**Załącznik 3 – Autoreferat do wniosku habilitacyjnego w języku angielskim**

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# “Asymmetric organocatalysis under high-pressure conditions - new opportunities and applications"

University of Warsaw
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Warsaw, April 2019

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**Ph.D. in Chemistry**, Institute of Organic Chemistry of the Polish Academy of Sciences, Warsaw
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Thesis Title: "*The enantioselective synthesis of 3,6-dihydropyran derivatives with application of chiral metallosalen complexes*", supervisor: Professor Janusz Jurczak

**M.Sc. in Chemistry**, Faculty of Chemistry, University of Warsaw
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|---|---|
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| | Princeton University, Department of Chemistry, USA (in the group of Professor David W. C. MacMillan**)** |
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**4**. **Indication of the scientific achievement** being the basis for habilitation procedure

**a) Title of the scientific achievement:**

**„Asymmetric organocatalysis under high-pressure conditions - new opportunities and applications**"

**b) List of scientific publications being the basis of scientific achievement:**

**H1.** P. Kwiatkowski,* K. Dudziński, D. Łyżwa, *„Effect of High Pressure on Organocatalytic Asymmetric Michael Reaction: Highly Enantioselective Synthesis of γ-Nitroketones with a Quaternary Sterogenic Centers”*
*Org. Lett.* **2011**, *13*, 3624-3627.
Highlighted in *Synfacts* **2011**, 1017 and *Organic Chemistry Portal* http://www.organic-chemistry.org/Highlights/2012/20August.shtm)
$IF_{2011}$ = 5.862 ($IF_{2017}$ = 6.492), number of citations: 37

**H2.** D. Łyżwa, K. Dudziński, P. Kwiatkowski,* *„High-Pressure Accelerated Asymmetric Organocatalytic FriedelCrafts Alkylation of Indoles with Enones: Application to Quaternary Stereogenic Centers Construction”*
*Org. Lett.* **2012**, *14*, 1540–1543.
Highlighted in *Synfacts* **2012**, 566.
$IF_{2012}$ = 6.142 ($IF_{2017}$ = 6.492), number of citations: 27

**H3.** P. Kwiatkowski,* A. Cholewiak, A. Kasztelan, *„Efficient and Highly Enantioselective Construction of Trifluoromethylated Quaternary Stereogenic Centers via High-Pressure Mediated Organocatalytic Conjugate Addition of Nitromethane to β,β-Disubstituted Enones*”
*Org. Lett.* **2014**, *16*, 5930–5933.
$IF_{2014}$ = 6.364 ($IF_{2017}$ = 6.492), number of citations: 29

**H4.** A. Kasztelan, M. Biedrzycki, P. Kwiatkowski,* *„High-Pressure Mediated Asymmetric Organocatalytic Hydroxyalkylation of Indoles with Trifluoromethyl Ketones*”
*Adv. Synth. Catal.* **2016**, *358*, 2962–2969.
$IF_{2016}$ = 5.646 ($IF_{2017}$ = 5.123), number of citations: 6

**H5.** M. Biedrzycki, A. Kasztelan, P. Kwiatkowski,* *„High-Pressure Accelerated Enantioselective Addition of Indoles to Trifluoromethyl Ketones with Low-Loading of Chiral BINOL-Derived Phosphoric Acid”*
*ChemCatChem* **2017**, *9*, 2453–2456.
$IF_{2017}$ = 4.674, number of citations: 7

**H6.** A. Cholewiak, K. Adamczyk, M. Kopyt, A. Kasztelan, P. Kwiatkowski,* “*High pressure-assisted low-loading asymmetric organocatalytic conjugate addition of nitroalkanes to chalcones*”
*Org. Biomol. Chem.* **2018**, *16*, 4365–4371.
$IF_{2017}$ = 3.423, number of citations: 1

**H7.** Book chapter: P. Kwiatkowski,* K. Dudziński, D. Łyżwa, “*Non-Classical Activation of Organocatalytic Reactions*” in “*Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*” P. Dalko, Ed., Wiley-VCH, Weinheim, **2013**, Vol. 2, Chapter 21, 581-615.
number of citations: 4

*The number of citations (without self-citations) is given on the basis of the Web of Science of April 18, 2019.*

**Summary of scientific achievement**

The total IF of publications **H1-H6** according to the year of publication is **32.11** ($IF_{2017}$ = 32.696).

The total number of citations of **H1-H7** according to the Web of Science without self-citations is **111**.

In all publications **H1-H7** I am the only corresponding author. Other co-authors, during the implementation of the research described in these publications, were students of the University of Warsaw.

## c) Description of the scientific aims and achievements of the above-mentioned publications

## I. Introduction

### *I.a. Asymmetric organocatalysis*

The synthesis of chiral organic compounds in a stereocontrolled manner for many years was the subject of intensive research, due to the need to obtain numerous substances in the enantiomerically and diastereomerically pure form. In particular, this applies to those stereoisomers of compounds that are not naturally occurring, and are necessary, inter alia, for the production of pharmaceuticals,[1] or have been used in agrochemistry, material chemistry, catalysis and other fields, as well as in smaller amounts for various types of scientific research. The growing demand for enantiomerically pure compounds stimulates the development of new methods of synthesis, or influences the improvement of known pathways, with particular emphasis on such aspects as atom economy or ecology.

Among the various strategies used in the synthesis of homochiral compounds, the asymmetric catalysis gained a special significance. Its intensive development in the last two decades of the twentieth century was focused on reactions with the use of chiral metal complexes and enzymes.[2] Occasionally, over the years of the last century, there have also been reports showing in the role of catalysts, readily available chiral organic compounds, such as for example, amino acids or cinchona alkaloids.[3] However, in the last years of the twentieth century several important publications[4] appeared that paid particular attention to the possibility

[1] a) V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.*, **2006**, *106*, 2734; b) H. Caner, E. Groner, L. Levy, *Drug Discovery Today* **2004**, *9*, 105; c) *Asymmetric Synthesis of Drugs and Natural Products*, A. Nag, Ed., CRC Press, **2018**.

[2] *Comprehensive Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds.; Springer, Berlin, **1999**, Vols. I-III.

[3] Selected examples: a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.*, **1974**, *39*, 1615; b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, *10*, 496; c) H. Wynberg, R. Heider, *Tetrahedron Lett.,* **1975**, *16*, 4057; d) R. Helder, R. Arends, W. Bolt, H. Hiemstra, H. Wynberg, *Tetrahedron Lett.* **1977**, *18*, 2181; e) S. Juliá, J. Masana, J. C. Vega, *Angew. Chem. Int. Ed.* **1980**, *19*, 929; f) S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata, H. Molinari, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317; g) H. Wynberg, E. G. J. Staring, *J. Am. Chem. Soc.* **1982**, *104*, 166; h) U. H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446; i) M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353.

[4] Selected important examples of organocatalytic reactions from the late 20th century: a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; b) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874; c) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; d) Y. Chen, S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2000**, *122*, 9542; e) Y. Iwabuchi, M.

of effective enantioselective catalysis with the use of low-molecular-weight chiral organic compounds, such as *L*-proline or other amino acid derivatives. These reports initiated a very intense development of the direction called organocatalysis, and defined in the year 2000 by Dawid MacMillan.[4a] In 2004, over 100 publications on asymmetric organocatalysis were published, and in the year 2007 there were already over 500.[5]

This dynamic development of catalysis with small chiral organic molecules in the last 15 years caused that now, along with catalysis involving chiral metal complexes and biocatalysis, it is the third major branch of asymmetric catalysis.[6] Such a large interest in organocatalysis is caused by many advantages of this approach, among which I can mention the relatively easy availability of a large group of potential catalysts,[7] their stability and low toxicity. Particularly important are the processes in which the use of organocatalytic reactions, allows to replace in the synthesis steps based on toxic reagents and catalysts, especially those containing heavy metals that may contaminate the final product. In addition, many organocatalytic reactions are carried out under low-demanding conditions, e.g. at room temperature, without the need for dry solvents and an inert gas atmosphere, which makes them exceptionally attractive. However, despite many unquestionable advantages of this approach, there are still significant limitations related to the activity of organocatalysts in selected types of reactions, especially in case of more sterically demanding substrates. A large group of reactions still requires a high concentration of catalysts (≥20 mol%) and long reaction times (≥three days) under classical conditions, which largely excludes or limits their use in practical applications. Some more advanced organocatalysts are also used for certain types of reactions, such as e.g. phosphoric acids BINOL derivatives[8] or triazole precursors of chiral *N*-heterocyclic carbenes,[9] whose relatively high synthesis costs significantly limit their use in practical applications, even with 5 mol% a loading.

