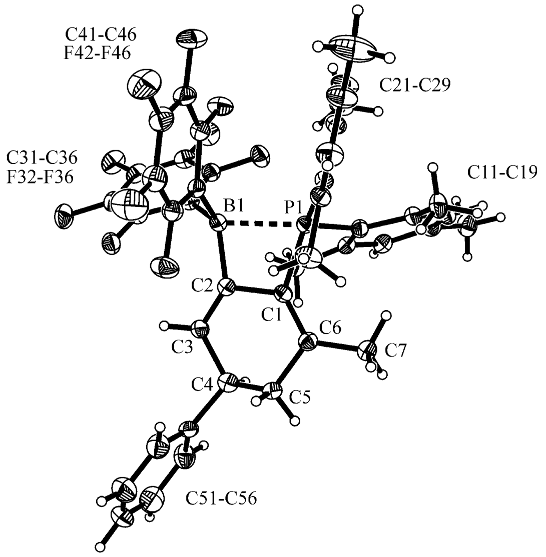


Figure 1. Molecular structure of 1,3-cyclohexadiene-derived FLP **7a** (R: Ph; thermal ellipsoids are shown with 30% probability). Selected bond lengths [Å] and angles [deg]: P1–B1 2.182(3), C1–C2 1.478(3), C1–C6 1.337(3), C2–C3 1.330(3), C4–C5 1.512(4); P1–C1–C2 98.3(2), B1–C2–C1 104.5(2).

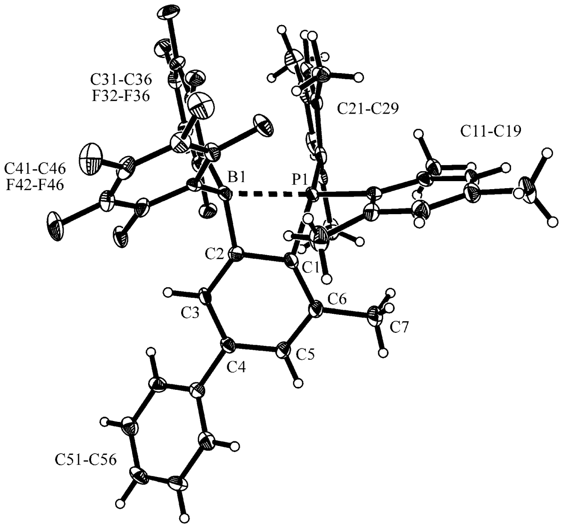


Figure 2. Molecular structure of the phenylene-bridged FLP **8a** (thermal ellipsoids are shown with 50% probability). Selected bond lengths [Å] and angles [deg]: P1–B1 2.203(6), C1–C2 1.402(7), C1–C6 1.398(7), C2–C3 1.399(8), C4–C5 1.419(7); P1–C1–C2 100.0(4), B1–C2–C1 106.9(4).

We have subsequently oxidized the cyclohexadiene core of the compounds **7a**,**b** to the respective aromatic phenylene-bridged FLPs **8a**,**b** by treatment with the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO; 2 equivalents).[11] H-atom abstraction from **7a** by the persistent nitroxide radical was achieved at 60 °C (2 d) to give **8a**, which was isolated in 84% yield. The compound **8a** shows typical FLP NMR features of the weakly interacting P/B Lewis base/Lewis acid pair at δ 5.5 ppm (^{31}P) and δ 5.8 ppm (^{11}B), respectively. The X-ray crystal structure analysis shows the presence of the newly formed carbocyclic aromatic nucleus with the PMes$_2$/B(C$_6$F$_5$)$_2$ pair in 1,2-position and the phenyl substituent attached at carbon atom C4 (see Figure 2).

