

Steric Control of Geminal Lewis Pair Behaviour: Frustration Induced Dyotropic Rearrangement

Éva Dorkó^a, Eszter Varga^a, Tamás Gáti^b, Tamás Holczbauer^a, Imre Pápai^a, Hasan Mehdi^a and Tibor Soós^{*,a}

^aHungarian Academy of Sciences, Research Centre for Natural Sciences, Institute of Organic Chemistry, Magyar tudósok körútja 2A, H-1117, Budapest, Hungary

^bServier Research Institute of Medicinal Chemistry, Záhony Street 7., H-1031 Budapest, Hungary

*E-mail: soos.tibor@ttk.mta.hu, Tel.: +36-1-382-6401

Received: The date will be inserted once the manuscript is accepted.

Abstract: A series of methylene linked boron/nitrogen geminal Lewis pairs were synthesized and the impacts of steric effect on their chemical behavior were systematically investigated. Increasing the steric demand around the boron atom is manifested first by an incremental change in the structure of the resulting dative adducts. Accordingly, in the case of phenyl substituents ($\text{Alk}_2\text{NCH}_2\text{BPh}_2$), formation of head-to-tail dimers/oligomers was observed, while such an intermolecular association was avoided when *o*-tolyl moiety was introduced ($\text{Alk}_2\text{NCH}_2\text{B}(o\text{-Tol})_2$), affording only an intramolecular dative complex. Further increase of sterical hindrance to a point (i.e. using mesityl substituents), however, caused a radical change in the structure, a dyotropic rearrangement occurred. Thus, steric interference induced a rearrangement in the germinal pair to relieve or minimize the frustration strain.

Key words: Lewis acids, boron, steric hindrance, dyotropic rearrangement, frustrated Lewis pairs

The activation of small molecules and unreactive bonds is perhaps one of the most important areas of modern chemistry. The concept of frustrated Lewis pairs (FLP), introduced by Stephan and coworkers, holds a promise as unique and complementary bond activation approach that has generated an immense scientific interest.⁽¹⁾ A frustrated Lewis pair is composed of bulky Lewis acid (e.g. borane) and Lewis base (e.g. amine or phosphine) that are unable to form a stable dative bond because of steric hindrance. This incapability of dative bond formation is the key element to a series of unprecedented chemical transformations among which the heterolytic hydrogen activation overtops.⁽²⁾

To increase further the cooperativity of the catalytic sites in FLPs, several intramolecular systems have been developed using appropriate covalent linkers⁽³⁾ (see Figure 1). Among the possible alternatives, the geminal $\text{P}/\text{Al}^{(3i)}$ and $\text{P}/\text{B}^{(3f,g,j)}$ Lewis pairs have attracted considerable interests due to their remarkable activity on small molecules activation. Therefore, our efforts have been devoted to prepare boron and nitrogen containing (B/N) geminal systems **1** to test the effect of sterical hindrance on their chemical behavior. This study was also triggered by a recent theoretical work of Wang group⁽⁴⁾ concluding that germinal aminoborane FLPs such as **2** (Figure 2) should act as a superior hydrogenation catalyst.

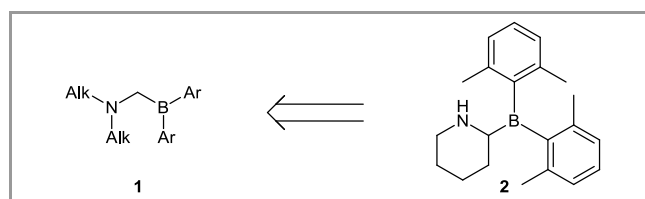


Figure 2 Envisioned geminal N/B pairs for H_2 activation

Since the envisioned geminal Lewis pairs were expected to trap ethereal solvents, the germinal N/B Lewis pairs were prepared through the metathesis of the $\text{R}_2\text{NCH}_2\text{SnR}_3$ (Scheme 1), in analogy to a reported procedure.^(3j) As outlined in Scheme 1, the **5a** and **5b** precursors were easily formed in the alkylation of pyrrolidine or piperidine with **4**, respectively⁽⁵⁾. The trimethylstannyl groups were then replaced with lithium in hexanes and the resulting lithium salts were isolated (**6a, b**). Reaction of these lithium salts with equimolar quantities of diarylboronhalides (**11-14**) bearing different steric demand around boron atom resulted in the formation of new N/B pairs. In case of diphenylboranes **7a-b**, the ^1H -NMR spectrum of the isolated product showed two groups of broad signals. We reasoned that this feature of the solution phase spectra might be due to a complex and dynamic mixture of monomers, dimers and oligomers. Finally, we could grow suitable crystals for single-crystal X-Ray diffraction analysis. The crystal structure determination verified the formation of a “head-to-tail” dimeric form of the desired product having intermolecular boron-nitrogen dative bonds (Scheme 1). Thus, a six-membered $\text{B}_2\text{C}_2\text{N}_2$ ring was formed that adopted a chair conformation despite the axial

