Organocatalysis in The Synthesis of Indole Alkaloids

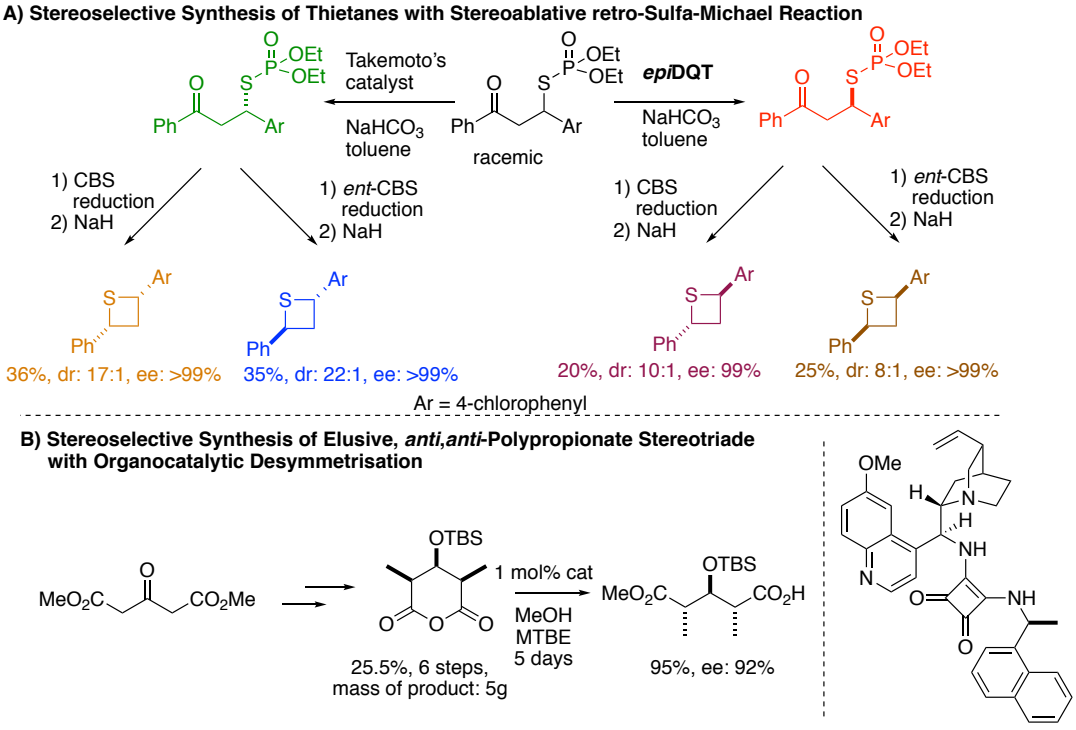
Introduction

The field of organocatalysis is nowadays counted as one of the most popular research areas. As indicated by the name, these catalytic processes use small, metal-free molecules, also called micro enzymes.[1] The most remarkable achievements of organocatalysis are connected to asymmetric reactions. Although this field of research is relatively new, the simplicity of the synthetic reactions and the wide scope of application raised its reputation, and by now, instead of remaining an auxiliary beside the widely-applied metal-based catalysis, it has become a strong competitor. Furthermore, the asymmetric organocatalysis is a powerful method for the synthesis of new chiral compounds, using catalysts from renewable sources.
Our research programme focused on the development of asymmetric organocatalytic transformations and their application in the synthesis of indole alkaloids.