In order to improve the efficiency of inefficient enantioselective reactions, two main directions of action can be distinguished: 1) search for more active catalysts with high enantioselectivity, or 2) optimization of the reaction conditions to reduce the loading of the known catalytic system. Often, the introduction of a new and more active organocatalyst is a very challenging task, while the classical optimization, including solvent screening, concentration and temperature increase or the use of various additives, also does not always bring the expected results. In such situations, it is worth considering to use non-classical activation methods as a supporting factor, which include, among others, high pressure, microwaves, ultrasounds as well as mechanochemical activation.[10] In my research, I paid particular attention on the possibility of supporting organocatalytic reactions with high-pressure method, which will be justified in the further part of the autoreferate, as well as confirmed by the results of my own research.

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Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219; f) E. J. Corey, M. J. Grogan, *Org. Lett.*, **1999**, *1*, 157.

[5] D. W. C. MacMillan, *Nature*, **2008**, *455*, 304.

[6] *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, P. Dalko, Ed., Wiley-VCH, Weinheim. **2013**, Vols. I-III.

[7] e.g. α-amino acids, cinchona alkaloids, 1,2-diaminocyclohexane and their simple derivatives.

[8] D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, 114, 9047.

[9] D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307.

[10] *Chemistry Under Extreme and Non-Classical Conditions*, R. van Eldik, C. D. Hubbard, Eds., John Wiley: New York, **1997**.

## *I.b. High-pressure technique in organic synthesis*

The influence of pressure on various types of classical organic reactions in solutions has been quite well recognized over the years.[11] The research carried out in the 1970s, especially the works of William G. Dauben,[12] was of great importance for the development of organic synthesis under high pressure conditions. Dauben showed a very significant effect of pressure on cycloaddition reactions, and in particular new possibilities in the Diels-Alder reaction under high pressure. In Poland at the end of the seventies prof. Janusz Jurczak,[13] was actively involved in the subject of high-pressure organic synthesis, and his first publications concerned the hetero-Diels-Alder reaction.

Over the years, pressure in the range of 8-15 kbar, and sometimes even 20 kbar or more, has been used to efficiently accelerate selected types of reactions. In laboratory experiments, the most popular are high-pressure piston-cylinder apparatus, with a working volumes in the range of 10-50 ml. This type of reactor (working volume approx. 40 ml, maximum pressure 13 kbar) was also used in our research (Figure 1).

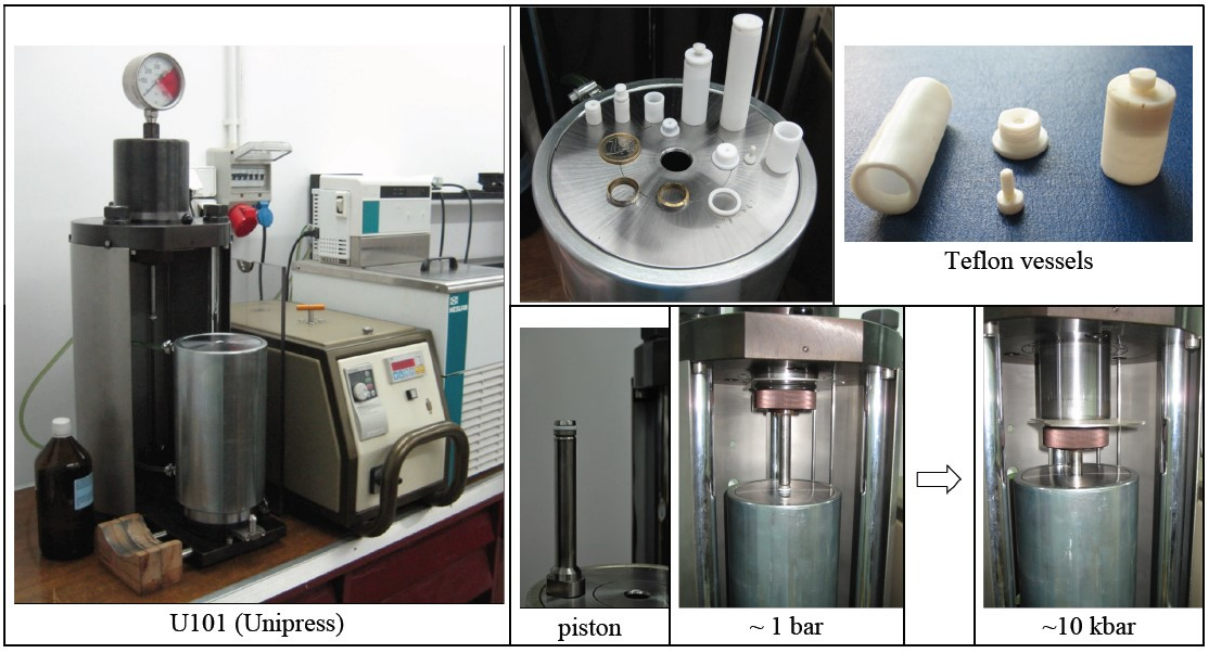


*Figure 1. High-pressure reactor at the Faculty of Chemistry UW, used in our investigations*

In one pressure experiment, even a dozen reactions can be carried out in parallel, because they are located in independent Teflon vessels immersed in a transmission liquid (e.g. petroleum ether). Typically, homogeneous reaction mixtures are investigated due to the lack of mixing option. The use of chambers enabling higher pressures (>20 kbar) is associated with a significant reduction in their working volume and thus also limits the scale of synthesis. In contrast, processes that are effectively accelerated below 8 kbar, allow for a significant

[11] a) *High Pressure Chemical Synthesis*, J. Jurczak, B. Baranowski, Eds., Elsevier, Amsterdam, **1989**; b) *Organic Synthesis at High Pressure*, K. Matsumoto, R. M. Acheson, Eds., Wiley: New York, **1991**; c) *High Pressure Chemistry: Synthetic Mechanistic and Supercritical Applications*, R. Van Eldik, F. G. Klaerner, Eds., Wiley-VCH: Weinheim, **2002**.

[12] a) W. G. Dauben, A. P. Kozikowski *J. Am. Chem. Soc.* **1974**, *96*, 3664; b) W. G. Dauben, H. O. Krabbenhoft *J. Am. Chem. Soc.* **1976**, *98*, 1992; c) W. G. Dauben, H. O. Krabbenhoft *J. Org. Chem.* **1977**, *42*, 282.

[13] The first publications of prof. Janusz Jurczak on high-pressure synthesis a) J. Jurczak, B. Baranowski *Polish J. Chem.* **1978**, *52*, 1857; b) J. Jurczak, M. Chmielewski, S. Filipek *Synthesis* **1979**, 41; c) J. Jurczak, M. Tkacz *Synthesis* **1979,** 42; d) J. Jurczak, M. Tkacz *J. Org. Chem.* **1979**, *44*, 3347.

increase in volume. A good example is the high-pressure chamber used for food preservation with a volume of approx. 100 liters able to generate pressure of about 6 kbar.[14]

High-pressure apparatus invented by Percy W. Bridgman[15] had a key impact on the development of scientific research under high pressure. Bridgman constructed the first one around 1910, and for his achievements in this area and research in the field of high pressure physics in 1946 received the Nobel Prize.