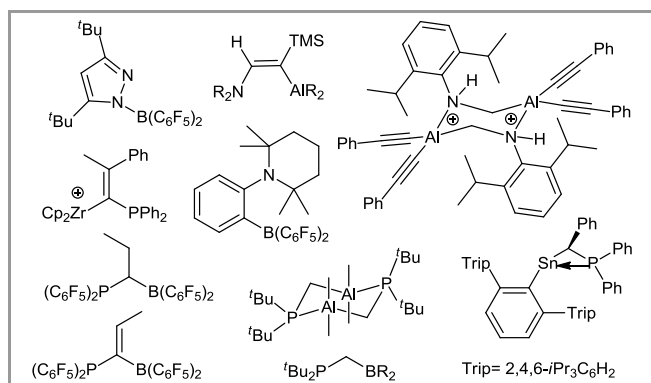
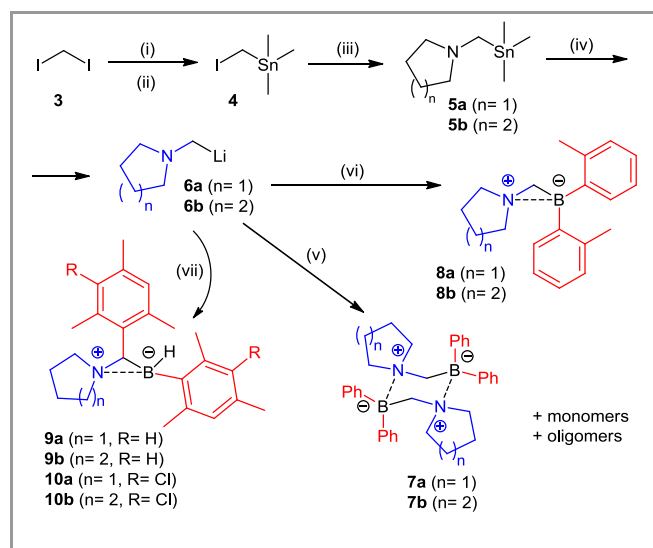


Figure 1 Representative examples of recently introduced intramolecular FLP-systems.

position of phenyl rings. Although we could detect the monomers of **7a** and **7b** in HRMS, these dative complexes proved to be rather stable in solution, they showed no capability of hydrogen activation.

In order to avoid the self-quenching of geminal pairs, we increased the steric congestion around the boron atom. By reacting **6a** and **6b** with bromobis(2-methylphenyl)borane (**12**) we isolated **8a** and **8b** N/B pairs, respectively (Scheme 1). The ^{11}B -NMR investigation confirmed an intramolecular B-N dative bond, thus the steric shielding of the tolyl groups shifted the position of the equilibrium of the dative complexes. Nevertheless, the dative bonds in these N/B pairs, despite their strained nature, turned out to be strong enough to make these species inactive towards hydrogen molecule. The relative stabilities of various forms of the synthesized geminal aminoboranes with pyrrolidine ring (**7a-8a**) were estimated via DFT calculations⁽⁶⁾ (see Supporting Information for details). The results were in accord with the observed structures.



The attempt to synthesize a frustrated geminal N/B pair led us to increase further the steric hindrance around the boron atom. We then performed the analogous salt metathesis reaction of **6a-b** with the fluorodimesitylborane **13**. These reactions, however, gave unexpected datively bound structures (**9a-b**) that were unambiguously confirmed by NMR and X-ray analysis. Accordingly, in a dyotropic reaction,⁽⁷⁾ one of the mesityl groups moved from the boron atom to the adjacent carbon, while simultaneously one hydrogen atom shifted from the carbon to the boron atom (Scheme 1). The same rearrangement was also observed when the less electron-rich 3-chloromesityl

groups were attached to the boron atom affording product **10a** and **10b**.

These experimental findings indicate that the geminal frustrated N/B pairs are prone to rearrange to minimize the frustration strain a capacity that was not yet observed in analogous geminal P/B and P/Al FLP pairs. During this process, however, the Lewis pairs gained stabilization, thus the entatic chemical nature, the FLP reactivity was lost.