Results

Development of Asymmetric Organocatalytic Transformations

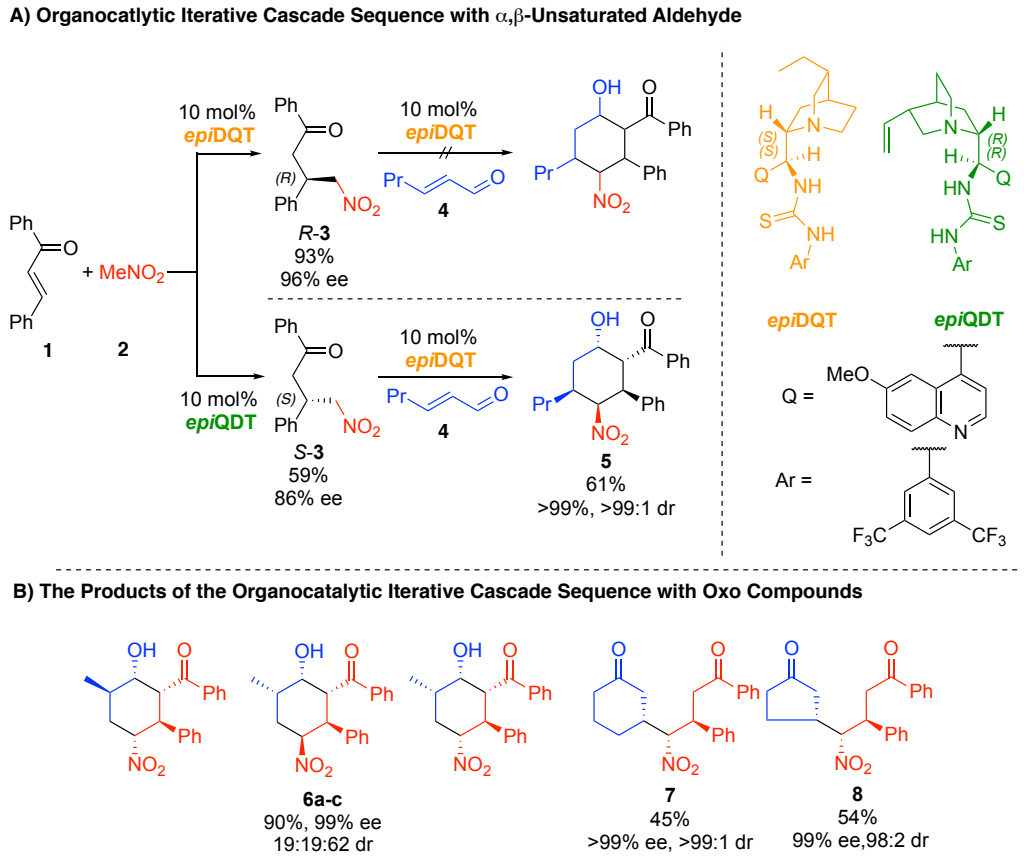
An important part of catalyst development is to show the applicability of the new catalysts. Based on the literature we used our bifunctional catalyst primarily in conjugated addition with carbon nucleophiles. We have also tried to expand the scope of the application of catalysts to sulfa-Michael additions[2], however, the process showed no significant enantioselectivity. This experience encouraged us to use the specific chiral recognition of the bifunctional catalyst. We have designed a retro-Michael based stereoablative process[3] in order to synthesise chalcone-thiol adducts, which are good starting materials to stereoselectively assemble chiral thietanes. The non-covalent cinchona-based bifunctional organocatalyst has a unique capacity to activate and organize the substrates via oxyanion-hole-like hydrogen bond network.[4] [1] Based on this activation mode we performed the synthesis of polypropionate stereotriads[5] via organocatalytic desymmetrisation on gram-scale, using only simple control methods. This approach is a new, scalable synthesis of the elusive, *anti*, *anti*-stereotriads from simple starting materials.



Scheme 1. Using Organocatalysis in the Synthesis of Chiral Building Blocks

[1] *Enantioselective Organocatalysis: Reactions and Experimental Procedures* (Ed. Peter I. Dalko), Wiley-VC, Weinheim 2007.
[2] (a) Enders, D.; Lüttgen, K.; Narine, A. A. *Synthesis*, **2007**, 959.; (b) Chauchan, P.; Mahajan, S., Enders, D. *Chem. Rev.* **2014**, *114*, 8807.
[3] (a) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924.; (b) Mohr, J. T.; Ebner, D. C.; Stoltz, B. M. *Org. Biomol. Chem.* **2007**, *5*, 3571.
[4] Kótai, B.; Kardos, Gy.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. *Chem. Eur. J.* **2014**, *20*, 5631.
[5] Hoffmann, R. W. *Angew. Chem. Int. Ed.* **1987**, *26*, 489.

