Research Summary for K116150

Development of new activation concepts in catalysis

Tibor Soós

1. *Introduction*

The vision and the proposed research activity were planned to exploit and explore the synthetic potential offered by a simple concept, the metal free bifunctional catalysis. This fundamental, organocatalytic activation concept hold a great promise to provide solutions for various challenging synthetic problems and foster the expansion of chemical space. Along these lines, target oriented catalyst developments have been accomplished which allowed to solve challenging synthetic problems. The results of the 4 year endeavours can be categorized around three themes.

2. *Development of novel H-bonded organocatalyst.*

Organocatalysis, the application of small organic molecules to promote organic transformation, is still one of the frontiers of modern organic chemistry.[1] Owing to the proven capacity, efficiency and broad utility, organocatalysis has become the third branch of the enantioselective catalysis, besides enzymatic and organometallic ones. Despite the enormous development and expansion of the field, further catalyst developments were needed to exploit the full potential of this field.

As we have evolved a synthetic program around the bifunctional thiourea /squaramide organocatalysis,[2] our first aim was to improve the efficiency and selectivity of bifunctional H-bonded catalysts. We have envisioned several structural features and embarked on their synthesis. This work revealed that an often neglected element of the catalyst structure, the substituent attached to the squaramide part (away from the catalytic cleft), significantly improved the catalyst performance. Specifically, after systematic structural modification, we found that introduction of binaphtalenyl group resulted in an organocatalyst with markedly better chiral induction capacity

---

[1] a) Science of Synthesis: Asymmetric Organocatalysis, 1st Ed.; B. List, K. Maruoka Eds.; Thieme: Stuttgart, **2012**. b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304.

[2] a) B. Vakulya, Sz. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967. b) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151. c) B. Vakulya, Sz. Varga, T. Soós, *J. Org. Chem.* **2008**, *73*, 3475. d) G. Tárkányi, P. Király, Sz. Varga, B. Vakulya, T. Soós, *Chem. Eur. J.* **2008**, *14*, 6078. e) Sz. Varga, G. Jakab, L. Drahos, T. Holczbauer, M. Czugler, T. Soós, *Org. Lett.* **2011**, *13*, 5416. f) G. Kardos, T. Soós, *Eur. J. Org. Chem.* **2013**, 4490. g) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631. h) Sz. Varga, G. Jakab, A. Csámpai, T. Soós, *J. Org. Chem.* **2015**, *80*, 8990.

and higher TOF. This allowed to lower the catalyst load to 2-3 mol%. Furthermore, this novel catalyst proved to be general, thus it can be used in several reactions with superior performance.

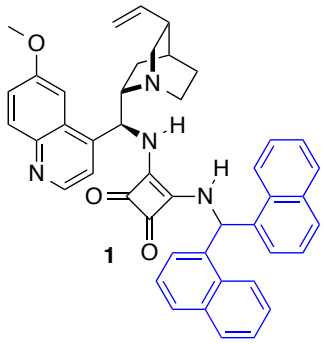


Figure 1. Novel binaphtalenyl organocatalyst **1**.

The first utilization of this advanced catalyst was to provide a new chiral building block for terpenoid chemistry. The *de novo* synthesis of terpenoids is a well-established discipline, however, apart from a few skeletal arrangements, their synthesis are still highly complex and challenging undertaking. The prominent element of these daunting challenges is the stereoselective construction of quaternary carbon stereocenters, of which terpenoids are richly endowed. These very features of terpenoids resulted in the frequent application of three key building blocks, the Hagemann's ester, the Wieland-Miescher ketone and the Hajós-Parrish ketone that have definite stereochemical and operational advantages in quaternary carbon stereocenter construction. We were intrigued to expand the list of easily accessible building blocks that might confer synthetic practicality in total synthesis of several decalin based terpenoids. Accordingly, we sought to identify synthetically exploitable structural subunits with quaternary carbon stereocenters in broad variety of sesqui- and diterpenoids, including drimanes, labdanes, clerodanes and kauranes. After deliberating over the list of biologically relevant targets, highly oxygenated cis- or trans-decalines **I** and **II** with contiguous stereocenters and suitable level of functionalities were selected (Figure 2). Accordingly, the goal that served to focus and unify our synthetic efforts was that of achieving a highly expedient and stereoselective synthesis of these chiral building blocks. This appeal was translated into expedient synthetic pathways, therefore it was envisaged that the decaline **I** and **II** structures could be assembled in a concise and divergent manner starting from cyclohexenones **2**.