These rearranged products have some interesting features in the solid state that deserves a comment. DFT calculations carried out for the **9a** complex predict notably different N-C and N-B bond lengths (1.52 and 1.63 Å) in the strained 3-membered ring. On the other hand, the X-ray analysis revealed rather symmetrical structures having formally the same N-C and N-B distances (1.58 Å). The reason for this discrepancy is the inverse placement in the asymmetric unit of **9a** (and also in **10a** and **10b**). In other words, the molecules are randomly placed in the crystal structures concerning the pseudo symmetric molecular arrangement with 50-50% site occupation of the B1 and C1 positions (see Figure 3, and SI).

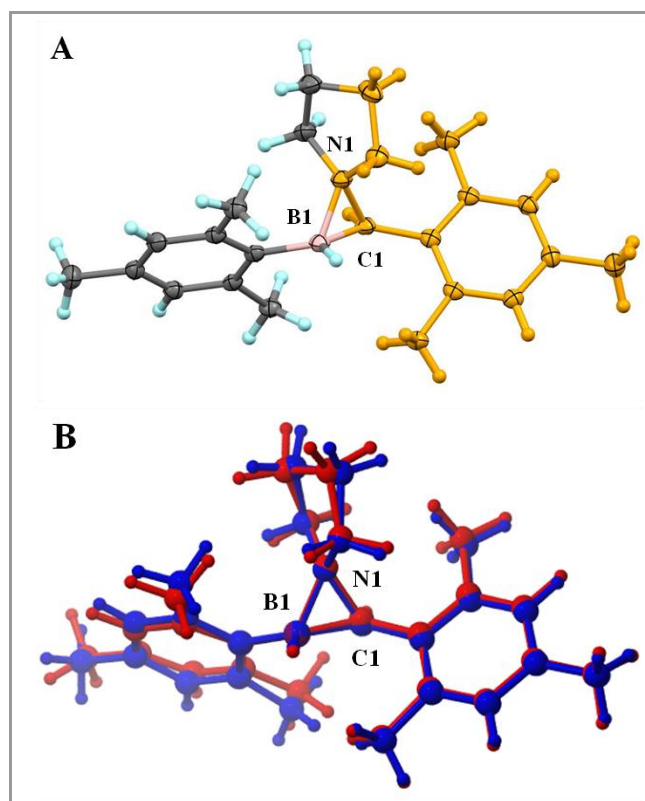


Figure 3 A. ORTEP plot of **9a** molecule. Half of the molecule can be found in the asymmetric unit. The other part of the molecule and the common N atom are represented by orange colour. The B1 and C1 atoms have symmetrical location with 50% occupation. **B.** Overlay structures of **9a**, determined by DFT calculations (blue) and by X-Ray analyses (red).

Subsequently, in a crossover experiment, we wished to find an answer whether the rearrangement occurs in an intramolecular or an intermolecular fashion.

Therefore, we reacted one equivalent of **6a** with a half equivalent of fluorodimesitylborane **13** and half equivalent of fluorodi(3'-chloromesityl)borane **14**. The HRMS analysis of the crude reaction mixture indicated that the rearrangement is unequivocally intramolecular, as we could not detect any crossover products.

The mechanism of the observed dyotropic rearrangement which affords **9a** was also examined computationally.⁽⁸⁾

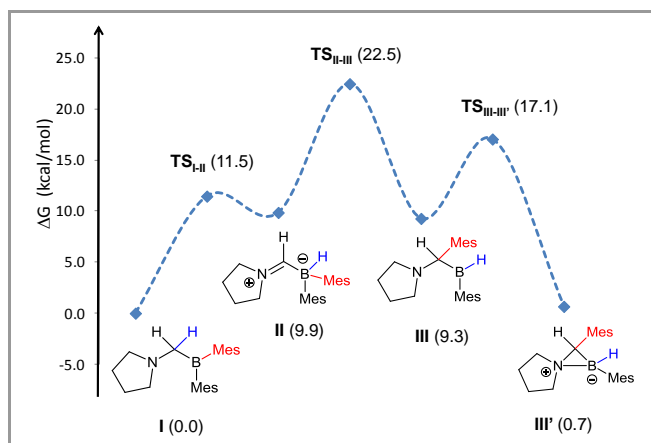


Figure 4 Gibbs free energy diagram computed for the dyotropic rearrangement which affords aminoborane **9a** (denoted as **III'**). Relative Gibbs free energies of intermediates and transition states are given in parenthesis (in kcal/mol). All structures are reported in the SI.

