FLP Catalysis

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Frustrated Lewis Pair-Catalyzed Cycloisomerization of 1,5-Enynes via a 5-*endo*-dig Cyclization/Protodeborylation Sequence

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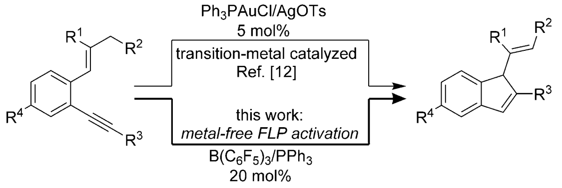
Abstract: *The first frustrated Lewis pair-catalyzed cycloisomerization of a series of 1,5-enynes was developed. The reaction proceeds via the π-activation of the alkyne and subsequent 5-endo-dig cyclization with the adjacent alkene. The presence of PPh_3 was of utmost importance on the one hand to prevent side reactions (for example, 1,1-carboboration) and on the other hand for the efficient protodeborylation to achieve the catalytic turnover. The mechanism is explained on the basis of quantum-chemical calculations, which are in full agreement with the experimental observations.*

Transition-metal catalysts have been very successfully applied in the cycloisomerization of enynes for the construction of molecular complexity through C–C bond formation. Most notably, palladium[1] and nowadays gold catalysts are commonly applied for the cycloisomerization of 1,*n*-enynes.[2] Frustrated Lewis pairs (FLP) derived from main-group elements have shown high potential as catalysts for the activation of small molecules.[3] The activation of double and triple bonds by FLPs has been reported but the catalytic turnover is obstructed by the formation of highly stable borate intermediates.[4] The bond activation of bis(ethynyl)benzenes through weak van der Waals complexes[5] with stoichiometric amounts of the strong Lewis acid $B(C_6F_5)_3$ (**1**) resulted in the formation of the pentalene scaffold[6] via a multistep cycloisomerization sequence including the 1,1-carboboration of highly reactive carbocationic intermediates. In analogy, the stoichiometric reaction of 1,6-enynes with $B(C_6F_5)_3$ (**1**) was recently reported leading to peripheral $B(C_6F_5)_2$-substituted five-membered carbo- and heterocycles.[7] Both examples suffer from the formation of either 1,1-carboboration and/or from the formation of stable onium borates precluding the highly desirable catalytic reaction. So far, only the $B(C_6F_5)_3$-catalyzed hydroamination of alkynes was realized through protodeborylation of the transiently formed ammonium borate.[8] This final proton transfer is of paramount importance to achieve catalytic turnover. We[9] and other groups[10] have shown that FLPs consisting of weak Lewis bases and Lewis acidic boranes are active catalysts. Therefore, the pK_a of the conjugate acid can be adjusted to the application by the choice of the appropriate Lewis base[9a,c,11] offering a handle to develop catalytic transformations. With the aim to extend FLP-reactivity to catalyzed C–C bond forming reactions, we set out to investigate the cycloisomerization of a 1,5-enyne (Scheme 1).



Scheme 1. Catalyzed cycloisomerization of an 1,5-enyne.

Herein we present the first FLP-catalyzed cycloisomerization of an 1,5-enyne for the construction of a complex indene scaffold. The catalytic cycloisomerization was achieved by the appropriate phosphine-derived Lewis base in combination with $B(C_6F_5)_3$ (**1**) as Lewis acid. Quantum-mechanical investigations disclosed the protodeborylation step as rate-determining with a free activation energy amounting to 21.1 $kcal\,mol^{-1}$. This finding is in very good agreement with the observed strong kinetic primary isotope effect of $k_H/k_D = 3.6$ and with the estimated activation energy of 20.9 ± 1.7 $kcal\,mol^{-1}$.

We started our investigation using 2-(1-isobutenyl)tolan (**2a**) as substrate, which has been successfully applied in the gold-catalyzed cycloisomerization (Scheme 1).[2a,12] First we conducted a stoichiometric reaction of **2a** with $B(C_6F_5)_3$ (**1**). Neither the cycloisomerization product **3a** nor the 1,1-carboboration product **4** was found, but rather the product **5** of the 5-*endo*-dig cyclization bearing the borane moiety distal to the isopropyl group (Scheme 2).