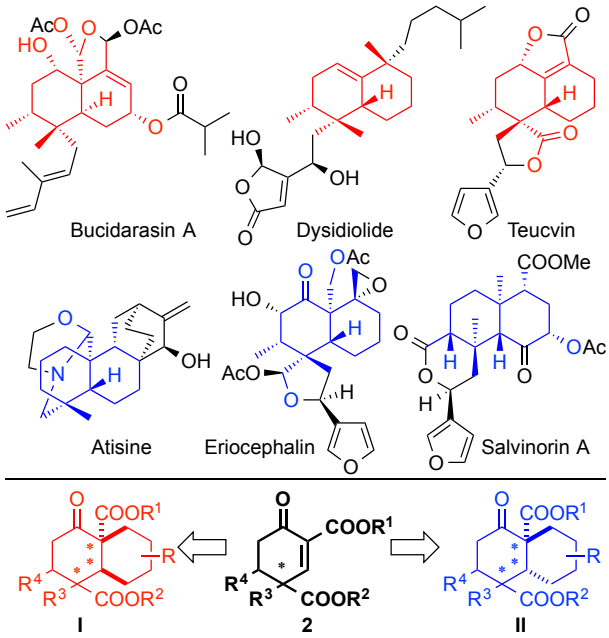
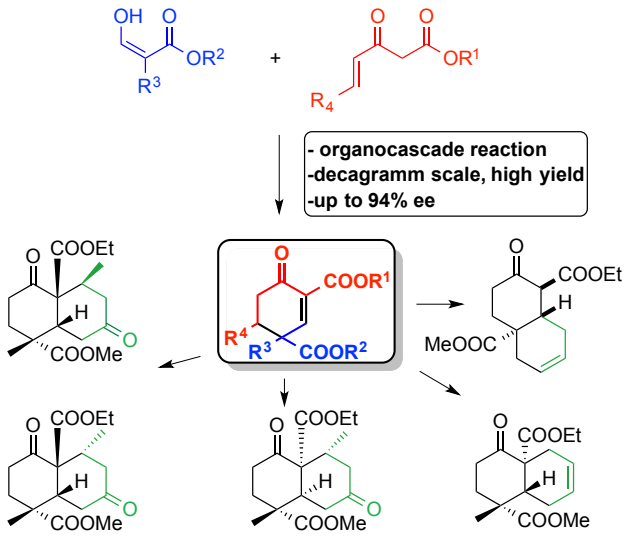


Figure 2. Selected examples of terpenoids having a decaline core and envisioned building block **2**.

As a critical step, an organocatalytic Robinson-type annulation of Nazarov reagent was realized that afforded cyclohexenones **2** bearing a quaternary carbon stereocenter (Scheme 1).[3] These chiral products have several useful synthetic features: (1) their synthesis is enantio-, diastereoselective and scalable (2) the stereogenic quaternary center of the scaffold allows exquisite diastereochemical control in the course of subsequent synthetic elaborations toward cis- and trans-decalines in multigram scale with contiguous quaternary and tertiary stereocenters. These rigid, polyfunctional three-dimensional scaffolds can facilitate the synthesis of many natural products and also be expected to be prime starting points for drug discovery program based on terpenoid-derived fragments.[3b,c] This work was published in Chemistry A European Journal in 2016 and used by our group in various total syntheses.

[3] a) B. Berkes, K. Ozsváth, L. Molnár, T. Gáti, T. Holczbauer, Gy. Kardos, T. Soós, *Chem. Eur. J.* **2016**, *22*, 18101. b) Sz. Varga, P. Angyal, G. Martin, O. Egyed, T. Holczbauer, T. Soós, ASAP in *Angewandte Chemie*. c) G. Martin, P. Angyal, O. Egyed, Sz. Varga, T. Soós, *Org. Lett.* ASAP.



Scheme 1. Organocatalytic Robinson annulation and access to terpenoid decalin cores.

As the above example demonstrates, the influence of organocatalytic platform reaches far beyond the domain of asymmetric methodology development; it has a profound impact on total synthesis owing to its unique capacity to deliver multifunctional scaffolds tailored to meet the needs of synthetic brevity. Interestingly, large efforts in this field have been devoted toward the use of meso or achiral cyclic anhydrides as inexpensive and easily accessible feedstocks (Figure 3). Despite the widespread success of these transformations, the substrate scope is limited to 5- or 6-membered cyclic anhydrides, a feature that can be attributed to both the aforementioned availability and their enhanced reactivity. Interestingly, the desymmetrization structurally similar bislactone-acylals was a neglected field, although this compound can be used in various total synthesis.

