Final Research Report

1. Introduction

The metal-free catalytic applications, organocatalysis have initiated immense research interest over the last two decades.[1] Especially, the recent emergence of frustrated Lewis pair (FLP) chemistry[2] triggered a surge of upheavals as this approach can emulate transition metals in catalytic reactions. These approaches employ specific Lewis acid (LA) and a Lewis base (LB) combinations that are incapable of forming stable dative complex due to steric hindrance. Thus, a 'quasi-metastable' state arises that can be utilized for bond activations, as exemplified by their most striking applications: the challenging H-H and Si-H activations and subsequent catalytic applications.

To shift the laboratory curiosity into practical applications, we have recently introduced a novel LA catalyst design, the size-exclusion design, in FLP chemistry to avoid or minimize the unwanted side-reactions of the first generation FLP catalysts.[3] As a result, we could significantly expand the scope and utility of FLP chemistry, we could develop the first water tolerant catalytic system, metal-free reductive amination and etherification have been demonstrated, and even catalytic endo-selective Diels-Alder reaction has been realized.[4]

The present research program aimed to expand further the synthetic potential and practical utility of the second generation of FLP catalysts. As a result of our efforts and serendipitous discovery, a new family of FLP catalyst has been developed, which can be utilized for the partial reduction of esters to aldehyde. Most importantly, our catalyst seems to have potential in industry to replace diisobutyl aluminium hydride (DIBAL-H) for the challenging ester to aldehyde transformation, owing to high selectivity, cost efficiency, simplicity, robustness and the high TOF and TON of the developed catalysts.

2. Background of the research topic

Aldehydes are useful products in perfumery industry/agrochemistry or important intermediates of the preparations of fine chemicals especially in pharmaceutical industry.[5] As esters are easily available and relatively cheap starting materials, the selective reduction of an ester functional group to the corresponding aldehyde is one of the fundamental reactions in organic chemistry and is used in many large-scale chemical processes, but also in academic laboratories. The challenge in this transformation is to avoid the overreduction of ester to alcohols, thus, the reactions should halt at the acetal intermediates. Up until now, special hydride reducing agents were used for ester to aldehyde transformations, such as DIBAL-H or lithium tri-tert-butoxyaluminium hydride. However, the use of these reagents is known to be

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[1] a) https://www.nobelprize.org/prizes/chemistry/2021/press-release/. b) Organocatalysis: Stereoselective Reactions and Applications in Organic Synthesis, **2021** , Ed. M. Benaglia, De Gruyter. c) S.-H. Xiang, B. Tan *Nat. Commun.* **2020**, *11*, 3786 and ref. therein.

[2] a) D. W. Stephan *Science* **2016**, 354, 1248. b) Frustrated Lewis Pairs, **2021**, Eds. J.C. Slootweg, A. R. Jupp, Springer.

[3] G. Erős, H. Mehdi, I. Pápai, T. A. Rokob, P. Király, G. Tárkányi, T. Soós, *Angew. Chem. Int. Ed.*, **2010**, *49*, 6559.

[4] a) Á. Gyömöre, M. Bakos, T. Földes, I. Pápai, A. Domján, T. Soós, *ACS Catal.*, **2015**, *5*, 5366. b) M. Bakos, Á. Gyömöre, A. Domján, T. Soós, *Angew. Chem. Int. Ed.*, **2017**, *56*, 5217. c) É. Dorkó, M. Szabó, B. Kótai, I. Pápai, A. Domján, T. Soós, *Angew. Chem. Int. Ed.*, **2017**, *56*, 9512. d) M. Bakos, Z. Dobi, D. Fegyverneki, Á. Gyömöre, I. Fernández, T. Soós, *ACS Sustainable Chem. Eng.* **2018**, *6*, 10869.

[5] The Chemistry of the Carbonyl Group, **2018**, T. K. Dickens, S. Warren, Wiley.

costly as they are required to conduct the reactions at low temperature (typically -78°C) to minimize overreduction to alcohols. Additionally, these reagents show the disadvantage of high flammability, violent reaction with water liberating extremely flammable hydrogen, spontaneous flammability in air and challenging work up procedure. Nevertheless, when the overreduction to alcohol cannot be avoided with these two reagents, an indirect, two-step protocol has been used to obtain the required aldehyde: the overreduction of ester to alcohol that was followed by selective oxidation of alcohol to aldehyde[6] While this indirect approach is often the only option, it is far from being economic, as a result of poor redox economy.