However, it is important to note that this technique can not be applicable in all reactions. The pressure effect is closely related to the activation volume ($\Delta V^{\neq}$),[16] defined as the difference between the partial molar volumes occupied by the transition state and the one occupied by reactants. The use of increased pressure accelerates reactions with negative volume of activation. In addition, if the reaction volume is also negative, the increase in pressure shifts the reaction equilibrium towards the products. For many types of reactions, the activation volumes were determined experimentally,[16] while it is worth to remember that the negative contribution to their value have elementary processes, such as bond formation, displacement, ionization, steric hindrance, as weel as cyclization.[17]

High pressure, which can significantly affect both the rate and equilibrium of chemical reactions, is used in organic chemistry primarily to carry out synthesis of compounds that often can not be obtained using other, generally available methods or are inefficient using classical approaches. To conclude, the range of many important chemical reactions can be broadened by using a high-pressure activation method.

### *I.c. High-pressure technique in asymmetric organocatalysis*

Although high-pressure technique has found a number of applications in organic synthesis, the influence of pressure on catalytic processes,[18] and in particular on enantioselective reactions, is still poorly explored for both the organocatalytic variant, presented in this dissertation, and for metal-catalysed processes.

When I published in 2011 the first paper (**H1)**[19] on this subject, 12 publications were available in the literature, which used chiral organic catalysts combined with high pressure (activation) in the range of 2-15 kbar. They concerned: Michael (2 publications, 80s),[20] Mority-Baylis-Hillman (3 publications, 90s),[21] nitroaldol (2002)[22] and aldol (3 publications, 2003-2006)[23], Mannich (1 publication, 2003)[24] and Diels-Alder (2 publications, 2010-2011). [25]

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[14] Avure Technologies: https://www.avure-hpp-foods.com/- high pressure food processing systems.

[15] P. W. Bridgman, *Proc. Am. Acad. Arts Sci.* **1914**, *49*, 627.

[16] a) T. Asano, W. J. Le Noble *Chem. Rev.* **1978**, *78*, 407; b) R. van Eldik, T. Asano, W. J. Le Noble *Chem. Rev.* **1989**, *89*, 549; c) A. Drljaca, C. D. Hubbard, R. van Eldik, T. Asano, M. V. Basilevsky, W. J. le Noble *Chem. Rev.* **1998**, *98*, 2167.

[17] B. Chen, R. Hoffmann, A. Cammi, *Angew. Chem. Int. Ed.* **2017**, *56*, 11126.

[18] a) O. Reiser, *Topics Catal.* **1998**, *5*, 105; b) the exception are simple variants of acid or base catalysis.

[19] I carried out the first preliminary experiments in 2009. This year, 10 publications (from 1981-2006) on asymmetric organocatalysis under high pressure were available in the literature.

[20] a) K. Matsumoto, T. Uchida, *Chem. Lett.* **1981**, 1673; b) A. Sera, K. Takagi, H. Katayama, H. Yamada, K. Mataumoto, *J. Org. Chem.* **1988**, *53*, 1157.

[21] a) A. Gilbert, T. W. Heritage, N. S. Isaacs, *Tetrahedron: Asymmetry* **1991**, *2*, 969; b) T. Oishi, H. Oguri, M. Hirama, *Tetrahedron: Asymmetry* **1995**, *6*, 1241; c) I. E. Marko, P. R. Giles, N. J. Hindley, *Tetrahedron* **1997**, *53*, 1015.

[22] Y. Misumi, R. A. Bulman, K. Matsumoto, *Heterocycles* **2002**, *56*, 599.

[23] a) Y. Sekiguchi, A. Sasaoka, A. Shimomoto, S. Fujioka, H. Kotsuki, *Synlett* **2003**, 1655; b) Y. Hayashi, W. Tsuboi, M. Shoji, N. Suzuki, *Tetrahedron Lett.* **2004**, *45*, 4353; c) H. Ikishima, Y. Sekiguchi, Y. Ichikawa, H. Kotsuki, *Tetrahedron*, **2006**, *62*, 311.

[24] Y. Hayashi, W. Tsuboi, M. Shoji, N. Suzuki, *J. Am. Chem. Soc.* **2003**, *125*, 11208.

Interestingly, as many as ten of them were done in Japan, mainly in groups of Kiyoshi Matsumoto (3 publications), Hiyoshizo Kotsuki (4 publications) and Yujiro Hayashi (2 publications).

The results of these publications were described in chapter **H7**,[26] devoted to non-classical activation methods used in asymmetric organocatalysis, including reactions conducted under high pressure, microwave, ultrasonic conditions and in ball mills (mechanochemistry). The review article presents the state of the art in this area until 2012, and also includes my results from **H1** and **H2**.

The first example showing the effect of pressure on an enantioselective reaction catalyzed by a chiral organic compound, was published in 1981 by Matsumoto and Uchida,[20a] when the asymmetric catalysis was still poorly developed. Japanese scientists studied the addition of nitromethane to chalcone (benzylideneacetophenone) catalyzed by cinchona alkaloids. The best results were obtained in the reaction using 10 mol% of quinidine in toluene under the pressure of 9 kbar, which proceeded quantitatively in 20-24 hours, with a relatively good enantiomeric excess at that time, reaching 60% ee. By comparison, this reaction did not proceed at atmospheric pressure at room temperature. A few years later, Matsumoto and co-workers published extended results of these studies, including the addition of ketoesters and thiols to selected enones,[20b] but in these cases the reactions took place under ambient conditions, and the pressure increase negatively affected the enantioselectivity. It should be pointed out that the reactions investigated by Matsumoto are not currently challenging and effective catalysts are already known for them. However, these pioneering work[20] by Matsumoto showed that in the quinidine-catalyzed addition of nitromethane to chalcone it is possible to maintain a similar level of enantioselectivity (58-60% ee) in the range of 4-9 kbar. In addition, these were the only reports[20] regarding the Michael reaction in the asymmetric and organocatalytic variant under high pressure at the time when I started my own research in this area.

From the remaining publications[21-25] (reported before 2011), the best results, especially in terms of enantioselectivty (ee> 90%), were obtained in the three-component Mannich reaction catalyzed with *L*-proline, between acetone, *p*-anisidine and various aldehydes at pressure of only 2 kbar and at –20 °C.[24] The pressure was generated in a sealed autoclave (at –20 °C) by water-freezing, as a result of increasing volume of ice. In most cases, a significant effect of this method on the yield of *N*-*p*-methoxyphenyl-β-aminoketones was observed. It was also the first example of a high-pressure reaction in which the enantioselectivity exceeded 90% ee. For a classical aldol reaction under high pressure (2-8 kbar) 90% enantiomeric excesses was observed only for single examples, and the effect on the reaction rate was clearly weaker.[23] Stereoselectivity up to 78% ee was reported in the hetero-Diels-Alder reaction at 10 kbar catalyzed by chiral thioureas containing a hydroxyl group.[25b] In the Michael reactions mentioned above, the enantioselectivity did not exceed 60%,[20] whereas in the case of the Morita-Baylis-Hillman reaction the best result was 47% ee.[21]

In most above disscused publications, from the point of view of current expectations, the enantioselectivity in general were rather moderate or low, which probably did not encourage to use high-pressure technique for asymmetric catalysis. However, it should be remembered that most of these papers (9 publications) were published before 2004, when the organocatalysis was just entering the phase of intensive development and many effective chiral organic catalysts and new types/variants of the reactions have not yet been known.

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[25] a) A. Mimoto, K. Nakano, Y. Ichikawa, H. Kotsuki, *Heterocycles*, **2010**, *80*, 799; b) K. Mori, T. Yamauchi, J. Maddaluno, K. Nakano, Y. Ichikawa, H. Kotsuki, *Synlett* **2011**, 2080.

[26] (**H7**) P. Kwiatkowski, K. Dudziński, D. Łyżwa, "*Non-Classical Activation of Organocatalytic Reactions*" in "*Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*" P. Dalko, Ed., Wiley-VCH, Weinheim. **2013**, *Vol. 2*, Chapter 21, 581-615.