In a dual effort to extend the narrow breadth of acylal-based substrates and investigate the synthetic limitation of organocatalytic desymmetrization platform, we became interested to develop the asymmetric organocatalytic desymmetrization of the venerable Fittig's lactones **3** (Figure 3). We envisioned that these easily available γ,γ-bislactone-acylals could be converted to ring-opened product via organocatalytic activation. Our systematic study revealed that the same bifunctional cinchona squaramide **1** were the best available catalyst which is able to promote the cleavage of this bislactone in a highly enantioselective manner and deliver multifunctional chiral building blocks. To investigate the scope of the reaction, various Fittig's lactones were synthesized using a simple one-pot and scalable process. Then their organocatalytic ring opening was investigated with different alcohols, among which the methanol gave the best result. Notably, we employed the relatively cheap CH3OD as a nucleophile for ring opening reaction to validate and monitor any racemization process of the stereogenic center upon desymmetrization.

When lower ee was detected, we assumed that it was the result of the racemization of the stereogenic center, as extensive H-D exchange was observed by 1H-NMR. In summary, the previously narrow scope of bislactone acylal desymmetrization could be expanded toward substrates having sluggish reactivity. We expect this synthetic method to be adopted in total synthesis developments as an efficient platform to generate complex chiral intermediates.

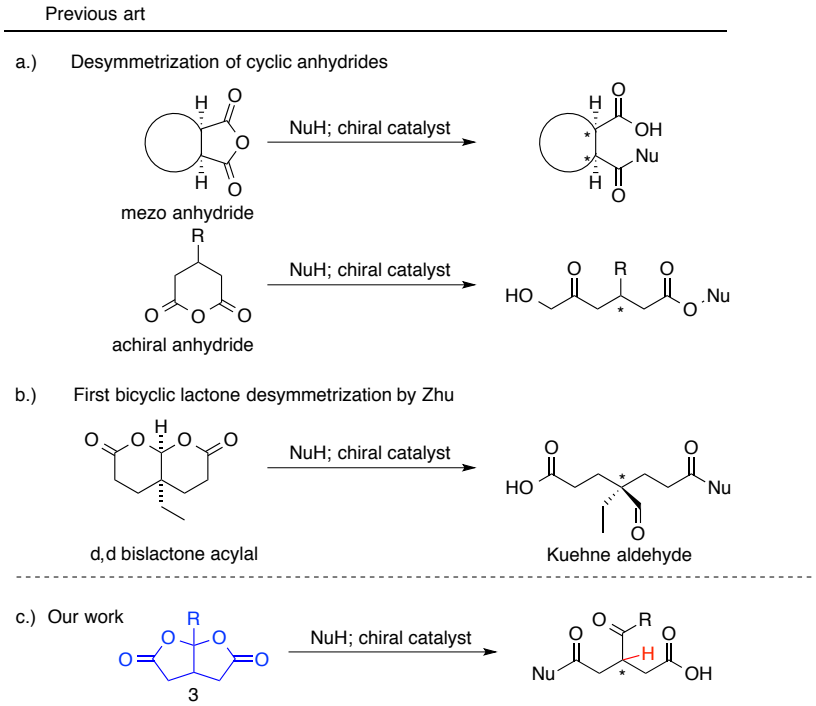


Figure 3. Organocatalytic strategies for desymmetrization of acyls.

It might be relevant to note that our work was published in a special, Golden Issue of Synthesis in 2019.[4] The journal celebrated its 50th anniversary, and we were invited to contribute to this special Synthesis Golden Issue.