One of the impressive applications of the asymmetric organocatalysis would be the construction of complex molecules via domino or cascade reactions. The bifunctional thiourea catalysts have seen much less utilization in organocascade reactions. Thus, it would be of interest to know whether a mechanistic reason exists behind this apparent discrepancy. To examine the potential of our catalyst in organocascade reactions we designed a Michael-Michael cascade addition, but only the first step was successful. We supposed that the incapacity of catalyst for the second Michael addition arose from an intriguing situation of double diastereocontrol.[6] To test the validity of double diastereocontrol we used the pseudoenantiomer of the quinine based thiourea catalyst for the second step. To our delight, the enantiomerically enriched Michael adduct, isolated after the first step, underwent a smooth catalytic reaction with nitroolefins.[7] The scope of the cascade reaction was extended to more challenging, less electrophilic α,β-unsaturated oxo compounds (**4**). The bifunctional organocatalysts were able to induce a Michael addition onto a α,β-unsaturated aldehyde (**4**) and then promote a direct intramolecular aldol reaction to selectively furnish the *syn*-ketocyclohexanol (**5**, **6a-c**). The selective ketol addition was explained by the well-defined transition state in the catalytic cleft of bifunctional organocatalyst. The scope of electrophiles was also expanded to α,β-unsaturated ketones, but in this case the second step was only a diastereoselective Michael reaction and the products contained acyclic stereotriads (**7**, **8**). [2]



Scheme 2. Using Organocatalysis in Iterative Cascade Reactions

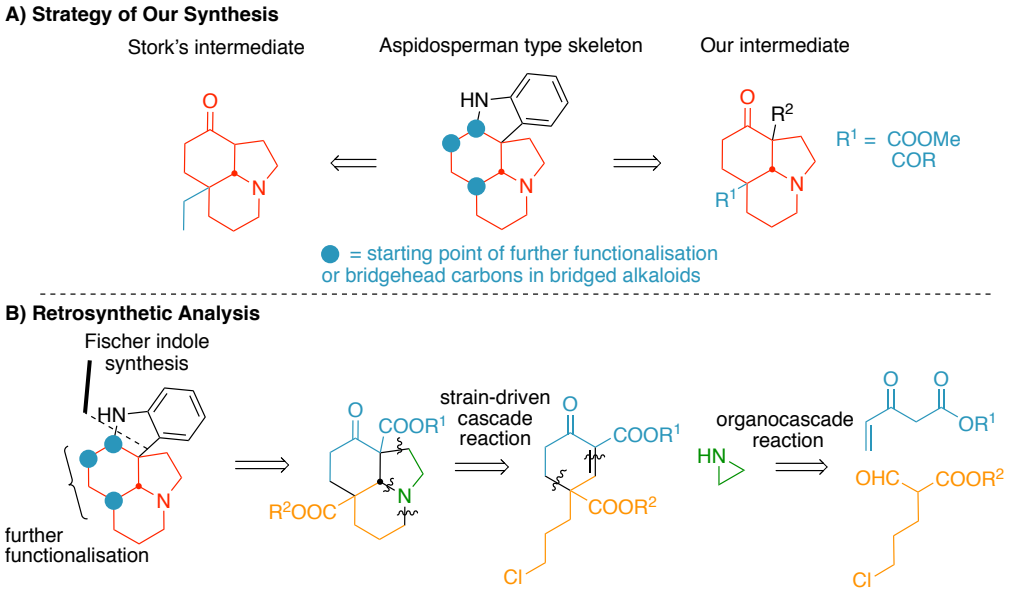
[6] (a) Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis,* University Science Books, Sausalito, CA, 2009.; (b) Sharpless, K. B. *Chem. Scr.* **1985**, *25*, 71.; (c) Masamune, S.; Choy. W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed.* **1985**, *24*, 1.

[7] Varga, Sz.; Jakab, G.; Drahos, L.; Holczabuer, T.; Czugler, M.; Soós, T. *Org. Lett.* **2011**, *13*, 5416.