After the year 2012 in the topic of high-pressure enantioselective organocatalysis, excluding my works (**H3**-**H6**), only two publications of prof. Kotsuki (2014 and 2015)[27] appeared. Japanese scientists investigated asymmetric Michael reactions catalyzed by chiral primary amines. In the first one, a high-pressure promoted desymmetrization of 4,4-disubstituted cyclohexadienones through malonate addition was described.[27a] In the second, the quaternary stereogenic center was generated in a highly enantioselective manner by high-pressure accelerated reaction of α-substituted cyclic ketones with acrylates.[27b] I also investigated similar reaction using 2-methylcyclohexanone, acrylates and chiral primary amines as catalysts, however, when the Kotsuki publication appeared in 2015, I have suspended further work on this reaction.

In conclusion, when I carried out the first experiments related to this project,[19] only 10 publications (1981-2006) on asymmetric organocatalysis under high pressure were available in the literature. In addition, in most of the works moderate or low enantioselectivity was obtained for reaction which can now be successfully carried out under classical conditions. Only few of them showed promising results, and only in cases of covalent catalysis (*via* enamine) with *L*-proline (Mannich and aldol reactions), enantioselectivity exceeding 80% was observed.

## II. Scientific goal and scope of the research

The main scientific objective was to investigate and understand the influence of high pressure on the course of selected types of enantioselective organocatalytic reactions, difficult to perform under classical conditions or requiring a high loading of chiral catalyst, as well as to demonstrate the new possibilities of combining this type of catalysis with high pressure activation. As the preliminary results proved to be promising, an important task was also to develop effective high-pressure methods for the synthesis of selected chiral products that are difficult to achieve using classical conditions, in particular compounds containing a quaternary stereogenic center.

Important factors contributed to the decision to focus on this research direction were:

- dynamic development of organocatalysis (especially in 2005-2010), resulting from many advantages of this approach and its growing importance in asymmetrical synthesis,
- the limitations and disadvantages of organocatalysis associated with long reaction time, high catalyst loading, narrow substrate scope and other problems related to reactivity often influenced by steric effects,
- high effect of hydrostatic pressure on the course of many classical organic reactions, including, e.g. Michael additions, as well as recent progress in the construction of high pressure chambers/reactors and easier access to them,
- poor state of knowledge on the effect of high pressure on asymmetrical catalytic reactions, in particular on enantioselective organocatalytic reactions. It was the most important argument encouraging me to examine more precisely the course of selected difficult enantioselective organocatalytic reactions under high pressure conditions. A small number of publications on this subject, especially in the years 2005-2010, when the interest in organocatalysis increased significantly, indicated that this was a unique direction, which may be of interest to a broad group of chemists, especially working on asymmetric catalysis.

[27] a) N. Miyamae, N. Watanabe, M. Moritaka, K. Nakano, Y. Ichikawa, H. Kotsuki, *Org. Biomol. Chem.* **2014**, *12*, 5847; b) R. Horinouchi, K. Kamei, R. Watanabe, N. Hieda, N. Tatsumi, K. Nakano, Y. Ichikawa, H. Kotsuki, *Eur. J. Org. Chem.* **2015**, 4457.

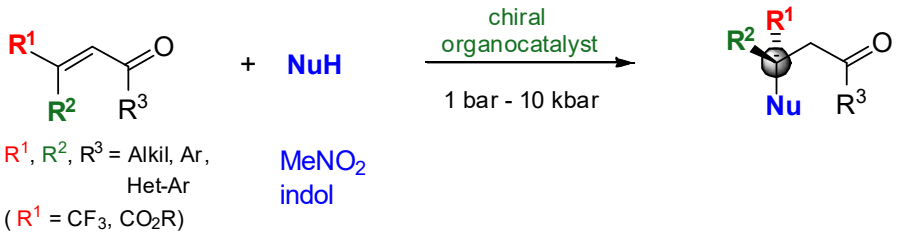
The growing importance of organocatalysis, and on the other hand its limitations and weak state of knowledge about the influence of pressure on asymmetric organocatalytic reactions, confirmed me that this is an important direction of research, requiring more detailed studies, including different types of activation, different reactions and groups of organocatalysts. Such studies could significantly increase the knowledge on the role and new possibilities of pressure in organocatalytic reactions, in particular, to understand its impact on the enantioselectivity of processes, which seems difficult to predict. It would also allow to better understand the relationship between the structure of reagents and organocatalysts and their activity under high-pressure conditions.

The general preliminary assumptions of the project were to investigate the effect of high pressure on various types of difficult asymmetric organic reactions, catalyzed by chiral organic molecules representing different classes of compounds and types of activation. I also assumed that the work will be carried out under pressure up to 11 kbar, because for higher pressures the main limitation is the decreasing working volume of high-pressure chambers, which also reduces the possibilities of practical applications

The use of high-pressure technique in organic synthesis is justified primarily in the case of processes that are difficult to carry out effectively at atmospheric pressure. That is why I focused on the variants of reactions for which no effective enantioselective methods have been described in the literature, as well as difficult reactions with sterically congested substrates (steric effects). Among the reactions of this type, the addition of *C*-nucleophiles to β,β-disubstituted Michael acceptors enabling the generation of quaternary stereogenic centers are especially challenging. When I started my research in this field, there were only few examples of such reactions in the enantioselective organocatalytic version described in the literature.[28] Additions of this type, due to the limited reactivity of such Michael acceptors, are still challenging, especially in the asymmetric organocatalytic version.

The second direction was to show the effect of high pressure on the course of more difficult reactions already described in the literature, but requiring a high catalyst loading, as well as long reaction time or higher temperature.

Preliminary results allowed to focus the work on selected promising problems involving β,β-disubstituted enones (Scheme 1). The choice of this group of Michael acceptors was caused (justified) by their diversity (different types of $R^1$, $R^2$ and $R^3$ substituents possible, including cyclic enrons) and the possibility to study both covalent and non-covalent activation (Scheme 1). The work with enones was mainly focused on the conjugate additions involving nitromethane and indole.




*Scheme 1. Conjugated additions do β,β-disubstituted enones*

The main types of enons used in the research are presented below (Figure 2). With the exception of a few commercially available cyclic ketones,[29] the vast majority of disubstituted enones required synthesis using literature methods.

[28] Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

[29] Commercially available β,β-disubstituted enones used in the studies: 3-methyl-2-cyclohexenone, 3-methyl-2-cyclopentenone, isophorone and 4-oxoisophorone.

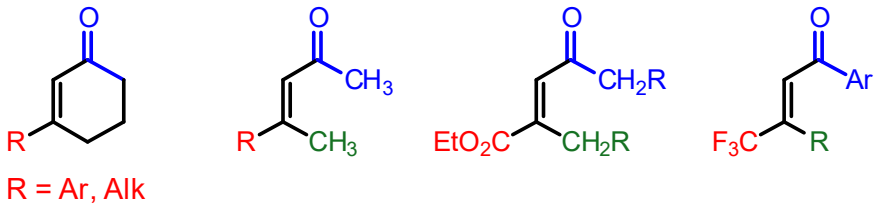



*Figure 2. Examples of β,β-disubstituted enons used in the studies*

An important group of substrates used in my studies were also prochiral trifluoromethyl compounds. Molecules containing this group, including chiral derivatives, are interesting objects from the point of view of biomedical chemistry. This is also confirmed by the large number of drugs based on such organofluorine compounds.[30] In addition to the reaction of nitromethane with enons containing the $CF_3$ group in the β position, an important part of my research was the reaction of indoles with trifluoromethyleketones.

In summary, the scope of the high-pressure research presented in the publications **H1-H6** includes the following reactions, problems and issues:

- Michael reactions, mainly with β,β-disubstituted enones and nitroalkanes,
- Friedel-Crafts type reactions between indoles and trifluoromethyl enones or ketones,
- reactions enabling the generation of quaternary stereogenic centers,
- asymmetric catalysis by covalent activation, involving chiral primary amines through the formation of the iminium ion, and non-covalent activation with tertiary amines, most often containing hydrogen bond donors and catalysis by chiral phosphoric acids,
- enantioselective synthesis of trifluoromethyl compounds.

The results presented in publications being the basis of scientific achievement are described in more detail below.