The borane **5** was isolated in 54 % yield and characterized by NMR spectroscopy and by single-crystal structure analysis (Figure 1).[14]

The ^{11}B chemical shift ($\delta = 68.9$ ppm) and the crystal structure corroborated the formation of a trigonal planar boron center (sum of angles 359°). The distance between C8 and C9 is 1.355(2) Å, which is typical for an indene C–C double bond (reported value 1.350 Å),[13] supporting the

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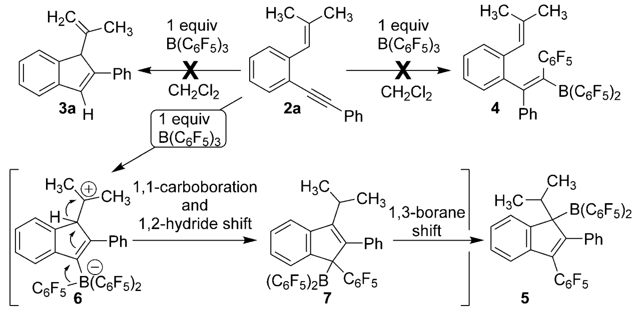
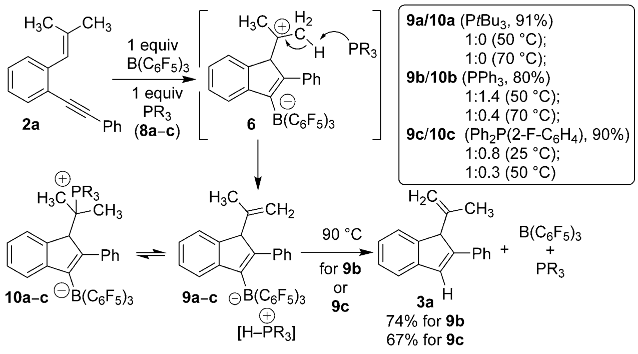


Scheme 2. Borane synthesis via 1,1-carboboration/rearrangement sequence.



Scheme 3. FLP-mediated cycloisomerization of **2**.

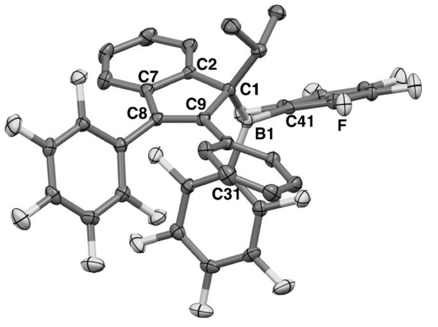


Figure 1. Molecular structure representation of **5**; selected bond lengths [Å] and angles [°]: B1–C1 1.586(2), C8–C9 1.355(2), C7–C8 1.457(2), C2–C7 1.408(2); C1-B1-C31 124.27(14), C1-B1-C41 124.72(14)°, C31-B1-C41 110.91(13). Hydrogen atoms are omitted for clarity; ellipsoids are set at 50% probability.[14]

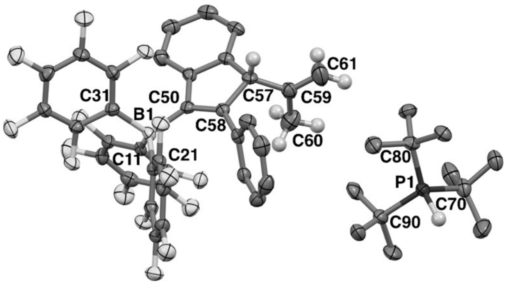
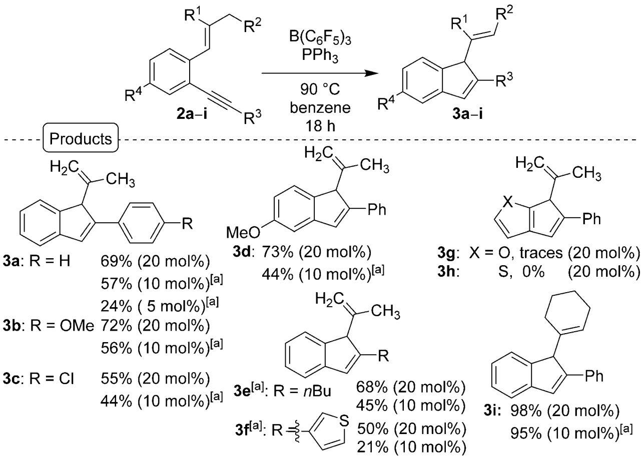


Figure 2. Molecular structure representation of **9a**; selected bond lengths [Å] and angles [°]: B1–C50 1.642(6), C50–C58 1.362(5), C59–C60 1.494(6), C59–C61 1.311(6); C11-B1-C21 112.3(4), C11-B1-C31 111.3(3), C21-B1-C31 103.0(3), C70-P1-C90 113.9(2), C70-P1-C80 114.5(2), C90-P1-C80 114.6(2). Selected hydrogen atoms were omitted for clarity; ellipsoids are set at 50% probability.[14]

indene core structure. This product was most likely formed by initial Lewis acid activation of the alkyne and intramolecular addition of the double bond to the vinylic carbocation, furnishing the zwitterionic intermediate **6** (Scheme 2), as supported by quantum-chemical calculations. Our DFT calculations reveal that the intermediate **6** is formed almost neutral in free energy over a low barrier of 12.9 kcal mol^{-1} (see the Supporting Information). In the absence of base or nucleophiles, the reactive carbocation site of **6** is not efficiently quenched, triggering a rearrangement sequence (Scheme 2). The intramolecular hydride shift proceeds with a moderate barrier of 19.0 kcal mol^{-1} followed by sequential C_6F_5 and rate-limiting $B(C_6F_5)_2$ shifts (**6**→**7**→**5**), which eventually lead to the stable rearrangement product **5**.