Usually, the unsaturated vicinal P/B systems **2** show no or only very low FLP reactivities.[7] The derivative **6b** is no exception. Compound **6b** did not react with H$_2$ under our typical FLP reaction conditions. In contrast, the cyclohexadiene-derived systems **7a**,**b** both are very active FLPs despite the presence of a pair of C(sp^2) centers in their vicinal bridge. Thus, compound **7b** (R: ^{t}Bu) splits dihydrogen rapidly at near to ambient condition (2 bar H$_2$, RT) to give the zwitterionic phosphonium/hydrido-borate product **9b**, which was isolated in 79% yield. It shows ^{11}B NMR resonances (243K) at δ −21.8 ppm (d, $^1J_{BH} = 90$ Hz) and at δ −22.6 ppm (d, $^1J_{BH} = 75$ Hz) and a 2:1 intensity pair of ^{31}P NMR signals (243K) at δ −26.2 ppm (d, $^1J_{PH} = 510$ Hz) and −28.1 (d, $^1J_{PH} = 500$ Hz). We assume that the occurrence of a pair of diastereoisomers in solution is due to the presence of an element of conformational chirality in addition to the carbon chirality center C4. In the crystal we observed a single isomer of compound **9b** (see Figure 3). It contains the cyclohexadiene core in its typical conformation with the ^{t}Bu substituent in a pseudo-equatorial position at carbon atom C4 and the PHMes$_2$ and BH(C$_6$F$_5$)$_2$ functionalities attached at the sp^2-carbon centers C1 and C2.

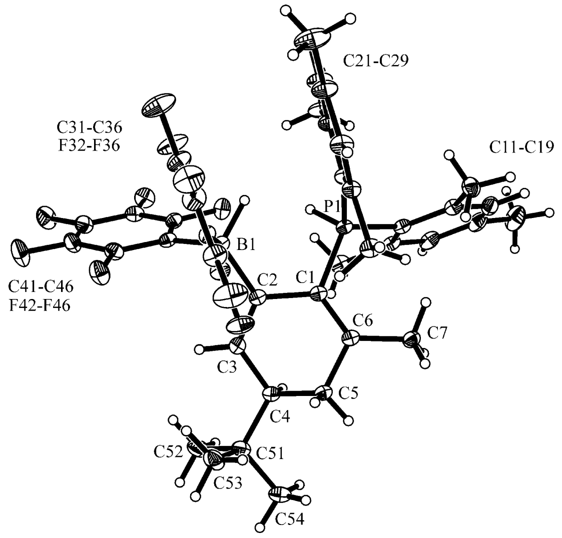


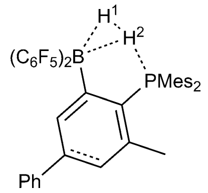
Figure 3. A view of the molecular structure of the FLP dihydrogen-splitting product **9b** (R: ^{t}Bu; thermal ellipsoids are shown with 30% probability). Selected bond lengths [Å] and angles [deg]: P1–B1 3.155, C1–C2 1.499(2), C1–C6 1.351(2), C2–C3 1.343(2), C4–C5 1.530(2); P1–C1–C2 114.8(1), B1–C2–C1 120.0(2).

Compound **7a** is an equally reactive dihydrogen splitting reagent. In a competition experiment it was shown that **7a** reacts only about six times slower with dihydrogen than the "parent" saturated vicinal P/B FLP Mes$_2$PCH$_2$CH$_2$B(C$_6$F$_5$)$_2$ **1**, which is one of the most active metal-free dihydrogen-activating systems.[2c,12] The PH/BH product **9a** was isolated in 84% yield (see the Supporting Information for its characterization by C, H elemental analysis, spectroscopy, and X-ray diffraction).

Both the aromatic systems **8a**,**b** behave as active FLPs and split dihydrogen under mild conditions (e.g. 2 bar H$_2$, CH$_2$Cl$_2$, RT, 2 d) to give the respective zwitterionic PH/BH products **10a**,**b**. Both were isolated (89% and 81% yield) and fully characterized including single-crystal X-ray diffraction (for details see the Supporting Information). The relative reactivity toward dihydrogen was determined by a competition experiment between the compounds **7a** and **8a**. The aromatic FLP system was about 38 times less active under the same reaction conditions. Both the compounds **7a** and **8a** are active metal-free catalysts for enamine hydrogenation[13] of pyrrolidino-cyclohexene (for details see the Supporting Information).