## III. Discussion of publications included in the habilitation cycle

The results described in publications **H1-H6** were discussed in two parts, and the main criterion was a type of nucleophilic reagent used. The first part deals with the addition of nitroalkanes, in particular nitromethane (**H1**, **H3** and **H6**), while the second describes reactions involving indoles as representatives of active heteroaromatic compounds (**H2**, **H4** and **H5**). I have paid special attention to the conjugate addition reactions with β,β-disubstituted enones enabling the formation of quaternary stereogenic centers. Many processes of this type are difficult to carry out, mainly due to limitations related to steric effects.

The book chapter **H7**[26] describes literature on non-classical activation methods used in asymmetric organocatalysis, including reactions accelerated by high pressure, microwaves, ultrasound (sonochemistry) and ball mills (mechanochemistry). This review covers the state of knowledge up to and including 2012, and publications related to high-pressure organocatalysis have already been discussed in chapter I.c.

[30] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432; c) B. G. de la Torre, F. Albericio, *Molecules* **2019**, *24*, 809.

Increasing interest in application of other non-classical activation methods (microwave, sonochemistry and mechanochemistry) in organocatalysis was observed since 2005, and resulted until 2012 in *ca.* 30 publications. Most often they described aldol and Mannich reactions, and the most popular of all methods was microwave activation, but in this case it is difficult to generalize the advantages because in some reactions with precise temperature control, it was shown that traditional heating gives similar results to the microwave activation. Sonication was very weakly explored in this context and its applicability was mostly proved for heterogenous systems, while ball mills were used in solvent-free reactions. However, for these three methods the problem that can be encountered is the difficulty in scaling up such experiments and problems with reproducibility, due to the equipment differences and issues related to proper temperature control. Comparing the above three methods with the results obtained with high-pressure activation, I am convinced that the latter method has good reproducibility and very high potential for reactions with negative values of activation.

## III.a. Effect of high-pressure on enantioselective organocatalytic conjugate addition of nitroalkanes to enones

(*Publications* **H1**, **H3** and **H6**)

Michael reaction is very widely used in organic synthesis for the formation of carbon-carbon bonds, often accompanied by generation of stereogenic center. Many enantioselective reactions of this type are known, including organocatalytic ones,[31] but in the majority of them they are limited to β-monosubstantiated Michael acceptors. One of my goals was to study enantioselective conjugate additions of *CH*-acids to β,β-disubstituted α,β-unsaturated carbonyl compounds, allowing the formation of a quaternary stereogenic center. Examples of such reactions in the organocatalytic variant until 2011 were very rare, due to the difficult course of this type of addition.[28,32]

My research has focused particularly on nitroalkanes additions, especially nitromethane, to β,β-disubstituted enones, which is demonstrated in publications **H1**[33] and **H3**.[34] The obtained products, containing a quaternary stereogenic center, are usually new compounds as well as interesting building blocks. The presence of a nitroalkyl fragment makes it possible to convert them to amine derivatives, including cyclic compounds, as well as carbonyl derivatives in the case of using the Nef reaction.

Finally, the influence of the pressure in the classical reaction with simple chalcones was also presented in publication **H6**,[35] which was a direct reference to the first report by Matsumoto.[20a]

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[31] For reviews on asymmetric organocatalytic conjugate additions, see: a) Y. Zhang and W. Wang, *Catal. Sci. Technol.*, **2012**, *2*, 42; b) J. Vicario, D. Badía, L. Carillo and E. Reyes, *Organocatalytic Enantioselective Conjugate Addition Reactions. A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*; RSC Publishing: Cambridge, 2010; c) D. Roca-Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero and P. Merino, *Tetrahedron: Asymmetry*, **2010**, *21*, 2561.

[32] Examples of intermolecular asymmetric organocatalytic conjugate additions to β,β-disubstituted Michael acceptors before 2011 a) C. E. T. Mitchell, S. E. Brenner, S. V. Ley, *Chem. Commun.* **2005**, 5346; b) C. E. T. Mitchell, S. E. Brenner, J. Garcia-Fortanet, S. V. Ley, *Org. Biomol. Chem.* **2006**, *4*, 2039; c) M. Malmgren, J. Granander, M. Amedjkouh, *Tetrahedron: Asymmetry* **2008**, *19*, 1934; d) P. Li, Y. Wang, X. Liang, J. Ye, *Chem. Commun.* **2008**, 3302; e) V. Wascholowski, H. M. Hansen, D. A. Longbottom, S. V. Ley, *Synthesis* **2008**, 1269; f) L. Bernardi, F. Fini, M. Fochi, A. Ricci, *Synlett* **2008**, 1857; g) A. Procopio, A. De Nino, M. Nardi, M. Oliverio, R. Paonessa, R. Pasceri, *Synlett* **2010**, 1849.

[33] (**H1**) P. Kwiatkowski, K. Dudziński, D. Łyżwa, *Org. Lett.* **2011**, *13*, 3624.

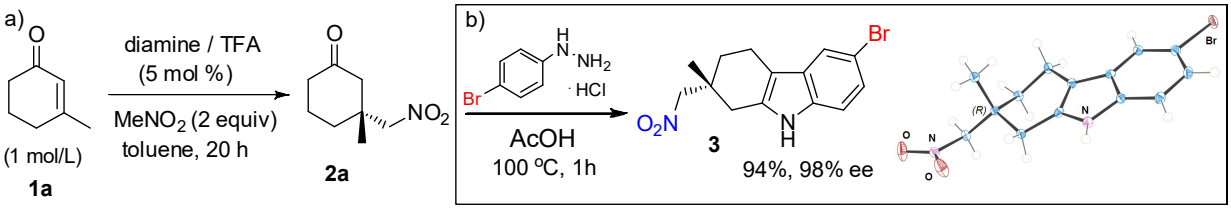
[34] (**H3**) P. Kwiatkowski, A. Cholewiak, A. Kasztelan, *Org. Lett.* **2014**, *16*, 5930.

[35] (**H6**) A. Cholewiak, K. Adamczyk, M. Kopyt, A. Kasztelan, P. Kwiatkowski, *Org. Biomol. Chem.* **2018**, *16*, 4365.

*Publication* **H1**[33]

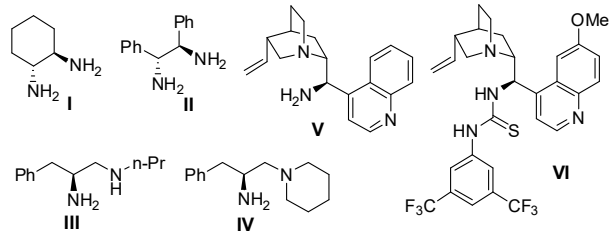
One of the first high-pressure experiments I conducted with chiral organocatalysts was the addition of nitromethane to the cyclic enone, namely the commercially available 3-methylcyclohex-2-enone (**1a**, Scheme 2a). In the literature, this reaction in the asymmetric organocatalytic variant was described in four publications.[32a-d] In three of them chiral pyrrolidine derivatives were used (10-15 mol%) and the best result obtained was 64% yield after three days and 91% ee. The catalyst based on the primary amine (10 mol%) proved more effective, which after 5 days allowed an interesting product with 82% yield and 94% ee.[32d] However, a much greater challenge and problem was to implement this method to other cyclic enons (having other substituents than the methyl group in the β-position).

In my initial research, I focused mainly on testing various chiral primary amines, in particular diamines **I-V** (Table 1), with trifluoroacetic acid (TFA) as a co-catalyst. At atmospheric pressure, the reactions proceeded with very low yield (Table 1), and in the presence of most active amine **III**, I obtained 9% of product **2a** with 80% ee (entry 3). In contrast, application of high pressure (10 kbar) and a catalytic amount of amines **I-V** (5 mol%) remarkably accelerated the reaction rate and high conversions were observed in some cases. The significant differences between conversion and yield were caused by side reactions. The best results in terms of yield (78%) and enantioselectivity (96% ee) was achieved with amine **V** (9-amino-9-deoxy-*epi*-cinchonine, entry 5) and this catalyst was selected for the optimization. Further experiments have shown that the addition of acid is necessary (entry 8), and better results can be obtained with only 2 mol% of **V** in the presence of benzoic acid (80% and 98% ee, entry 7). The product of this reaction (**2a**) was efficiently transformed into the interesting tetrahydrocarbazole **3** (Scheme 2b), which was used to confirm the absolute configuration by X-ray crystallographic analysis.