Besides stochiometric reagent-based processes, catalytic reductions of esters to aldehydes are also known. Thus, several publications have described the use of silanes as alternative reducing agents for ester substrates, together with metal and even some non-metal catalysts. The preferred silane for these types of reductions was triphenyl silane (Ph_3SiH), diethyl silane (Et_2SiH_2) or triethylsilane (Et_3SiH).

In a pioneering work, Piers and coworkers reported the reduction of esters to silyl acetals with Ph_3SiH and a metal-free catalyst, tris(pentafluorophenyl) borane, $B(C_6F_5)_3$.[7] Although the process can be used for various substrates, these reactions were always accompanied with substantial overreduction (5-30%) to silyl ethers and even alkanes. Amongst the few metal-based catalyst or catalytic systems known to perform selective reductions of esters to silyl acetals,[8] it should be mentioned the Ir catalyst-based procedure developed by Cheng and Brookhart.[9] Compared to other metal-based catalytic systems, this method requires lower amount of catalyst, in the order of 0.1-0.5 mol% and as a reducing agent Et_2SiH_2. Nevertheless, this method uses a catalyst which is not only toxic, but also prohibitively expensive. Furthermore, the functional group tolerance was rather limited, e.g. ester substrates having olefinic functional group were not reported.

So, despite reagents and catalytic processes being known for the partial reduction of esters, there remains a clear need for alternative, broadly utilized, functional group tolerant and industrially acceptable reagents and processes for producing aldehydes from esters. Especially suited for this purpose are novel catalysts which enable processes to proceed with low catalyst loading, high conversion and high chemoselectivity for molecules containing an ester functionality and allowing the use of mild experimental conditions, without the exclusion of oxygen and humidity.

3. Results

For the present two-year research project, our point of departure was an interesting observation from our laboratory that a mesityl type, size-exclusion borane was able to promote the selective hydrosilylation of esters to silyl-acetals with triethylsilane (TESH) that can be hydrolyzed to aldehyde in a subsequent step (Scheme 1.).[10] Thus, a promising method was in our hand to effect aldehyde formation from ester. Despite the promising results,

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[6] a) D. B. Dess, J. C. Martin *J. Org. Chem.* **1983**, *48*, 4155. b) K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651. c) S. Barriga *Synlett* **2001**, 563.

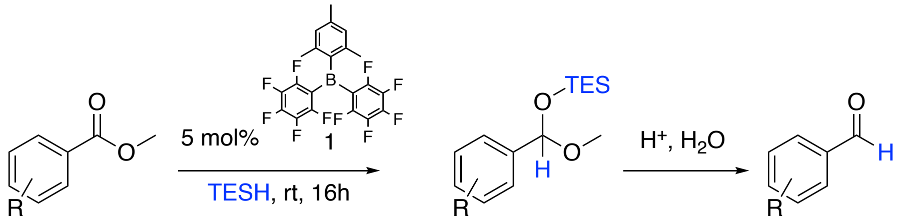
[7] D. J. Parks, J. M. Blackwell, W. E. Piers *J. Org. Chem.* **2000**, *65*, 3090.

[8] S. Hosokawa, K. Teramoto, Y. Motoyama *Chem. Select* **2018**, *3*, 2958. b) H. Li, L. C. Misal Castro, J. Zheng, T. Roisnel, V. Dorcet, J.-B. Sortais, C. Darcel *Angew. Chem. Int. Ed.* **2013**, *52*, 8045. c) D. Wei, R. Buhaibeh, Y. Canac, J.-B. Sortais *Chem. Commun*. **2020**, *56*, 11617.

[9] C. Cheng, M. Brookhart *Angew. Chem. Int. Ed.* **2012**, *51*, 9422.

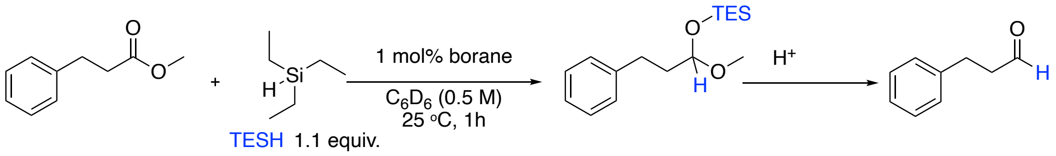
[10] D. Fegyverneki, Ph.D. thesis, **2018**, ELTE

however, the relatively high catalyst load and the rather extended reaction times indicated that there is a room for further developments.