The dihydrogen activation reactions of both the FLPs **7a** and **8a** were investigated by DFT analysis (for details see the Supporting Information). The dihydrogen splitting reactions were both found to be markedly exergonic. They both show rather low activation barriers. The DFT calculations indicated that the cyclohexadiene-derived system is a more reactive FLP than the phenylene-bridged analog. For the **7a** + H_2 reaction we found a by about 5 kcal mol^{-1} lower Gibbs activation energy as for the H_2-cleavage reaction by the P/B FLP **8a** at the aromatic backbone (see Figure 4). The calculated transition-state geometry of both dihydrogen activation reactions is characterized by a close to linear H^1-H^2-P arrangement with a side-on contact of the H^1-H^2 moiety to the adjacent boron atom (see Table 1 and Figure 4).

Table 1: DFT-optimized (TPSS-D3) distances [Å] and angles [deg] of the transition-state structures for hydrogenation of FLPs **6a**, **7a**, and **8a** (see Figure 4).



	TS7a/9a	TS8a/10a	TS6a
H^1–H^2	0.767	0.763	0.753
B–H^1	1.947	2.110	2.097
B–H^2	1.995	2.132	2.211
P–H^2	2.416	2.403	2.348
P–H^2–H^1	166.2	165.4	156.2

We also carried out the DFT analysis of the H_2-splitting reaction of the open unsaturated P/B precursor system **6a** (see Figure 4c). It revealed an endergonic reaction course; H_2 splitting in this case is not observed on thermodynamic grounds. In addition, our DFT calculation has found a substantially increased activation barrier for the H_2 reaction at this system, by about a factor of two larger than obtained for the reactive P/B FLP **7a**. Our DFT analysis revealed that the trend in increasing activation energies parallels the increase in deformation energy of the FLPs on going to the transition states in the order **6a** > **8a** > **7a** (for details see the Supporting Information).

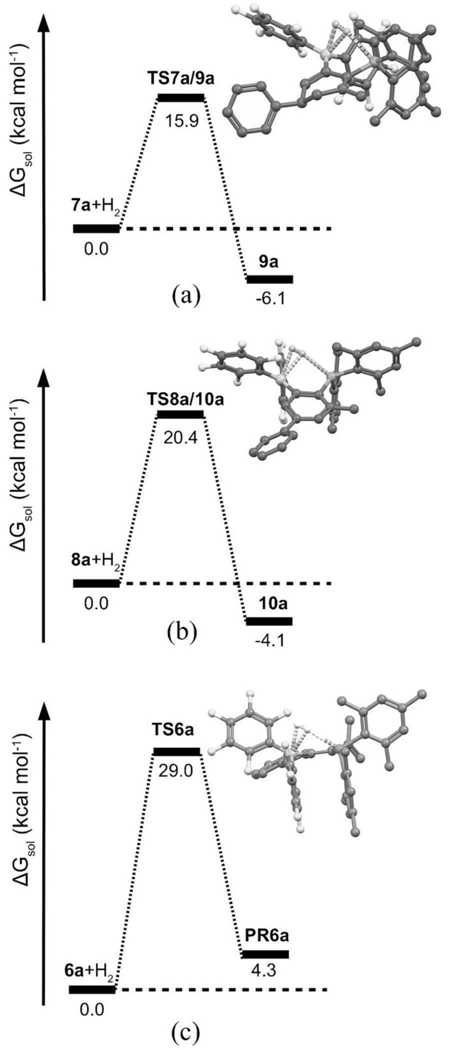
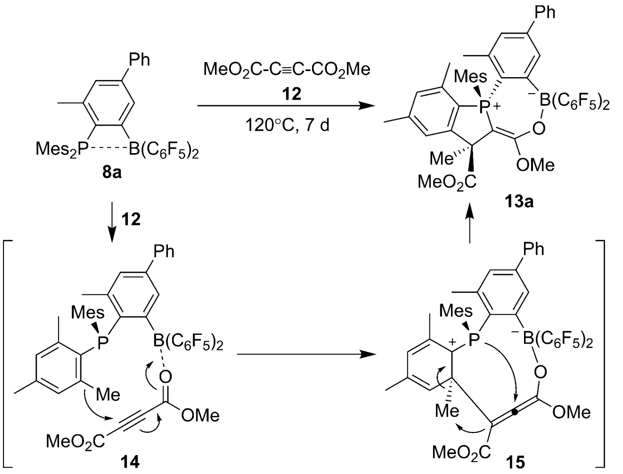