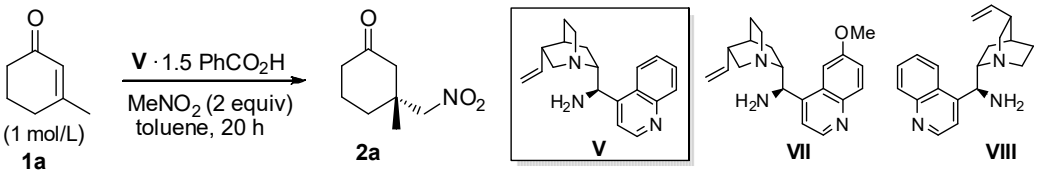

*Scheme 2. a) Addition of nitromethane to 3-methylcyclohex-2-enone b) Synthesis of tetrahydrocarbazole*

*Table 1. Optimization of nitromethane addition to 3-methylcyclohex-2-enone*




| entry | amine (5% mol) | acid additive (5% mol) | **1 bar** (24h) yield (%) | **10 kbar** (20h) yield (conv) (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **I** | TFA | 6 | 55 (95) | 75 (*R*) |
| 2 | **II** | TFA | 2 | 55 (60) | 98 (*R*) |
| 3 | **III** | TFA | 9, 80% ee | 70 (77) | 82 (*S*) |
| 4 | **IV** | TFA | <1 | 55 (99) | 73 (*S*) |
| 5 | **V** | TFA | 1 | 78 (91) | 96 (*R*) |
| 6 | **V** | BzOH | 3 | 75 (99) | 98 (*R*) |
| 7 | **V** (2%) | BzOH 2% | <2 | 80 (96) | 98 (*R*) |
| 8 | **V** | No acid | 1 | 36 (89) | 85 (*R*) |
| 9 | **VI** | No acid | <0.1 | 36 (43) | 92 (*R*) |

Finally, in the model reaction 2 mol% of **V** with 3-4 mol% of benzoic acid had the best effect at pressure of 10 kbar, (Scheme 3 and Table 2, entry 1), however, lowering the catalyst loading to 1 mol% also gave very satisfactory results (84%, 98% ee, entry 4). The pressure increase has a huge impact on this reaction, as shown in Figure 3. To obtain a high yield pressure of 8 kbar is sufficient in this case, and very optimistic observation is a very small change in enantioselectivity (99-97.5% ee) in a very broad pressure range (1bar-11 kbar).




*Scheme 3. Optimization of nitromethane addition to 3-methylcyclohex-2-enone*

*Table 2. Model Reaction Optimization Studies*

| entry | amine ·1.5 BzOH (mol %) | pressure | conv. (%) | yield (isol.) (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **V** (2) | 10 kbar | 96 | 87 (85) | 98 (*R*) |
| 2 | **VII** (2) | 10 kbar | 96 | 91 | 98 (*R*) |
| 3 | **VII** (2) | 10 kbar | 96 | 90 (87) | 97 (*S*) |
| 4 | **V** (1) | 10 kbar | 87 | 84 | 98 |
| 5 | **V** (0.2) | 10 kbar | 27 | 26 | 98 |
| 6 | **V** (5) | 10 kbar (5h) | 93 | 87 | 98 |
| 7 | **V** (10) | 1 bar | 5 | 4 | ~98 |
| 8 | **V** (10) | 1 bar (60 °C) | 26 | 25 | 98 |

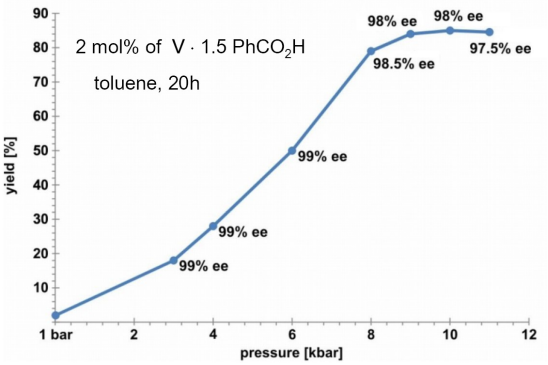



*Figure. 3. Influence of pressure on the model reaction*

The catalyst action in this reaction is based on the covalent activation of the enone by the formation of the iminium ion, and the acid addition promotes the process.[36] However, for the nitromethane activation a presence of base is necessary, and if too much of stronger acid is used (e.g. **V** ·2TFA), the organocatalyst is inactivated and the reaction is suppressed. When a weaker benzoic acid is added in excess the effect is different; even when a four times more of $PhCO_2H$ is used the result is still good (2 mol% **V** ·4 $PhCO_2H$: 79%, 98% ee).

The high-pressure method proved to be effective also in the case of the nitromethane reaction with other cyclic enones, including five- and seven-membered ring, as shown in Figure 4. Replacing the methyl group in the β-position with another (larger) substituent results in a decrease in the enone activity. In some cases it is necessary to increase the catalyst loading to 5 mol%, and sometimes also the amount of nitromethane (from 2 equiv to 5 equiv) in order to obtain a yield higher then 70%. In most cases the observed enantiomeric excess was very high (96-99% ee), with the exception of two products: **2i** and **2j**. In addition, this reaction is also possible with other nitroalkanes such as 2-nitropropane and nitroethane, which allowed to obtain products **2l** and **2m** with high yield and enantiomeric excess. In the case of addition of nitroethane (product **2m**), a second stereogenic center with a nitro group is formed, but with little or no diastereoselectivity (dr ~ 1:1).

[36] it is also possible to form dienamine; A. Moran, A. Hamilton, C. Bo, P. Melchiorre, *J. Am. Chem. Soc.* **2013**, *135*, 9091.

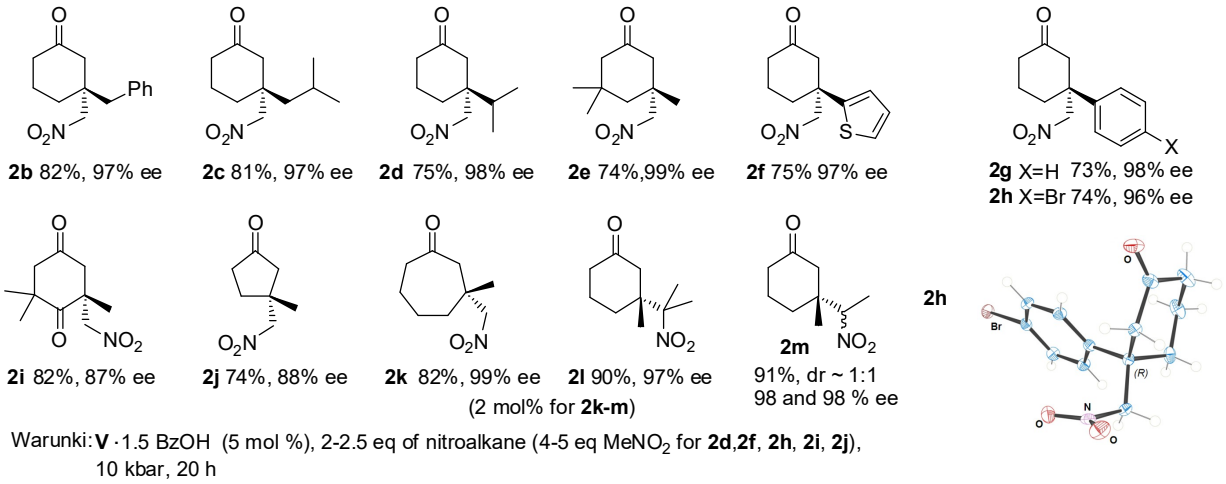
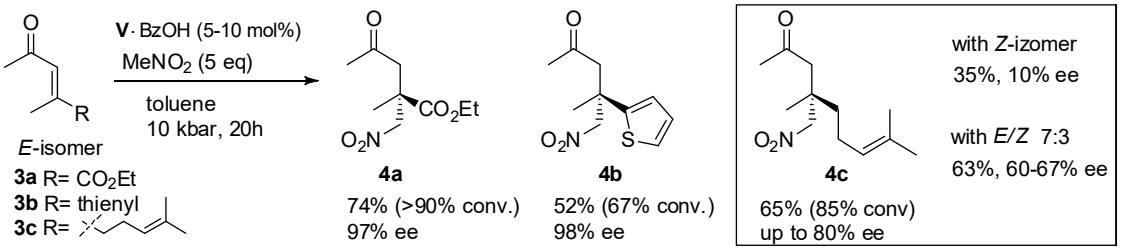