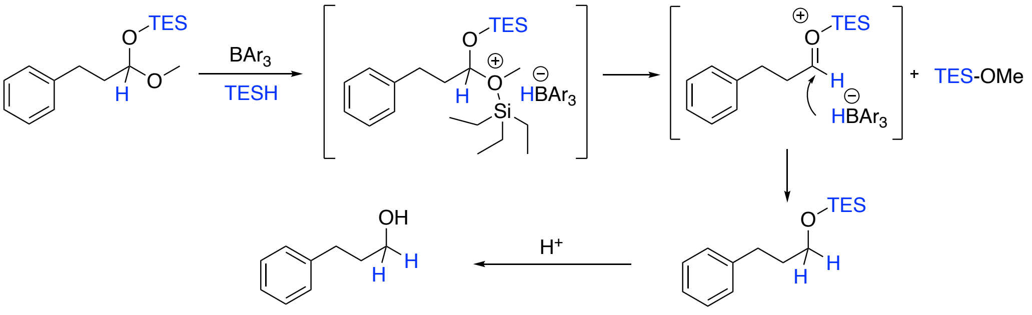
Scheme 1. Preliminary results for ester to aldehyde catalytic conversion

Thus, in this research initiative, we aimed to push the present boundary further and investigate the hydrosilylation reactions of esters using various frustrated Lewis-pair (FLP) borane catalysts with size-exclusion design. For a comparative study, methyl 3-phenylpropionate was chosen as a model compound and TESH (Scheme 2.) was selected as a reagent.



Scheme 2. Model reaction for evaluation various borane catalysts

From applicability and selectivity point of view, it is important to note that the preliminary test reactions indicated that the most significant side reaction was the overreduction of the silyl acetal to silyl ether (Scheme 3.). Thus, the more sterically accessible and basic oxygen atom (the methoxy moiety) of the mixed acetal could initiated a Si-H activation with the applied borane (BAr_3). After hydrolysis, the corresponding alcohol could be obtained from this silyl ether product.



Scheme 3. Overreduction of mixed silyl acetal

The suppression of this side reaction is almost as important as achieving high conversion and yield. This overreduction can be especially important in certain pheromone syntheses, as the purification of the alcohol side product is cumbersome for long chain, often unsaturated fatty acid derived sex pheromone aldehydes. The alcohol impurities are relevant, as most of them act as a behavioral antagonist, as Wang and coworkers have recently demonstrated.[11] Thus, the alcohol content of the reaction product cannot exceed a certain level in the final products for pheromone applications. Therefore, the suppression of overreduction (preferably having almost exclusive selectivity for silyl acetal formation) is often a key technological feature for relevant application areas.

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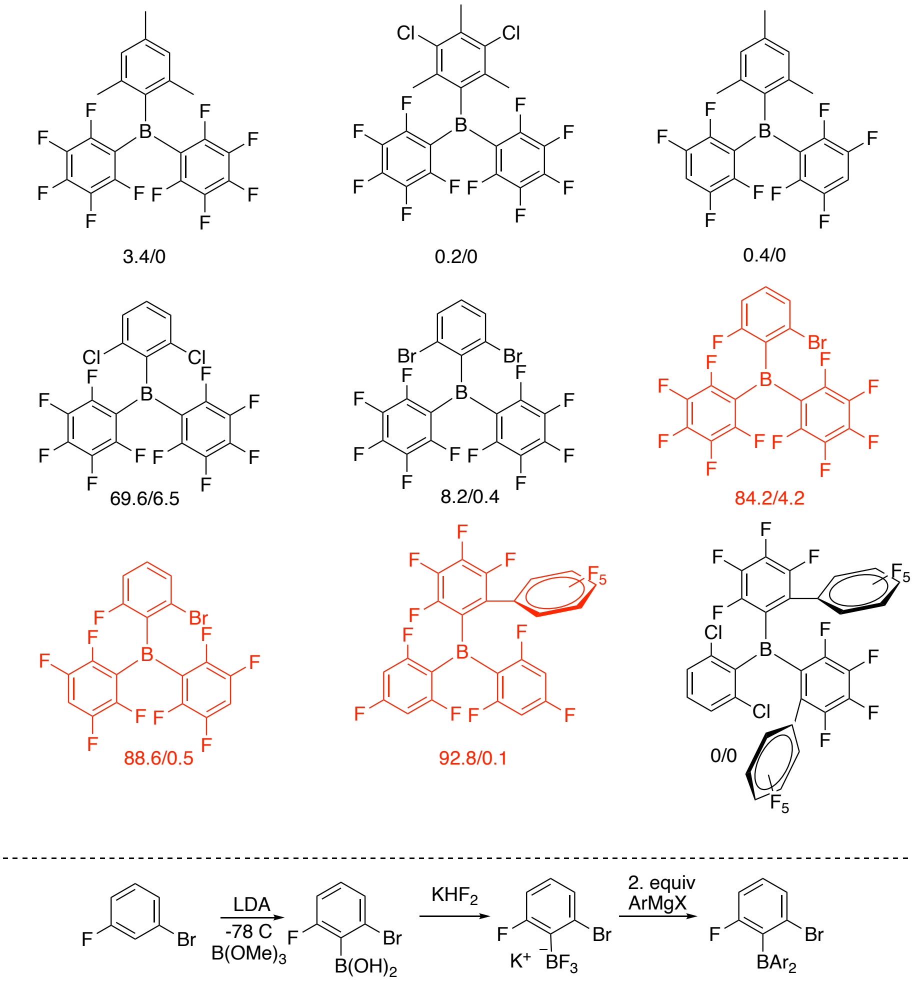
[11] M. Xu, H. Guo, C. Hou, H. Wu, L.-Q. Huang, C.-Z. Wang *Sci. Rep.* **2016**, *6*, 22998.