Possible reaction pathways towards the rearranged product were explored by locating transition states for envisioned H and Mes migration steps along with the corresponding reaction intermediates. As illustrated in Figure 4, the calculations revealed that the rearrangement of the putative, first formed aminoborane (**I**) is initiated by a hydride-transfer to the boron center yielding an iminium-hydroborate intermediate (**II**), which lies 9.9 kcal/mol above **I**. The structure of the transition state of this step is depicted in Figure 5 (**TS_{I-II}**), and the computed barrier towards **II** is fairly low. This zwitterionic species can easily revert to the reactant state (via barrier of 1.6 kcal/mol) implying that complex **II** should be considered as a transient intermediate in this reaction. Species **II** can also undergo B-to-C mesityl migration via transition state **TS_{II-III}** (see Figure 5).

This migration process represents the rate-limiting step of the overall transformation. The computed overall activation barrier (22.5 kcal/mol with respect to **I**) is rather low which is consistent with the fact that no formation of **I** was detected. The aminoborane species formed upon Mes migration (**III** in Figure 4) lies fairly high in free energy (at 9.3 kcal/mol) pointing to a notable strain in this molecule,⁽⁹⁾ however, the reorientation of the bulky Mes groups gives rise to a thermodynamically more favored isomeric form, which is actually identical to the

observed **9a** product (**III'** in Figure 4). The free energy balance of the overall **I**→**III'** transformation is predicted to be close to zero, which may imply that the intramolecular rearrangement might be reversible.⁽¹⁰⁾ Nevertheless, we did not observe such an equilibrium in the NMR experiments.

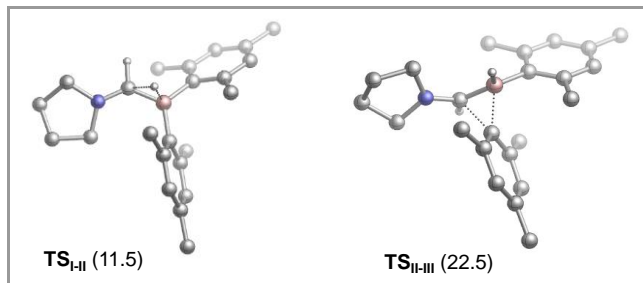


Figure 5 Transition states of H and Mes transfer steps in the dyotropic rearrangement which affords aminoborane **9a**. Relative Gibbs free energies (relative to complex **I**; in kcal/mol) are given in parenthesis.

In summary, in this study the chemical behaviour of geminal Lewis pairs has been extended to easily accessible N/B pairs. We carried out a systematic study on the impact of the steric effect on chemical behavior. The investigation indicated that while phenyl derivatives (**7a-b**) associated through intermolecular B-N bond, the *o*-tolyl derivatives (**8a-b**) afforded an intramolecular B-N dative complex. More interestingly, when mesityl groups were attached to the boron precursor (**9a-b**) a dyotropic rearrangement took place to gain stabilization in the geminal pair. Thus, the steric congestion was revealed by the exchange of the mesityl group with the neighbouring H atom. We examined this intramolecular rearrangement by DFT calculation, which suggested a quasi-stepwise mechanism, which is at the borderline with a concerted/asynchronous mechanism. These findings demonstrate the inherent capacity of germinal FLPs to promote dyotropic rearrangement and draw also the attention to the importance of the careful structural design of bifunctional frustrated Lewis pairs if one's goal is to develop efficient hydrogenation catalysts.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

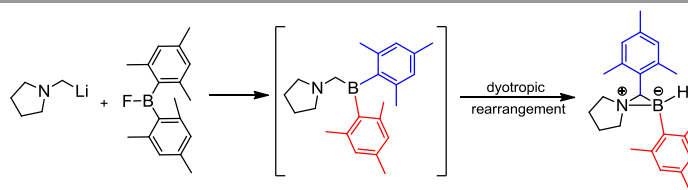
Acknowledgment

We are grateful for the financial support of the Lendület Program E13/11/2010. Financial support from the Hungarian Scientific Research Fund (OTKA, grant K-81927) is also acknowledged. We thank László Drahos of the Hungarian Academy of Sciences for measuring the high-resolution mass spectra. Eszter Varga is grateful to Bianka Kótai for her assistance in the initial phase of the computational work. The X-Ray diffractometer purchase grant from the National Office for Research and Technology (MU-00338/2003) is gratefully acknowledged.