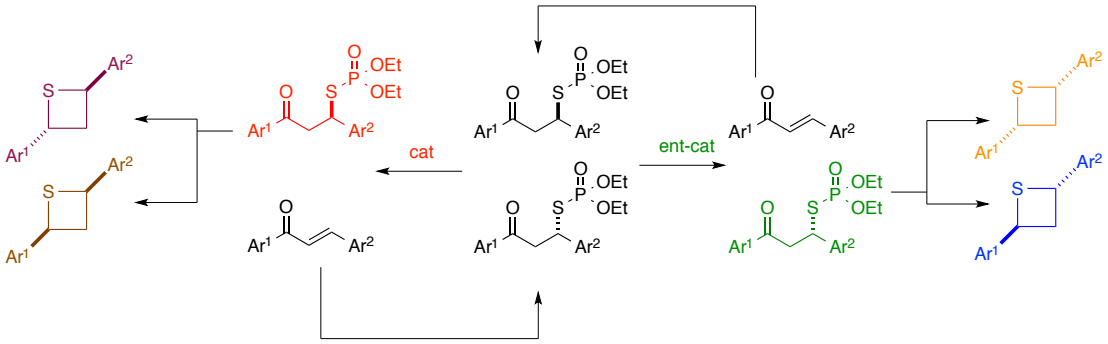
Since the inception of the bifunctional thiourea or squaramide organocatalysis, the primary focus had been to explore the catalytic conversion of achiral molecules into chiral ones. Accordingly, the transformation of chiral substrates in bifunctional non-covalent organocatalysis, even as a chiral intermediate of an organocascade reaction, had been comparatively scant as we demonstrated earlier.[2e,h] Among possible organocatalytic transformations, one could identify a still rather rare, but distinct class of strategic approach, the enantioselective stereoablative reactions. These processes deliver enantioriched compounds via destroying stereogenic elements. Despite being

[4] P. Spránitz, P. Sőregi, B. B. Botlik, M. Berta, T. Soós, *Synthesis* **2019**, *51*, 1263.

complexity reduction method, there can be several practical advantages that merited further exploration.

After several experiments, we could develop a catalytic stereoablative retro-sulfa-Michael reaction that was promoted by bifunctional thiourea catalysts (Scheme 2). Importantly, this was the first reported organocatalytic stereoablative process to the best of our knowledge. Furthermore, the synthetic utility of this chiral protocol was demonstrated via developing a concise and enantio- and diastereoselective synthesis of 2,4-diaryl-thietanes. In this approach, the stereoablative procedure was combined with CBS-reduction which afforded the diastereoselective synthesis of all possible stereoisomers of 2,4-diaryl thietanes.

This paper was also part of a special issue of Synthesis, dedicated to Prof. Dieter Enders on the occasion of his 70th birthday.[5]



Scheme 2. Development of stereoablative organocatalytic processes and utilization of diastereoselective syntheses of thietanes.

3. *Development of frustrated Lewis pair (FLP) catalysts*

In 2006, Stephan and coworkers disclosed a revolutionary bifunctional activation mode, the frustrated Lewis pair chemistry (FLP) which became a new paradigm in the cooperative small-molecule activation and catalysis.[6] Essentially, the FLP chemistry has empowered main group elements to emulate the frontier orbitals of transition metals, thus, it has significantly expanded the capacity of bifunctional, cooperative catalysis. This approach employs sterically encumbered Lewis acid-base pairs in which the steric hindrance impedes stable Lewis adducts formation. Accordingly, a "quasi-metastable" state emerges that can abruptly release the strain energy in the ensuing bond activation step.[7] Over the last 13 years, number of papers has been published in this area that chronicles the constant interplay between conceptual catalyst developments and exploration of FLPs reactivities.[6b]

---

[5] A. Bacsó, M. Szigeti, Sz. Varga, T. Soós, *Synthesis* **2017**, *49*, 429.

[6] a) G. C. Welch, R. R. S. Juan, J. D. Masuda and D. W. Stephan, *Science* **2006**, *314*, 1124–1126. b) D. W. Stephan, *Science*, **2016**, *354*, 1248.

[7] T. A. Rokob, A. Hamza, A. Stirling, T. Soós, I. Pápai, *Angew. Chem. Int. Ed.* **2008**, *47*, 2435.

Recently, we have introduced a novel design concept into FLP field, the size-exclusion concept to significantly improve the functional group tolerance of FLPs.[8]

In the present project, we aimed to expand further the utility of size-exclusion FLPs in synthetic chemistry. Specifically, steric factors were deliberately modified to solve key and fundamental chemical problems in challenging transformations.

After judicious fine tuning of F-strain in catalyst **3a,b** with chlorine substituents and electronic properties with fluorine subtituents, we explored this type of catalysts for metal-free reductive etherification using etheral type solvents as base (Figure 4). It was envisioned that these FLPs would have the ability to reversibly "turn on" Brønsted acid catalysis beside the FLP hydrogenation in the combined action of the appropriate Lewis acid and a weakly basic oxygen-based Lewis base on H_2, R-OH or H_2O. This *in situ* generated strong Brønsted acid then can promote the formation of acetals or ketals from aldehydes and ketones or other transacetalization process. Finally, acetals and ketals can be reduced by the FLP generated borohydride.