However, in the presence of the Lewis bases tri(*tert*-butyl)phosphine (**8a**; pK_a 11.4[15]), triphenylphosphine (**8b**; pK_a 8.8[16]), or (2-F-C_6H_4)PPh_2 (**8c;** pK_a 4.6[9c]), the transient carbocation **6** was deprotonated to yield the stable onium borate intermediates **9a–c** in good to excellent yields (Scheme 3).

The molecular structure of **9a** was unambiguously confirmed by X-ray single-crystal structure analysis (Figure 2).[14] The sum of the C-P-C and C-B-C angles deviate by 17° and 33° from 360°: 343° (Ref. [11a]: 342.9°), 327° (Ref. [6a]: 328°), supporting the tetragonal structure of the P and B centers. The bond lengths of 1.494 Å and 1.311 Å in the C59/C60/C61 fragment are in the typical range of a propenyl unit. The [H-P*t*Bu$_3$] structural element in **9a** was supported by a doublet in ^{1}H and ^{31}P NMR spectra (^{1}H-NMR: $\delta = 5.04$ ppm and ^{31}P-NMR: $\delta = 60.9$ ppm) with a $^1J_{\text{P-H}}$ coupling constant of 426 Hz. Surprisingly, in contrast to **9a**, the less bulky triaryl-substituted phosphines were in equilibrium with their addition products **10b** and **10c** observed by ^{1}H NMR (**10b**: $\delta = 1.35$ ppm, $^3J_{\text{P-H}} = 18.3$ Hz; **10c**: $\delta = 1.35$ ppm, $^3J_{\text{P-H}} = 19.4$ Hz) and ^{31}P NMR (**10b**: $\delta = 35.9$ ppm; **10c**: $\delta = 36.1$ ppm). This finding corroborates the transient nature of the isopropylidene carbocation during borane-induced cyclization. A similar intermediate has been detected in the FLP-catalyzed hydrogenation of olefins.[9c] However, the ratio of **9b**/**10b** and **9c**/**10c** was highly temperature-dependent and shifted to the hydrophosphonium species **9** at higher temperatures, increasing the concentration of Brønsted acid available in solution (Scheme 3). The triphenylphosphine derivatives **9b** and **9c** underwent protodeborylation at a temperature of 90 °C to provide the cycloisomerization product **3** and the FLP **1**/**8b** or **1**/**8c** in 74% and 67% yields, respectively. The activation energy of this final critical step for regeneration of the FLP **1**/**8b** was estimated by Arrhenius analysis to 20.9 ± 1.7 kcal mol^{-1} (**9b**→**3** + FLP) and is in excellent agreement with the calculated value of 21.4 kcal mol^{-1} from our DFT studies. Indeed, this step was found as the rate-determining step for this reaction, exhibiting a strong primary isotope effect of $k_H/k_D = 3.6$. The protodeborylation was not observed with the comparably basic P*t*Bu$_3$ in **9a** supporting the importance of the appropriate pK_a of the phosphonium component for the protodeborylation. After the feasibility of the stepwise FLP-mediated cycloisomerization was demonstrated, we turned our attention to the development of the catalytic version of this reaction using the catalyst system, which provided the highest yields in the protodeborylation (Scheme 4).



Scheme 4. FLP-catalyzed cycloisomerizations of 1,5-enynes. [a] The yield was determined by ^{1}H NMR spectroscopy using hexamethylbenzene as internal standard.