Figure 4. DFT-calculated (PW6B95-D3//TPSS-D3) Gibbs free energy profiles of the hydrogenation of FLP **7a** (a), **8a** (b) and with the inactive system **6a** (c) for comparison. For all reactions, the geometry of the transition structure is shown, non-reacting hydrogen atoms have been omitted for clarity.

The FLPs **7** and **8** are rather robust compounds. Retro-hydroboration, an often observed decomposition pathway of intramolecular FLPs, is prohibited by their special structures. Compound **7b** underwent a slow intramolecular nucleophilic aromatic substitution reaction[10] at 100 °C (1 day) to give the deactivated product **11b** (see Scheme 2; isolated in 88% yield and characterized by X-ray diffraction, see the Supporting Information). The aromatic FLP systems **8a**,**b** are thermally even more stable. Compound **8a** remained unchanged at 160 °C for prolonged periods of time and only slowly underwent the intramolecular nucleophilic aromatic substitution (S_NAr) reaction at temperatures of 180 °C or higher.

This allowed us to investigate some FLP reactions with these systems under more forcing reaction conditions. We reacted the new P/B FLP **8a** (R: Ph) with one molar equivalent of dimethyl acetylenedicarboxylate (**12**). The reaction was slow. It took 7 days at 120 °C in toluene solution to go to completion to give the product **13a**, which was isolated as a white solid in 80% yield (see Scheme 3). It turned out that it had undergone a carbon–carbon coupling reaction with one P-mesityl unit. During the reaction a methyl



Scheme 3. The new P/B frustrated Lewis pair **8a** (R: Ph) reacts with dimethyl acetylenedicarboxylate (**12**).

group from the arene had migrated to the alkynyl building block.

The X-ray crystal structure analysis of the product **13a** (see Figure 5) revealed that the FLP boron Lewis acid had added to one carbonyl oxygen atom forming a borane-stabilized ester enolate. The phosphorus atom was attached to the β-carbon atom (C8) of this enolate. A mesityl substituent at phosphorus had been involved in the process. One of its *o*-methyl groups was removed and is now found attached at the former acetylene carbon atom C9. Phosphorus and boron are still bridged by the planar *o*-phenylene group which bears the phenyl substituent at its ring carbon atom C4. Compound **13a** contains two chiral centers, a phosphorus center (P1) and a carbon center (C9). In the crystal we observe the diastereoisomer that has the remaining intact mesityl group at phosphorus and the newly introduced methyl group (C27) at carbon atom C9 *trans*-oriented at the newly formed phosphorus-containing five-membered heterocyclic substructure.