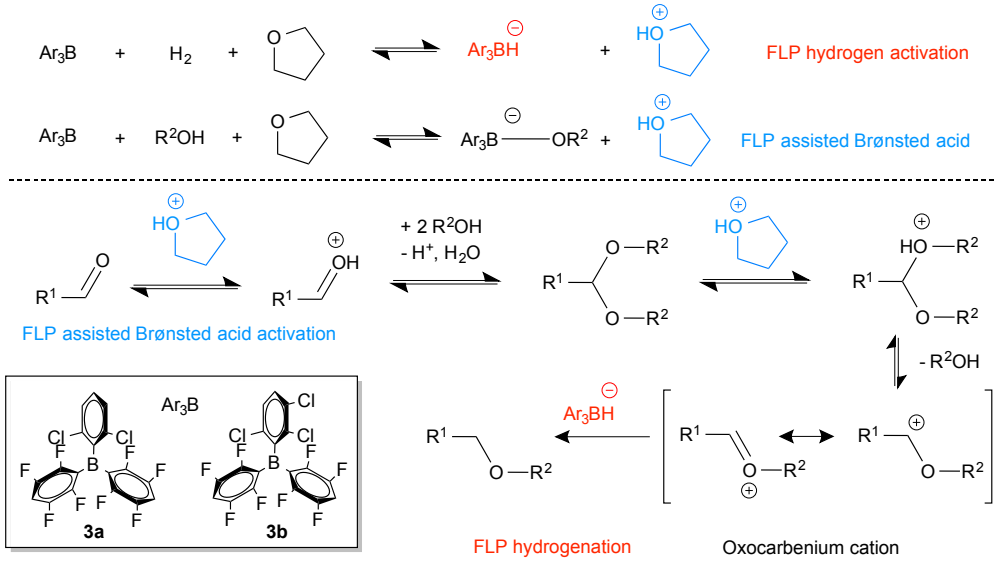


Figure 4. Proposed mechanism for FLP mediated reductive etherification.

Our approach proved to be successful, the deliberate combination of FLP hydrogenation and FLP-assisted Brønsted acid in an auto-tandem catalysis allowed us to develop a unique, metal-free reductive etherification protocol.[9] Numerous examples were presented to demonstrate that the process has a broad scope, functional group tolerance and selectivity. It should be also noted that this FLP-based reductive etherification method is not only a complementary metal-free approach, but also a niche procedure.

---

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

[9] M. Bakos, Á. Gyömöre, A. Domján, T. Soós, *Angew. Chem. Int. Ed.* **2017**, *56*, 5217.

It enables the synthesis of various ethers that would be either synthetically inconvenient or even intractable to access by alternative synthetic strategies (e.g. the Williamson ether synthesis from secondary or tertiary halides). The experimental ease of this methodology is also worth emphasizing as all of those reactions were set up in open-air, using technical grade solvents without relying on Schlenk techniques. Conceptually, this auto-tandem catalysis can be considered as an on–demand acid/reduction catalysis. In this context, the introduced FLP method established a starting point for further work in this area.

Next, an even more challenging transformation was probed the reductive FLP amination. The challenge stemmed from the fact, that water tolerance and functional group tolerance of FLPs had been limited to boron/oxygen centered FLPs, and the state of the art boron-based Lewis acids (LA) were, as it was previously claimed, fundamentally incompatible with water if more basic Lewis bases (LB), such as amines or phosphines are incorporated into the FLP hydrogenation catalyst.[10] This restrain was not merely a technical concern, but it represented a major obstacle to expand the utility of FLP hydrogenation toward hydrogenation-condensation tandem reactions when amine was applied.