As a first goal, we tested various mesityl derivatives (Scheme 4.), thus, beside the original catalyst, we modified the electronic properties of these boranes via introducing chlorine substituents into the mesityl ring or changed the amount of fluorine atoms in the fluorinated rings. Under the test reaction condition, the original mesityl borane proved to be poor catalyst, only 3.4% yield was detected by NMR. Unfortunately, these modifications did not provide better results and indicated that neither substrate, nor product inhibition of the catalyst was the result of the poor catalyst activity. Then, we replaced the methyl group to isosteric chlorine atoms in ortho position (the ortho positions are related to the bond connecting to the boron atom) to enhance the Lewis acidity of the borane. This modification although resulted in a markedly enhanced reactivity (69.6% yield), nevertheless, the overreduction proved to be significant, around 10%. Thus, we decided to enhance further the steric crowding via introducing bromine atoms in ortho positions. Toward this goal, we had to develop first a synthetic route toward this challenging borane. Finally, an ortho-lithiation protocol afforded the required boronic acid derivatives and allowed to construct the targeted borane (analog general protocol, below Scheme 4.). Having this borane in our hand, we probed this highly congested system in the test reaction. Although the selectivity was better than that of the chlorinated catalyst, the catalyst activity dropped significantly.

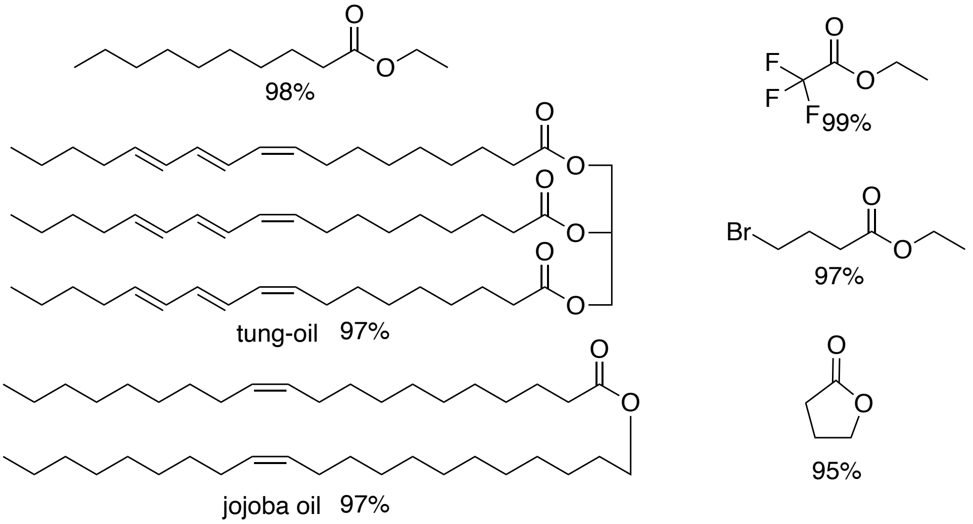


Scheme 4. Selected examples of evaluated catalysts and general procedure for the synthetic strategy to access triarylboranes.