Synthesis of Aspidosperman Type Alkaloids via Cascade Reactions

An important direction of modern total synthesis is to find a more efficient, economic and concise route to natural products and their analogues.[8] One of the most promising answers to this problem is the application of cascade reactions. This approach gives a powerful tool to increase rapidly the molecular complexity, since it involves several bond-forming transformations that take place under the same conditions in one-pot.

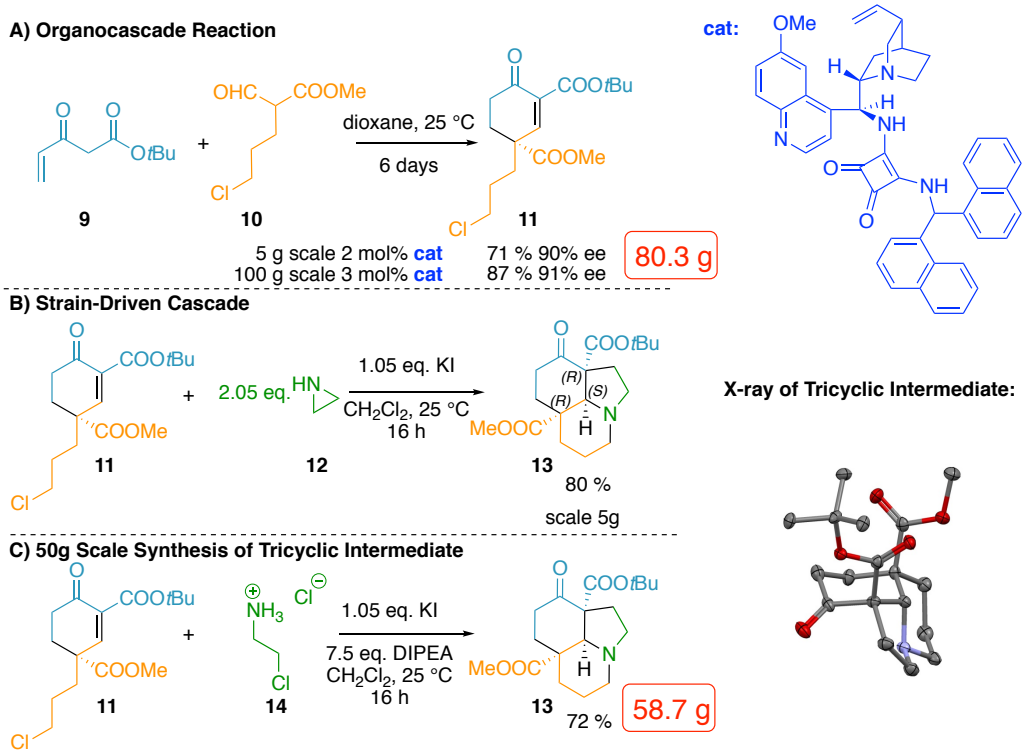
Monoterpenoid indole alkaloids are evergreen targets of organic synthesis, not only owing to their biological activity but their syntheses have been demonstrated the state of the art of synthetic methodology as well.[9] We designed a divergent synthesis of Aspidosperma type alkaloids using a cascade route. Our synthetic plan focused on expansion of the classical Stork's approach[10] to complex, oxidised and bridged monoterpene indole alkaloids. (Scheme 3A) The key intermediate of the planned synthesis is a tricyclic compound, which contains oxidised side chain (R^1), and it is the starting point of the Fischer indolisation and further functional group interconversions to assemble natural products. To construct the advanced key intermediate, we designed to use consecutive cascade reactions and start from simple starting materials. (Scheme 3B)