*Figure 4. The scope of the high-pressure method with cyclic enones*

The addition of nitromethane to acyclic β,β-disubstituted enones of type **3** with a methyl at the carbonyl group (Scheme 4) proved to be more difficult in comparison to cyclic ones. The best results in terms of yield and enantioselectivity was obtained with enone **3a** containing electron withdrawing group in the β-position. In the case of a ketone **3b** with a heteroaryl substituent, it was necessary to increase the loading of **V** · $PhCO_2H$ (10 mol%) to obtain the product with yield about 50%. Importantly, both products (**4a** and **4b)** were created with a very high enantiomeric excess. The situation is more complicated with enone **3c** having two different alkyl groups in β-position. Starting from *E*-isomer of **3c** we obtained acceptable yield and enantioselectivity up to 80%. Surprisingly, with *Z*-isomer low yield and the same direction of asymmetric induction was observed, but with very low enantioselectivity. This result can be explained by *E/Z*-isomerisation of enone **3c** in the presence of catalyst and higher reactivity of *E*-isomer.




*Scheme 4. Reactions of nitromethane with acyclic β,β-disubstituted enons*

The results of the studies shown in Scheme 4 were the first literature example of the enantioselective organocatalytic addition of *C*-nucleophile to the acyclic β,β-disubstituted enone. In addition, the work being discussed is also the first example of effective enantioselective iminium activation under high-pressure conditions.

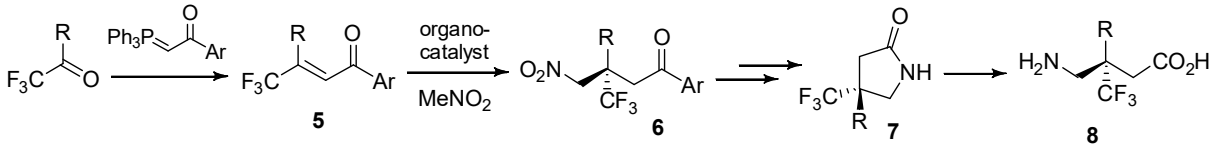
Four years after the publication of **H1**, Ye and Dixon[37] have developed an effective method of addition of nitromethane to cyclic enones (**2**) at atmospheric pressure, using a similar catalyst to **III**, which was the most active in our preliminary experiments at ambient conditions (Table 1). The catalyst by Ye and Dixon (in the comparison with **III**) has a *tert*-butyl group instead of benzyl and a cyclohexyl substituent on the nitrogen instead of *n*-propyl. Reactions described under atmospheric conditions usually require 10 mol% of the mentioned active organocatalyst (with benzoic acid) and depending on the enone used, are carried out for

[37] X. Gu, Yu. Dai, T. Guo, A. Franchino, D. J. Dixon, J. Ye, *Org. Lett.* **2015**, *17*, 1505.

2-7 days.[37] A good example to compare is adduct **2g** with the phenyl group for which Ye and Dixon used 20 mol% of catalyst and after 5 days isolated 52% with 98% ee. The high-pressure method developed by us allows obtaining this product with 5 mol% of cheaper catalyst (**V**) with 73% yield after 20 hours and 98% ee. On the other hand, additions to acyclic enons of type **3** are still remain out of the range of classical methods.

*Publication* **H3**[34]

My further studies on the conjugate addition of nitroalkanes were mainly concentrated on acyclic β,β-disubstituted enones with an aryl substituent on the carbonyl group. Particular attention was paid to the corresponding α,β-unsaturated compounds of type **5** (Scheme 5) with the trifluoromethyl group at the β-position. They can be easily obtained by Wittig reaction from the corresponding trifluoromethyl ketones.[38] The addition of nitromethane to enones **5** lead to γ-nitroketones **6**, containing at the β-position the quaternary stereogenic center with trifluoromethyl group. The Michael adducts **6** can then be transformed into chiral 2-pyrrolidones **7**, and finally to very interesting γ-amino acids **8**, the new trifluoromethyl analogs of γ-aminobutyric acid (GABA).[39] Several chiral drugs with a similar structure with a hydrogen atom in place of the trifluoromethyl group are known, such as Rolipram, Baclofen or Pregabalin,[39] while at the time there were no described enantioselective methods for the synthesis β-trifluoromethyl amino acids of type **8** with a quaternary stereogenic center.




*Scheme 5. Reactions of β-trifluoromethyl enones – application in the synthesis of γ-amino acids*

Studies on the addition of nitromethane to β-trifluoromethyl enones, I started with the model reaction shown in Scheme 6. The used enone **5a** is structurally similar to chalcone, however, apart from the trifluoromethyl group, the difference is also in geometry because the phenyl and COPh are in different locations.

As expected, primary amines of type **V** and **VII**, very effective in the reactions of cyclic enons with nitromethane, turned out to be completely inactive in the corresponding reaction with **5a** (Scheme 6, Figure 5). So I decided to test catalysts that have worked well in similar reactions with chalcones, i.e. chiral tertiary amines, most often derivatives of cinchona alkaloids, containing hydrogen bond donors, such as thioureas[40] or squaramides.[41] The use of 10 kbar pressure and only 2 mol% of amine-thioureas **VI**, **IX**, **X** and **XII** allowed to obtain product **6a** with high yield (>95%) and enantiomeric excess in the range of 90-95% (Figure 5). The most active was the dihydroquinine derivative **X**, and even under the pressure of 8 kbar allowed to receive a high yield exceeding 90%, while for the others (**VI**, **IX** and **XII**) it was 70-80%. This was also confirmed under atmospheric pressure: with **X** after two weeks 9%[42] of

[38] K. Matoba, H. Kawai, T. Furukawa, A. Kusuda, E. Tokunaga, S. Nakamura, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed.* **2010**, *49*, 5762.

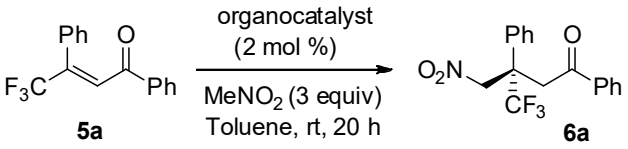
[39] K. Gajcy, S. Lochyński, T. Librowski, *Curr. Med. Chem.* **2010**, *17*, 2338.

[40] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967.

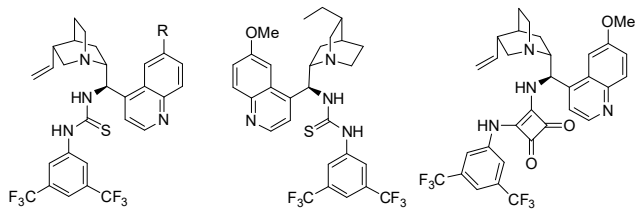
[41] W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450.