References

- (1) Welch, G. C.; San Juan, R. R.; Masuda, J. D.; Stephan, D. W. *Science*, **2006**, *314*, 1124.
- (2) Recent reviews: (a) Stephan, D. W., Erker, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 46.; (b) Topics in Current Chem.: Frustrated Lewis Pairs I, Ed: Stephan, D. W., Erker, G., Springer Press, **2013**, Vol. 332; (c) Topics in Current Chem.: Frustrated Lewis Pairs II, Ed: Stephan, D. W., Erker, G., Springer Press, **2013**, Vol. 334.
- (3) (a) Theuergarten, E.; Schlüns, D.; Grunenberg, J.; Daniliuc, C. G.; Jones, P. G.; Tamm, M. *Chem. Commun.*, **2010**, *46*, 8561; (b) Chernichenko, K.; Nieger, M.; Leskelä, M.; Repo, T. *Dalton Trans.*, **2012**, *41*, 9029; (c) Holtrichter-Rößmann, T.; Rösener, C.; Hellmann, J.; Uhl, W.; Würthwein, E.-U.; Fröhlich, R.; Wibbeling, B. *Organometallics*, **2012**, *31* (8), 3272; (d) Zheng, W.; Pi, C.; Wu, H. *Organometallics*, **2012**, *31* (10), 4072; (e) Freitag, S.; Henning, J.; Schubert, H.; Wesemann, L. *Angew. Chem. Int. Ed.* **2013**, *52*, 5640.; (f) Stute, A.; Kehr, G.; Fröhlich, R.; Erker, G. *Chem. Commun.*, **2011**, *47*, 4288; (g) Rosorius, Ch.; Kehr, G.; Fröhlich, R.; Grimme, S.; Erker, G. *Organometallics*, **2011**, *30*, 4211; (h) Xu, X.; Kehr, G.; Daniliuc, C. G.; Erker, G. *J. Am. Chem. Soc.*, **2013**, *135* (17), 6465; (i) Bertini, F.; Hoffmann, F.; Appelt, Ch.; Uhl, W.; Ehlers, A. W.; Slootweg, J. Ch.; Lammertsma, K. *Organometallics*, **2013**, *32*, 6764; (j) Bertini, F.; Lyaskovskyy, V.; Timmer, B. J. J.; de Kanter, F. J. J.; Lutz, M.; Ehlers, A. W.; Slootweg, J. Ch.; Lammertsma, K. *J. Am. Chem. Soc.*, **2012**, *134*, 201.
- (4) Zhao, L.; Lu, G.; Huang F.; Wang, Z.-X. *Dalton Trans.*, **2012**, *41*, 4674.
- (5) Cox, Ph. J.; Doidge-Harrison, S. M. S. V.; Howie, R. A.; Nowell, I. W.; Taylor, O. J.; Wardell, J. L. *J. Chem. Soc., Perkin Trans. I.*, **1989**, 2017.
- (6) In the present study, the DFT calculations were carried out using the ω B97X-D functional. The energy values reported in the paper correspond to solution phase Gibbs free energies that are based on ω B97X-D/6-311++G(3df,3pd) electronic energies and all additional terms (thermal contributions and solvent effects) obtained at the ω B97X-D/6-311G(d,p) level. For further details, see Supporting Information.
- (7) For a review on dyotropic reactions, see: Fernández, I.; Cossío, F.; Sierra, M. A. *Chem. Rev.*, **2009**, *109*, 6687.
- (8) For a selection of recent theoretical mechanistic studies of dyotropic rearrangements, see: (a) Davis, R. L.; Leverett, C. A.; Romo, D.; Tantillo, D. J. *J. Org. Chem.* **2011**, *76*, 7167; (b) Leverett, C. A.; Purohit, V. C.; Johnson, A. G.; Davis, R. L.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 13348; (c) Fernández, I.; Bickelhaupt, F. M.; Cossío, F. P. *Chem. Eur. J.*, **2012**, *18*, 12395. (d) Gutierrez, O.; Tantillo, D. J. *J. Org. Chem.* **2012**, *77*, 8845.
- (9) Short H...H bond distances measured in the equilibrium structure of **III** are clear indications of the internal strain (see Supporting Information).
- (10) The computed free energy balance cannot be regarded as a very accurate prediction due to the inaccuracy of the present computational approach. The error bar on the relative Gibbs free energies reported in the present work is expected to be about 3-4 kcal/mol.

Short title: Frustration Induced Dyotropic Rearrangement



Manuscript submission checklist

- Statement of significance of work.
- Full mailing address, telephone, and fax numbers and e-mail address of the corresponding author.
- Graphical abstract.
- 5 key words.
- Original Word file.
- Original graphics files.

Proceed to submit your article via our online submission system at <http://mc.manuscriptcentral.com/synlett>. When prompted to "Add an Editor", please select the Editor who invited you to submit this Cluster article.