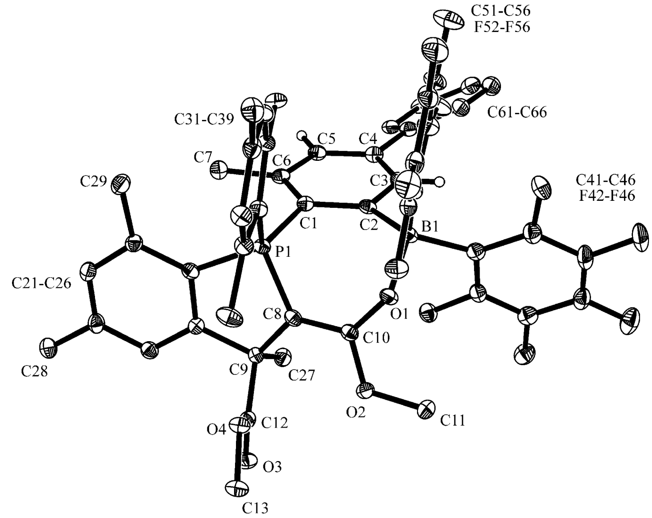
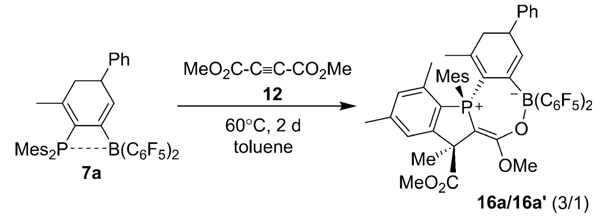


Figure 5. A view of the C–C activation product **13a** (thermal ellipsoids are shown with 30% probability; hydrogen atoms were obmitted for clarity, except at positions C5 and C3).

In solution (CD_2Cl_2) we have only observed the NMR signals of the single **13a** diastereoisomer. It shows the heteronuclear magnetic resonance signals at δ 1.4 ppm (^{11}B) and δ 15.9 ppm (^{31}P) and the ^{19}F NMR resonances of a pair of C_6F_5 substituents at boron with hindered rotation around the B–C vector at 299 K, giving rise to a total of ten separate signals. Likewise, the remaining mesityl group at phosphorus shows hindered rotation (^1H NMR: three methyl signals, two aromatic methine resonances). The *ipso*-substituted arene at phosphorus shows two CH_3 ^1H NMR signals and two CH resonances. The methyl group newly introduced at the former acetylene carbon atom shows a ^1H NMR singlet at δ 1.56 ppm. Compound **13a** shows a pair of $^1H/^{13}C$ OCH_3 resonances.

We assume a reaction pathway that is initiated by boron Lewis acid activation of the acetylenic ester[14] followed by electrophilic attack of the activated reagent at the *o*-position of one mesityl group to generate the intermediate **15** (see Scheme 3). The allenic moiety in **15** contains an orthogonal pair of nucleophilic ester enolate and electrophilic α,β-unsaturated ester. Phosphane nucleophile attack at the Michael position of the latter concomitant with nucleophilic substitution of the activated methyl group[15] would then lead to transfer of the methyl substituent with regeneration of the aromatic π system.

The cyclohexadiene-containing FLP **7a** is more reactive than **8a**. It reacted with dimethyl acetylenedicarboxylate during 2 days at 60 °C to yield the analogous C–C coupling product **16a** (see Scheme 4). It was isolated as a mixture of two diastereoisomers (ca. 4:1). Single crystals suitable for the X-ray crystal structure analysis were obtained from dichloromethane/pentane at −35 °C that allowed for the characterization of one diastereoisomer by X-ray diffraction (see the Supporting Information for details).



Scheme 4. The cyclohexadiene-containing FLP **7a** reacts with dimethyl acetylenedicarboxylate to yield the coupling product **16a**.

From the systems **6a**,**b** we have prepared in a rather straightforward way two pairs of thermally robust intramolecular vicinal P/B frustrated Lewis pairs (**7a**,**b** and **8a**,**b**). These systems featuring pairs of adjacent sp^2-carbon atoms in their respective bridges represent surprisingly highly reactive FLPs in contrast to their substituted -CR=CR- bridged relatives. The compounds **7** and **8** actively cleave dihydrogen under mild conditions, and they can probably be used to search for new reactions in a markedly increased temperature range that can be carried out at the antagonistic functionalities[16] in such systems.

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Keywords: aromatization reaction · electrocyclic ring closure · frustrated Lewis pairs · *ipso* substitution · metal-free dihydrogen activation

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