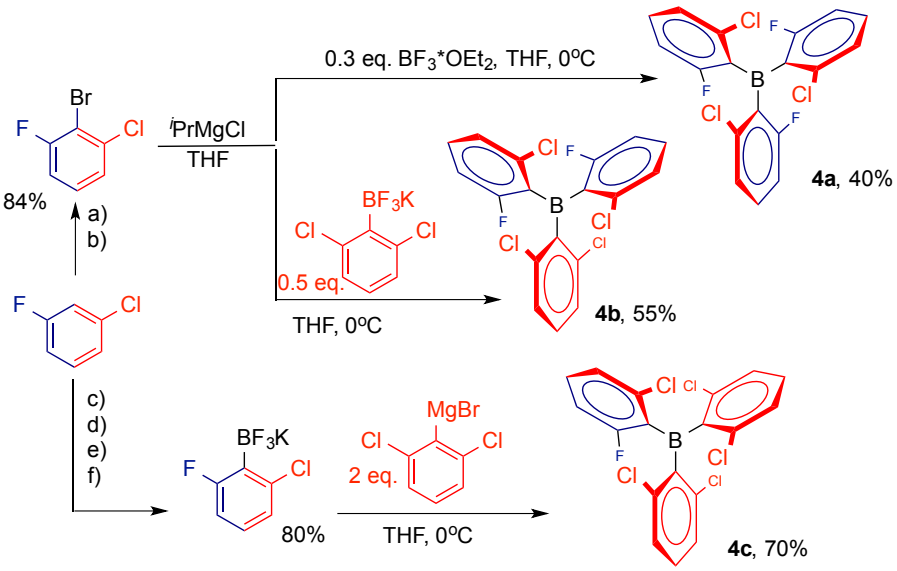


Figure 5. Synthesis of boranes **4a–c** with gradually varying front- and back-strains upon dative bond formation.

After a thorough physico-chemical study of novel chloro-fluoro boranes **4a–c** (Figure 5), we discovered that the modulation of back-strain is a critical design element to tackle one of key constrains of B/N centered FLP hydrogenation, the water inhibition.[11] While the enhanced front-strain of

[10] D. J. Scott, N. A. Phillips, J. S. Sapsford, A. C. Deacy, M. J. Fuchter, A. E. Ashley, *Angew. Chem. Int. Ed.* **2016**, *55*, 14738.

[11] É. Dorkó, M. Szabó, B. Kótai, I. Pápai, T. Soós, *Angew. Chem. Int. Ed.* **2017**, *56*, 9512.

boron-based Lewis acids secured size-dependent selectivity upon complexation, the growing back-strain (via F-Cl replacement) engendered the Lewis acid "spring-loaded" that makes water binding increasingly reversible. In this way, we could maintain the preferential hydrogen activation ability while suppressing the interference of the water with FLP (we created a pseudo soft Lewis acid by ligand design). The utility of this designer FLP catalyst was then demonstrated in reductive amination of various carbonyls. The method showed high chemoselectivity, it tolerated several functionalities that are prone to reduction, including chlorine, bromine, cyclopropyl, olefin and acetylene. Even the double methylation of primary amine was accomplished using the aqueous solution of formaldehyde. So, this novel metal-free method displayed a notable broad chemoselectivity and generality.