Finally, we found serendipitously that the high selectivity and reactivity can be achieved by such triaryl borane type catalyst where the aryl groups have a special substituent pattern. Namely, in two of the aryl groups only small-size groups F atoms should be in the ortho positions while in the third aryl group there should be a small-size F atoms in one of the ortho positions and a large-size group (having larger steric demand) in the other ortho position (e.g. Br, C_6F_5). The other substituents have secondary importance, but they secure the optimal Lewis acidity character of the catalyst molecule. If not one, but two "non-symmetrical" aryl rings were introduced into the borane catalyst, even no activity was detected.

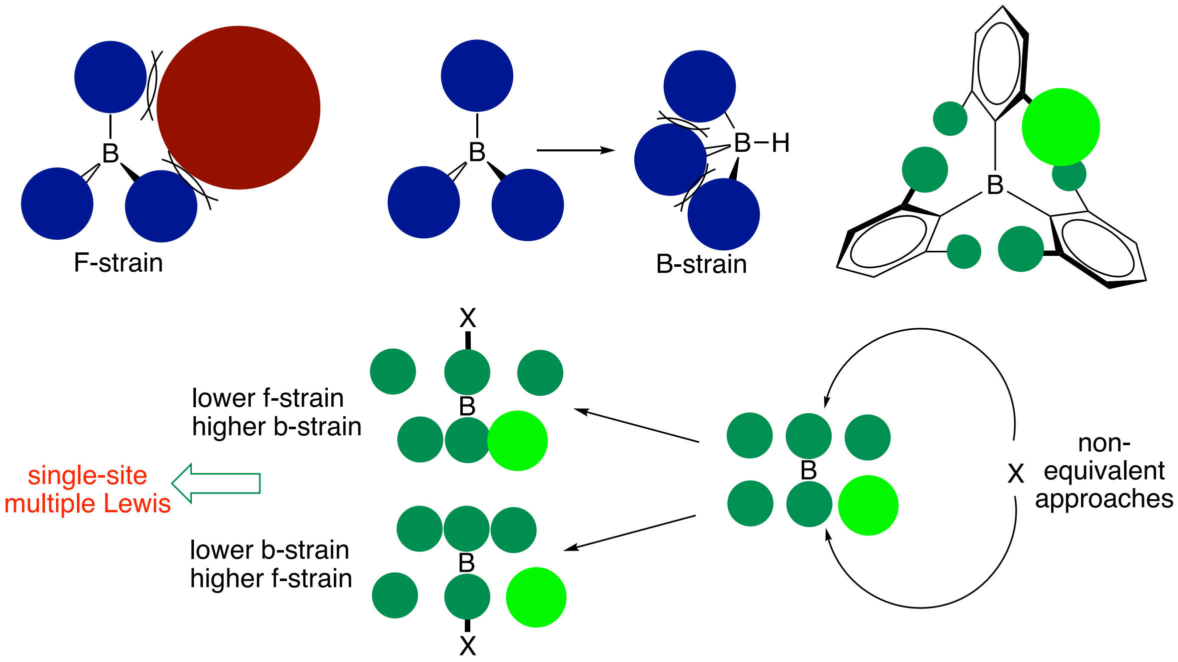
Triggered by the above findings, we continued the investigation of the catalyst load using the easily accessible BrF/F4 catalyst. As the applied reducing agent is a liquid, the reaction can be conducted without any solvent, thus, one can significantly lower the catalyst load. Using this simplified conditions, the reaction load was reduced to 0.01 mol% without corroborating the yield (although the reaction time was longer, 6h). Nevertheless, this catalyst load and efficacy are sufficient for industrial application.