Scheme 3. Strategy and Plan to Synthesis Aspidosperman Type Alkaloids

The essential requirement of an efficient and divergent natural product synthesis is the scalable synthesis of the key intermediate. To solve this problem, we chose as starting materials simple, bifunctional compounds (the **9** Nazarov's annulation reagent[11] and the **10** formylester compounds[12]) and transformed them in an organocascade reaction to synthesise the **11** cyclohexeneone. The yield and enantioselectivity was high on small, as well as on large scale (Scheme 4A). To form the **13** tricyclic intermediate, the second step was a strain-driven cascade reaction, in which the source of *N* and ethylene moiety was the aziridine (**12**). The substitution–Michael–ring-opening–ring-closing process gave diastereoselectively the **13** key intermediate with good yield (Scheme 4B). To implement the scale-up synthesis of the **13** intermediate, the harmful and explosive aziridine needed to be replaced and we used the 2-chloroethylamine hydrochloride (**14**), which is the precursor of aziridne. Thus, we achieved the synthesis of the **13** key tricyclic compound, which is an advanced analogue of the Stork's intermediate, on ca. 50 g scale with high enantio-, and diastereoselectivity in two steps. The relative and absolute configuration of the **13** tricyclic diester was validated with NMR spectroscopy and X-ray crystallography. (Scheme 4C)

[8] Hayashi, Y. *Green. Chem.* **2016**, *7*, 866.
[9] Lopchuk, J. M. in *Progress in Heterocyclic Chemistry*, Vol. 23 (eds. Gribble, G. W.; Joules, J. A.) Elsevier, Oxford, 2011, pp 1.
[10] Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872
[11] Zibuck, R.; Streiber, J. *Org. Synth.* **1993**, *71*, 236.
[12] Nakatsuji, H.; Nishikado, H.; Ueno, K.; Tanabe, Y. *Org. Lett.* **2009**, *11*, 4258.



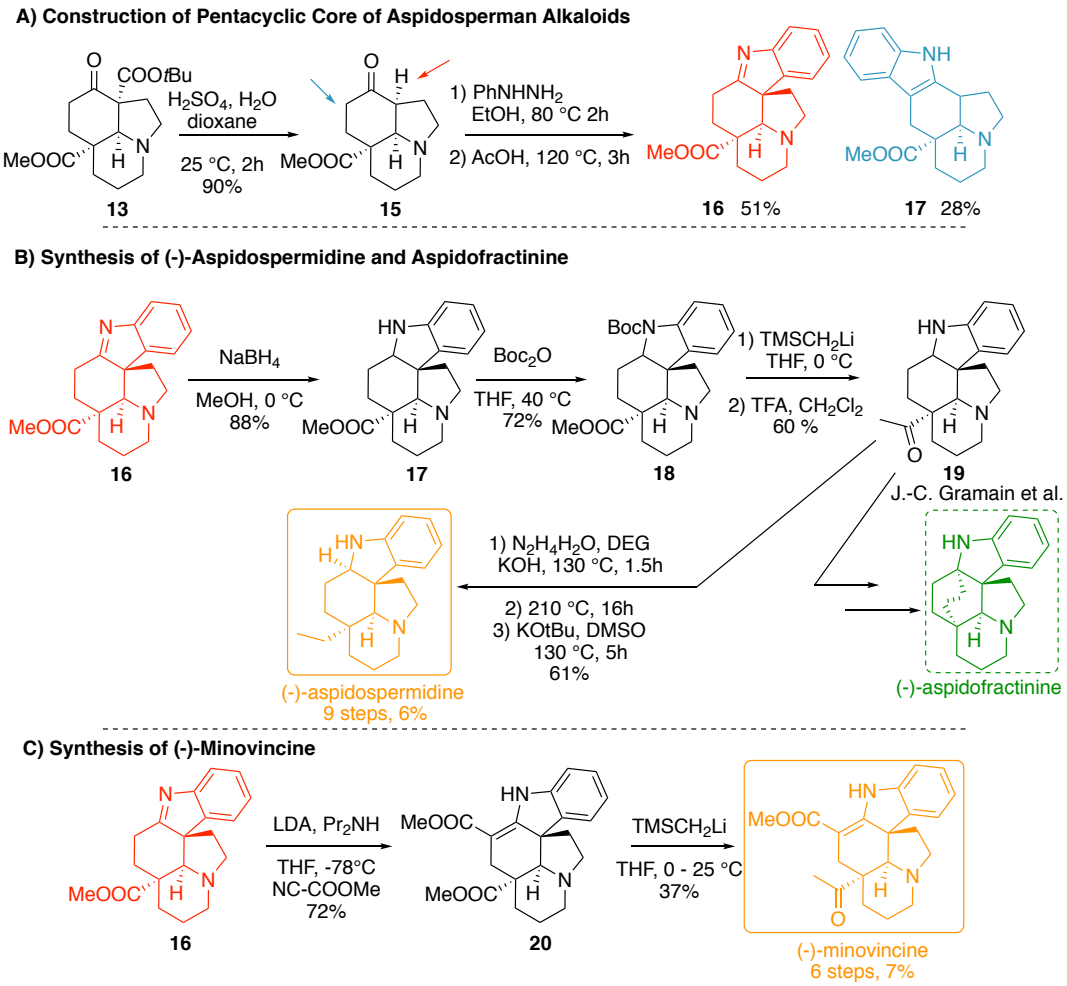
Scheme 4. Assembly and Structure of the Key Intermediate of our Synthesis