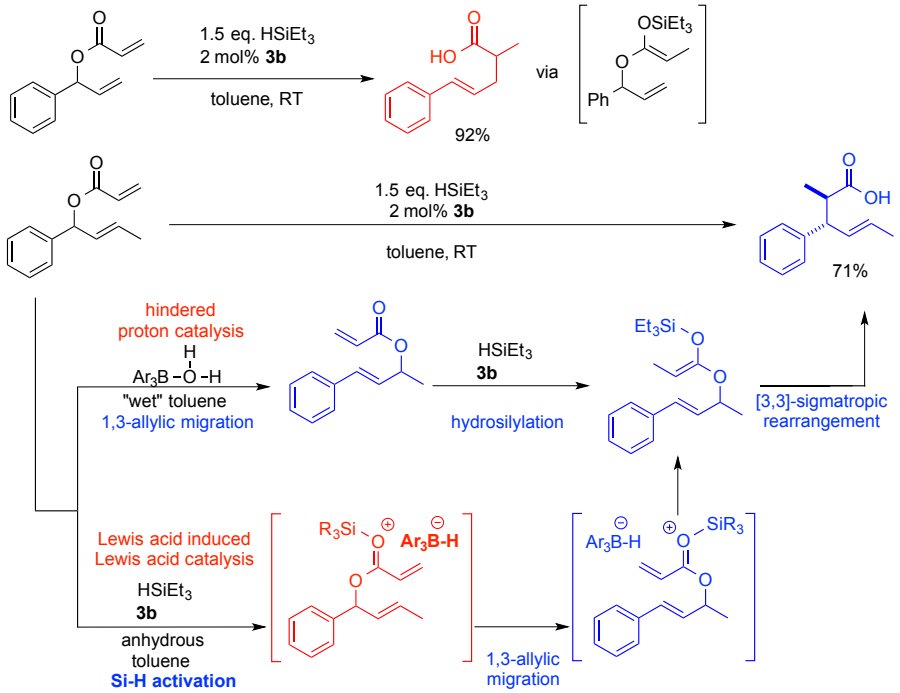
The above studies indicated that although the identity of the basic component can influence certain catalytic behavior, the primary challenge is to select the right Lewis acidic component for FLP hydrogenation. Therefore, methods to analyze and quantify the impact of steric and electronic properties of Lewis acids on their reactivity were needed to make a rational and informed decision upon FLP catalyst development. Along this line, the goal of the next study was to fine-tune the electronic properties of boron-based Lewis acids and identify trends across them that could accelerate the FLP catalyst development for imine hydrogenation. Therefore, a series of boranes with default sterical setting has been synthesized and their electronic properties were systematically varied and evaluated by various experimental and theoretical methods. More specifically, gradually substituting meta- and para-hydrogen atoms to fluorines or chlorines, a series of seventeen triaryl-boranes with a general $B(X_2Y)$ structure was generated (X and Y are halogenated aryl rings) for FLP hydrogenation and comprehensively characterized using combined experimental and theoretical methods.[12] As a consequence of our structural design, this series of boranes has a default sterical setting around the boron center and their electronic properties were gradually varied. As demonstrated, the venerable Gutmann-Beckett method had a limited capacity to gauge the Lewis acidity of these highly congested Lewis acids and correlate their FLP hydrogenation utility. Nevertheless, our study revealed that the calculated hydride affinity is a useful tool to quantify the electronic effects on Lewis acidity and predict the hydrogenation capacities of these boranes. As a general trend, the hydrogen-fluorine replacement in meta-positions resulted in a significant enhancement of Lewis acidities, however, the H/Cl replacements on the bulkier aromatic ring have only negligible effects. These observations revealed important properties

[12] É. Dorkó, B. Kótai, T. Földes, Á. Gyömöre, I. Pápai, T. Soós, *J. Organomet. Chem.* **2017**, *847*, 258.

affecting Lewis acidity and FLP reactivity and can guide future catalyst developments.

As it was envisioned in the proposal, the FLP mediated Claisen reaction was investigated. More specifically, its most popular and general variant, the Ireland-Claisen rearrangement was targeted. We assumed that the our FLP borane catalyst **3a,b** would promote both the 1,4-hydrosilylation of allyl acrylates and also the rearrangement of the formed silyl ester enolate to afford the appropriate Ireland-Claisen product in a one-pot manner. Additionally, it was expected that utilization of boron-based catalyst would be advantageous as these metal-free catalysts exhibit different chemoselectivity and functional group tolerance than transition metal catalysts in alternative reductive processes.

After a systematic study, a metal-free, one-pot reductive Ireland-Claisen rearrangement had been developed (Scheme 3).[13] With the applied air and moisture tolerant borane Lewis acid **3b** a two or three-step tandem reaction cascade could be processed to form the Claisen products with good yields and high diastereoselectivity. As the *syn* diastereomer product proved to be the major product of the reaction, the 1,4-hydrosilylation step should form the Z-enolate respectively, which preference is the opposite of the metal catalyzed alternatives.



Scheme 3. Hydrosilylation/ Ireland-Claisen tandem reactions forming classical and formal valence isomer products

[13] D. Fegyverneki, N. Kolozsvári, D. Molnár, O. Egyed, T. Holczbauer, T. Soós, *Chem. Eur. J.* **2019**, *25*, 2179.

The utilization of designer boron Lewis acid **3b** represented not only a metal-free alternative, but alleviated various restrictions of previous rearrangements, thus, the synthetic manipulations could be performed at the laboratory bench without the reliance and dependence on glove box and there was no need for purification of the solvent and reagents. Since the method requires mild reaction conditions, it establishes a practical alternative over the traditional Ireland-Claisen methods.

The previous developments demonstrated the unique capacity of sterically overcrowded boron Lewis acids in various challenging transformations. Nevertheless, those catalyst facilitated the formation of compounds along the favored routes. Thus it seemed a rather challenging undertakings to reroute the reaction pathway toward disfavored products. This challenge triggered us to exploit further the FLP chemistry and reroute the known endo-selectivity of Diels-Alder reaction.