Indeed the catalytic cycloisomerization of **2a** was achieved by using the FLP-catalyst derived from B(C_6F_5)$_3$/PPh$_3$ (**1**/**8b**). Catalyst loadings of 20–10 mol% provided the product in high yields while the reduction of the catalyst loading to 5 mol% resulted only 24% yield of **3a**. The application of 20 mol% of the FLP catalyst proved most reliable for the cycloisomerization of the 1,5-enynes **2a**–**i**. Electron-donating and electron-withdrawing substituents on the peripheral phenyl ring were well-tolerated (**3b**: 72% and **3c**: 55%) as well as core substitution (**3d**: 73%). Substrates with substitution of the terminal phenyl ring by the *n*butyl (**2e**) or the 3-thiophenyl group (**2f**) provided the indene derivatives **3e** and **3f** in slightly diminished yields. Substrates with furanyl (**2g**) and thiophenyl (**2h**) rings as central aromatic moiety were not susceptible to the cycloisomerization, probably as a result of the increased alkyne–alkene distance. However, such reaction has not even been reported for gold-derived catalysts, illustrating the challenging nature of the substrate. Substitution of the isopropylidene group by cyclohexylidene (**2i**) afforded a highly reactive substrate for the cycloisomerization, so that **3i** was obtained in 98% yield or 95% yield in the presence of 20 mol% or 10 mol% catalyst, respectively.[17]

The mechanism of the B(C_6F_5)$_3$/PPh$_3$ catalyzed reaction is explained by DFT calculations. The reaction free energy paths have been calculated at the dispersion-corrected PW6B95-D3/def2-QZVP + COSMO-RS(CH_2Cl_2)// TPSS-D3/def2-TZVP + COSMO(CH_2Cl_2) level of theory (Figure 3).[18] The combination of **1**/**8b** forms a "thermally"[19] frustrated Lewis pair at 50 °C, which is in well accord of an activation energy of 13.1 kcal mol^{-1} to liberate the active Lewis acid and Lewis base. The free Lewis acid **1** forms a weak π-complex with **1·2a** in solution. The electrophilic attack of the C≡C bond on the propenyl unit, which is nearly in-plane, leads to ring-closure via transition state TS$_1$ with a low barrier of 12.9 kcal mol^{-1} to form the cyclic, transient carbocation, which is almost neutral in free energy (−1.0 kcal mol^{-1}). In the presence of a base, for example PPh$_3$ (**8b**), the reactive carbocation can undergo two intermolecular reactions via either C–P adduct formation to **10b** or via proton transfer from one of the adjacent methyl groups to form **9b**. The DFT calculations show that the free energy barriers for the C–P adduct formation (TS$_2$, **10b**) and the proton transfer to PPh$_3$ (TS$_{2'}$, **9b**) are almost the same, consistent with the experimental observation of both phosphonium borates in equilibrium. Owing to slightly higher entropy penalty (of about 0.5 kcal mol^{-1} at 298 K), the C–P adduct formation channel is expected to be somewhat disfavored at higher temperature, as observed experimentally. The formation of the protodeborylation product **3a** is strongly exergonic via the transition state TS$_3$ with a barrier of 21.4 kcal mol^{-1}.

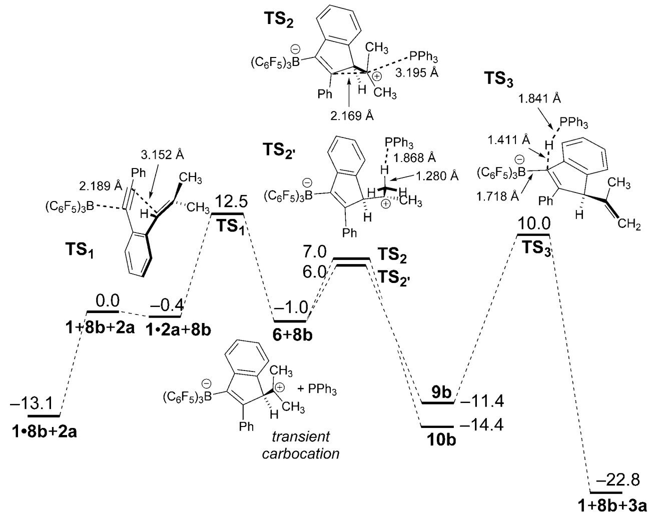


Figure 3. Calculated free energies for the FLP-catalyzed cycloisomerization of **2a** (values in kcal mol^{-1}; DFT PW6B95-D3/def2-QZVP + COSMO-RS(CH_2Cl_2)// TPSS-D3/def2-TZVP + COSMO-(CH_2Cl_2)).

In summary, we have developed the first FLP-catalyzed cycloisomerization of 1,5-enynes with the protodeborylation as key step to achieve the catalytic turnover. The reaction proceeds through π-activation of the alkyne and subsequent 5-*endo*-dig cyclization. Herein, the presence of a suitable Lewis base is of utmost importance directing the reaction to the borate intermediate preceding the protodeborylation. This substrate scope clearly shows that notoriously unreactive borate intermediates can be recycled through protodeborylation, and enable catalytic transformations, giving rise for novel FLP-catalyzed transformations in the future.

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Keywords: 1,5-enynes · cycloisomerization · frustrated Lewis pairs · kinetic isotope effect · protodeborylation

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