The second part of our synthetic programme was to transform the key intermediate to the pentacyclic aspidosperman skeleton and complete the synthesis of natural products. Firstly, the tertiary butyl ester group, which was the activating group in the first two cascade steps, was removed with acidic cleavage. Secondly, the core was formed with Fischer indolisation, in which the regioselectivity was not so high, despite the accurate optimisation (different solvent, acids, additives, temperature, etc.). (Scheme 5A)

In the end game, we used the **16** pentacyclic indolene compound as a point of divergence of our synthetic route. After the reduction of carbon-nitrogen double bound, to interconvert the ester moiety to keto group, trimethylsilyl-methyllithium was used at 0 °C. Althoughr, this method was an efficient way to form the desired product, the acidic NH group had to be protected to avoid the decomposition of the starting material. We chose BOC as an easily accessible and cleavable protecting group. After the deprotection of NH group, we wanted to reduce the oxo group to methylene moiety. This reaction required special conditions, on one hand only a narrow scope of reagents is known in the literature to perform that transformation, on the other hand this functionality is at a sterically hindered position. We tested several conditions and the best results were obtained with a modified Huang Minglon-Cram method. Therefore, we finished a concise synthesis of (-)-aspidospermidine with overall 9 steps and 6% yield. The optical rotation of the product matched the absolute configuration, which has been shown the X-ray structure of the **13** key building-block. The **19** keto compound was also an intermediate of the formal synthesis of (-)-aspidofractinine, which synthesis could be finished based on the literature[13]. (Scheme 5B)

The (-)-minovincine, which was described as a "biogenetic turntable" between the vindoline and kopsinine type alkaloids, was also chosen as a target molecule of our synthetic route. It was assembled from the **16** indolene derivative in two steps. In the first step, the second ester group was introduced with Mander's protocol, with good yield. After using a special charge control, we synthesised the (-)-minovincine with trimethylsilyl-methyllithium. In this case, the negative charge of deprotonated NH deactivated the less hindered carboxylic esters and resulted a selective transformation. Thus, we synthesised the (-)-minovincine with overall 6 steps and 7% yield, which is the third asymmetric and the shortest synthesis in the literature.[14] (Scheme 5C) [3]

[13] M. Dufour, J.-C. Gramain, H.-P. Husson, M.-E. Sinibaldi, Y. Troin *Tet. Lett.* **1989**, *30*, 3429.
[14] (a) Laforteza, B. N. Pickworth, M.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11269.; (b) Morikawa, T.; Harada, S.; Nishida, A. *J. Org. Chem.* **2015**, *80*, 8859.



Scheme 5. Synthesis of Aspidosperman Type Alkaloids

Summary

In summary, we developed new methods to synthesise chiral building blocks with enantio-, and diastereoselective organocatalytic processes. Moreover, we used bifunctional cinchona-based catalyst in organocascade reactions to assemble cyclohexene derivatives. As a second part of our research programme, we designed and performed concise synthesis of three natural products and multigram, scalable synthesis of the key intermediate with enantio-, and diastereoselective cascade reactions.