Albeit the major application of Lewis acids is to facilitate the formation of endo product in Diels-Alder reaction, some specific Lewis acids have been developed to reverse the endo/exo selectivity. In these efforts, a primary breakthrough was the discovery that the steric bulk was a critical structural element of the developed catalysts. It was conceived that the steric repulsion restricted the conformational possibilities of the Lewis acid-dienophile complex, reduced the number of competing transition states, and destabilized the endo-transition state. Thus, the combination of these factors together rendered the reaction exo-selective. The sterical encumbrance of the catalyst was also recognized as the causative effect for exo-selective Diels-Alder reaction of enals. The bulky $B(C_6F_5)_3$ Lewis acid, the archetypical Lewis acid component of frustrated Lewis pairs (FLP), showed inverse endo/exo selectivity as compared to common Lewis acids such as $BF_3{\cdot}Et_2O$, or $AlCl_3$.[14] However, the theoretical calculations by Fernández and coworkers on this reaction revealed that the observed selectivity switch was not the result of the previously envisaged steric destabilization of the endo-transition state, but the occurrence of a significant CH···F non-covalent interaction between the reactants along the exo pathway.[15] Most importantly, the calculations suggest that fluorine atoms in ortho position have a decisive contribution to the stabilization of the exo-transition state.

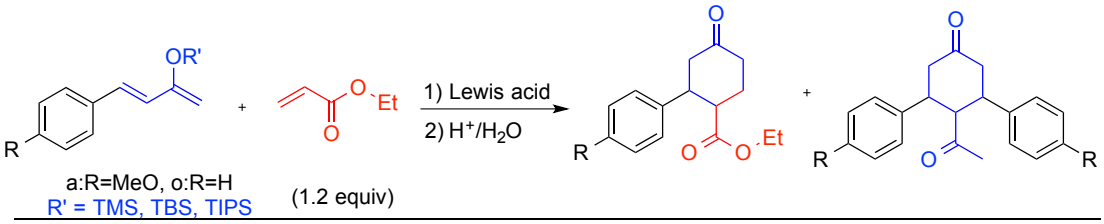
This alternative, steric attraction driven mechanistic rationale triggered us to exploit our size-exclusion Lewis acids, that we originally developed for FLP hydrogenation. Our further attempt was to expand the exo-selective Diels-Alder reaction in substrate scope. We aimed to explore easily available, synthetically useful, but still challenging substrates. Previous research has shown that the substitution pattern of the diene influences the selectivity, i.e.

---

[14] J.-H. Zhou, B. Jiang, F.-F. Meng, Y.-H. Xu, T.-P. Loh, *Org. Lett.* **2015**, *17*, 4432.

[15] D. Yepes, P. Pérez, P. Jaque, I. Fernández, *Org. Chem. Front.* **2017**, *4*, 1390.

lack of terminal substituents on the "butadiene" core typically led to endo-preferred reaction. As we aimed to revert this type of selectivity, we chose to examine the selectivity of silyloxy dienes in the test reaction. Furthermore, ethyl acrylate was selected as dienophile because such a low reactive substrate has not been proved as a competent substrate in Lewis acid promoted exo-selective Diels-Alder reaction (Scheme 4).



Scheme 4. Model reaction to test the size exclusion borane mediated exo-selective Diels Alder reaction.

After a systematic structural optimization of the catalyst, we could suppress the formation of unwanted diene dimer and reroute the original endo selectivity.[16] The selected catalyst proved to be competent catalyst for various dienes having electron-donating and deficient substituents on the aryl ring. To our delight, even dienes with heteroaromatic groups (thiophene, furane) could be also applied in this catalytic reaction. As the calculations suggest, the key to the success of exo selectivity was the enhanced steric hindrance around the catalytic center which engendered steric attraction for substrates and helps to reroute the reaction along a higher energy pathway. We anticipate that these Janus face behaviour can result in the further valorization of exo-selective Diels-Alder reaction and trigger to unlock even more of its potential in organic synthesis and medicinal chemistry.

4. Miscellanous results

Over the last four year, the principal investigator has been involved in other organic chemistry driven project of his group. As a result, 4 additional papers have been published in the last four year. Importantly, these work are only tangential to the subject of the proposal, therefore their detailed presentation is omitted.

[16] M. Bakos, Z. Dobi, D. Fegyverneki, I. Fernandez, T. Soós, *ACS Sustainable Chem. Eng.* **2018**, *6*, 10869.