Next the scope and limitation of this catalytic procedure was investigated (Scheme 5.). Due to the high selectivity, near perfect conversion and yield was achieved with long-chain fatty ester. Thus, there was no need for further purification of the crude reaction product after the acetal hydrolysis. This is not only cost efficient, but also practical issue, as for long chain aldehydes the purification is generally cumbersome. It turned out also that the catalyst tolerated various functionalities that tend to be reduced by metal-catalysts. These functionalities include olefin bonds, halogens. Importantly, no isomerization of the olefinic bonds was detected upon reduction. Most importantly near quantitative yield and selectivity was observed, even tung oil, as a natural triglyceride, could be directly reduced. In a similar manner, jojoba oil was reduced to the appropriate C-20 aldehyde. These result als indicate that the procedure tolerates methyl, ethyl, but more complex esters. Further studies indicated that conjugated esters gave not the aldehyde acetal product, as an 1,4 adduct instead of 1,2 addition occured. Moreover, certain functionalities can fully inhibit the catalyst, such as nitro, nitrile and sterically non-demanding amines, which observation indicates the limitation of this methodology.



Scheme 5. Selected examples of borane catalyzed partial reduction of esters.

Finally, we made efforts to understand why this special substitution pattern is required for high selectivity. After thoroughly studying the catalyst structure, an exciting proposition was raised that these effective boranes can display orientational anisotropy, as a result of steric crowdedness and non-symmetrical ortho substitutions (Scheme 6.).



Scheme 6. Orientational anisotropy, multiple Lewis acidity

Thus, they might have an unprecedented phenomenon: these boranes display multiple Lewis acidity. Owing to the large steric difference between the ortho substituents, the different steric repulsion is expected to be raised upon Lewis adduct formation. When the large group is located at the opposite face of incoming Lewis base then a lower facial strain but a larger back strain will evolved (so called buttressing effect would emerge). As a result, an energetically different and less stable adduct will form. Because of these special steric set up, not only different Lewis acidity exists, but also two chemically different B-H could form after Si-H activation. The preliminary theoretical work indicated that the silane is expected to be cleaved by the less crowded face of the borane (approaching from 3 fluorines face) which would result a less stable, more reactive, thus "spring-loaded" borohydride. So, after Si-H activation from the more accessible face, the transfer of the H^- to the carbonyl center would occur nearly without activation barrier. Thus, the half-life of active silylium intermediate is expected to be very low and the chances of isomerization (jumping into other O atoms), side-reaction seem to be negligible.

Along this line, a systematic joint theoretical-experimental study was undertaken to support the above proposition.[12] For the first time, we were able to prove that orientational anisotropy can indeed result unprecedented properties among Lewis acids, a single-site, but multiple Lewis acidity. The static and dynamic properties of the dative complex ensemble was also investigated by NMR spectroscopy and DFT computations. Notably, the buttressing effect influenced not only the thermodynamics but also the kinetics of the dissociative equilibrium and the conformational interconversion of the dative complexes. These findings supported the proposition we raised, and most importantly, might open new avenues for further catalyst developments.

In summary, a novel family of FLP catalyst has been serendipitously discovered and exploited for highly selective and efficient ester-to-aldehyde conversion. These catalysts are

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[12] Orientational Anisotropy and Buttressing Effect of Triaryl-Boranes: Illuminating their Janus type, multiple Lewis acidity. B. Kovács, M. Szabó, T. Földes, B. Kótai, É. Dorkó, T. Holczbauer, I. Pápai, A. Domján, T. Soós submitted

not only highly active and robust (allowing to reduce the catalyst load) but highly selective, only minimal overreduction can be detected. Due to the simplicity, practicality and efficacy of this novel catalytic methodology, we expect that our results will be used for ester-to aldehyde reactions in academic laboratories and very conceivable it will penetrate into industry.

Additional information: The serendipitous discovery of this novel family of boranes shifted the focus little bit in the second year, thus the transfer hydrogenation and investigation of water tolerant system topics received less attention in the second year and these project were continued using other funds later. However, the above advances have been served as a basis for 3 patents. The first patent was submitted in 18.12.2020 (P2000437, Triaryl borane catalysts and method for selective hydrosilylation of esters or lactones using said catalysts) to secure priority in this field. These developments followed by a special application of these catalysts on lipid synthesis (P2100257, An improved process for the preparation of cationic lipids and the relating novel intermediary compounds). Finally, the previous art was expanded and PCT was also submitted (PCT/HU2021/050073 Triaryl borane catalysts and method for selective hydrosilylation of esters or lactones using said catalysts) in 18.12.2021. Furthermore, a spin-off company was established to commercialize proprietary catalysts and methodologies. As expected, we could not publish any direct and indirect results (e.g Janus type multiple Lewis acidity) prior the publication date of the first patent, so the series of publications is targeted in the second half of 2022. Nevertheless, the first industrial application (500kg scale) has been realized in 2022 January.