Applied Methods

In the synthesis of compounds, we have used classical organic chemical laboratory techniques. The structure of synthesised compounds was determined by high resolution NMR spectroscopy, mass spectrometry and single crystal X-ray diffraction. The optical purity was determined by chiral HPLC methods.

Presentation of Results

[1] *Diasteroselective Synthesis of Thietans with Organocatalytic Stereoablation*

- Poster
  Stereoablative Synthesis of Chiral β-substitued Ketones Using Bifunctional Organocatalysts (*Bacsó, A.; Szigeti, M.*; *Varga, Sz.*; *Soós, T.*) 16th Blue Danube Symposium on Heterocyclic Chemistry, Balatonalmádi, 14-17. 06. 2015
- Lecture
  Stereoablation with Bifunctional Organocatalysis (Bacsó, A.; Szigeti, M.; Varga, Sz.; Soós; T.) National Symposium on Heterocyclic and Organometallic Chemistry, Balatonszemes, 18-20. 05. 2016

- Article
  Bacsó, A.; Szigeti, M.; Varga, Sz.; Soós, T.: Bifunctional Thiourea-Catalyzed Stereoablative Retro-Sulfa-Michael Reaction: Concise and Diastereoselective Access to Chiral 2,4-Diarylthietanes, *Synthesis* **2017**, *49*, 429.

[2] *Using Organocatalysis in Iterative Cascade Reactions*

- Article
  Varga, Sz.; Jakab, G.; Csámpai, A.; Soós, T.: Iterative Coupling of Two Different Enones by Nitromethane Using Bifunctional Thiourea Organocatalysts. Stereocontrolled Assembly of Cyclic and Acyclic Structures, *J. Org. Chem.* **2015**, *80*, 8990.
  Selected to a Feature Article by editors of J. Org. Chem.

[3] *Synthesis of Aspidosperman Alkaloids*

- Poster
  - *Organocatalytic Approach to Indole Terpenoids (Varga, Sz.*; *Angyal, P.; Egyed, O.*; *Soós, T.)* 16th Blue Danube Symposium on Heterocyclic Chemistry, Balatonalmádi, 14-17. 06. 2015
  - *Organocatalytic Approach to Indole Terpenoids (Varga, Sz.*; *Angyal, P.; Egyed, O.*; *Soós, T.)* 19th European Symposium on Organic Chemistry, Lisboa, 12-16. 07. 2015
    This Poster was awarded with Chemical Communications' Prize.
  - *Cascade Reactions in the Synthesis of Aspidospermans (Varga, Sz.*; Martin, G.; *Angyal, P.; Egyed, O.*; *Soós, T.)* 15th Belgian Organic Synthesis Symposium, Antwerpen, 10-15. 07. 2016
  - *Divergent Synthesis of Aspidospermans Using Cascade Reactions Aspidospermans (Varga, Sz.*; Martin, G.; *Angyal, P.; Egyed, O.*; *Holczabuer, T.; Soós, T.)* 25th International Symposium Synthesis in Organic Chemistry, Oxford, 17-20. 07. 2017
- Lecture
  - *Efficient Synthesis of Aspidosperman Skeleton Using Cascade Reactions* (Varga, Sz.; Angyal, P.; Egyed, O.; Soós, T.) National Symposium on Heterocyclic and Organometallic Chemistry, Balatonszemes, 29. 05. 2015
  - Collective Synthesis of Aspidosperman Alkaloids (Martin, G.; Varga, Sz.; Angyal, P.; Egyed, O.; Holczbauer, T.; Soós, T.) National Symposium on Heterocyclic and Organometallic Chemistry, Balatonszemes, 15-17. 05. 2017
  - Cascade Based, Concise Synthesis of Aspidospermans (Varga, Sz.; Martin, G.; Angyal, P.; Egyed, O.; Holczabuer, T.; Soós, T.) 17th Blue Danube Symposium on Heterocyclic Chemistry, Linz, 30. 08. - 02. 09. 2017
- Article
  Varga, Sz.; Martin, G.; Angyal, P.; Egyed, O.; Holczabuer, T.; Soós, T. manuscript in preparation