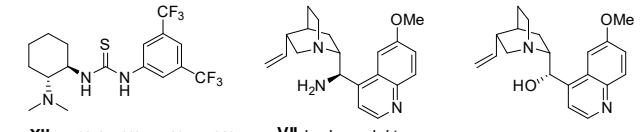
[42] Even 10% mol of **X** catalyst and elevated temperature (50 ° C) did not allow to efficiently carry out this reaction (28% after 7 days).

the product **6a** was formed, while in the case of other catalysts, its quantity did not exceed 2%. The mechanism of non-covalent activation and the stereochemical model for a similar reaction of chalcone with nitromethane in the presence of **X**, have been clarified in recent years on the basis of DFT calculations.[43]




*Scheme 6. Model reaction of β-trifluoromethyl enone with nitromethane*




1bar: with **VI**, **IX**, **XI**, **XII**, **XIII** 0.5-2% yield after 14d
with **X** ~0.5% ater 24h, 9%, 96.5% ee after 14d

Warunki: 2% mol kat. c[**5a**]=0,5 mol/L, 8 kbar (10 kbar), rt , 20h

*Table 3. Optimization of $MeNO_2$ addition to **5a***

| entry | catalyst (mol %) | pressure | time | yield (isol.) (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **VI** (2%) | 6 kbar | 20h | 60 | 97 (*S*) |
| 2 | **VI** (2%) | 8 kbar | 20h | 87 | 96 (*S*) |
| 3[a)] | **VI** (2%) | 10 kbar | 20h | 97 (92) | 95.5 (*S*) |
| 4 | **VI** (1%) | 10 kbar | 20h | 84 (80) | 95.5 (*S*) |
| 5 | **VI** (2%) | 10 kbar | 5h | 86 | 95.5 |
| 6 | **VI** (2%) | 10 kbar | 2h | 58 | 96 |
| 7 | **X** (1%) | 10 kbar | 20h | 97 (91) | 96.5 (*R*) |
| 8 | **X** (0.5%) | 10 kbar | 20h | 81 (78) | 96 (*R*) |
| 9 | **X** (1%) | 10 kbar | 5h | 83 | 97.5 |
| 10 | **X** (2%) | 10 kbar | 2h | 72 | 97.5 |
| 11 | **X** (2%) | 6 kbar | 20h | 81 | 98 |
| 12 | **X** (10%) | 1 bar, 50 °C, 7d | | 28 | 96 |

c[**5a**]=1,0 mol/L, toluen

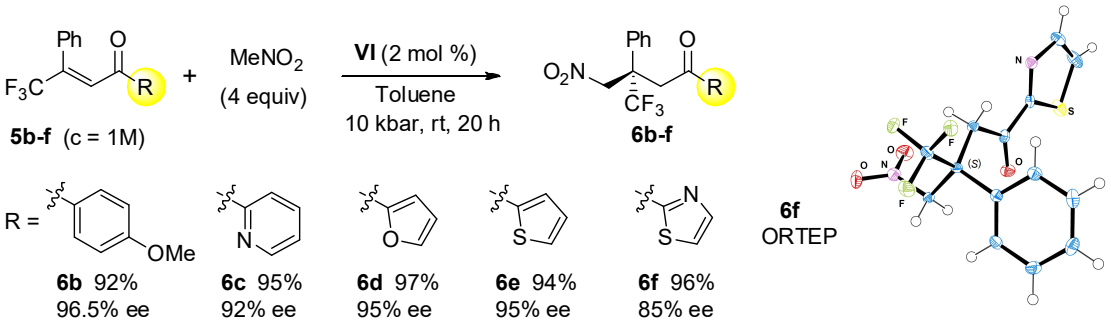
[a)] z **5a** *E/Z*: 94:6: 86% ee

*Figure 5. Catalysts of the reaction of enone **5a** with $MeNO_2$*

For further optimization (Table 3) I chose complementary organocatalysts **VI** and **X**, which allowed to obtain the opposite enantiomers of compound **6a**. The efficiency and enantioselectivity of the process was positively influenced by the increase in the concentration of the reaction mixture from 0.5 to 1 mol/L, which is very important, because the volume in high-pressure reactions is a limiting factor. At pressure of 10 kbar 1 mol% of **VI** is good enough to obtain a satisfactory result (80-84%, 95.5% ee, entry 4) after 20 hours; however, if the catalyst was changed to **X** (1 mol%) we obtained comparable efficiency after 5 hours (entry 9). With this catalyst (2 mol% of **X**) good results can be obtained even at 6 kbar (81%, 98% ee after 20h, entry 11). In the discussed experiments we used enone **5a** containing at least 98% of the *E* isomer, because *E/Z* ratio has a very important influence on the enantioselectivity. For instance application of **5a** as a 94:6 *E/Z* mixture decreased the enantiomeric purity of the product **6a** to 86%.

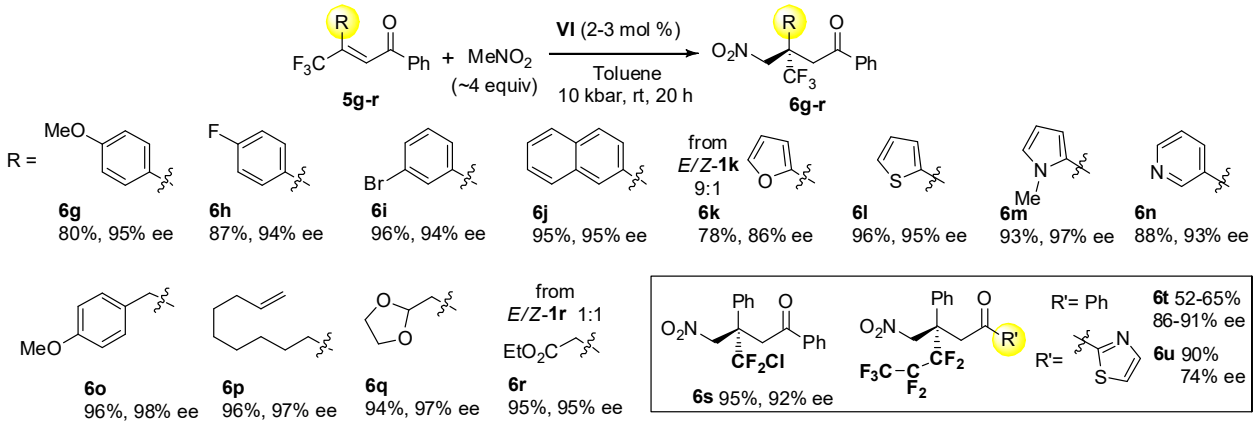
I decided to investigate the scope of applicability of high-pressure method with less active catalyst **VI** (2 mol%, 10 kbar, 20h), which allowed to obtain the enantiomer (*S*)-**6a**. A good result with this catalyst means that obtaining the opposite enantiomer with more active **X** will be even easier. At the beginning, we checked the influence of the aromatic substituent on the carbonyl group in enone on the course of this reaction (Scheme 7). It turned out that under the applied conditions all products (**6b-f**) were obtained with very high yields, as well as high enantioselectivities (92-96.5%), with one exception for thiazole enone, where the enantioselectivity decreased to 85% ee.

[43] For mechanism and origin of stereoselectivity based on DFT calculations, see: a) M. N. Grayson, *J. Org. Chem.* **2017**, *82*, 4396; b) M. N. Grayson, K. N. Houk, *J. Am. Chem. Soc.* **2016**, *138*, 1170.




*Scheme 7. Effect of substituents on the carbonyl group of the trifluoromethyl enone*

We focused more attention on reactions of various β-trifluoromethylated enones with different substituents in β-position, because it has a direct effect on the diversity of the created quaternary stereogenic center. We tested various enones with the phenyl substituent on carbonyl and trifluoromethyl group at β-position (Scheme 8). We successfully performed addition of nitromethane to various enones **5g-r**, where the aryl, heteroaryl and alkyl substituents were located in the β-position (Scheme 8). In all cases, we used 2-3 mol% of catalyst **VI** and pressure of 10 kbar. The yields obtained were usually higher then 90%, and the enantiomeric excess was in the range of 93-98%. The only exception was the product with the 2-furyl substituent (**6k**, 78%, 86% ee), however, the lower enantiomeric excess resulted from the use of difficult to separatet mixture 9:1 of *E*/*Z*-**5k**. The limitation of this method is the use of enones with the *ortho*-substituted phenyl group in the β position, due to their low reactivity (only a small amount of the adduct was observed). For this type of enones, it is probably more difficult to adopt a suitable conformation, required for the effective course of the Michael reaction.

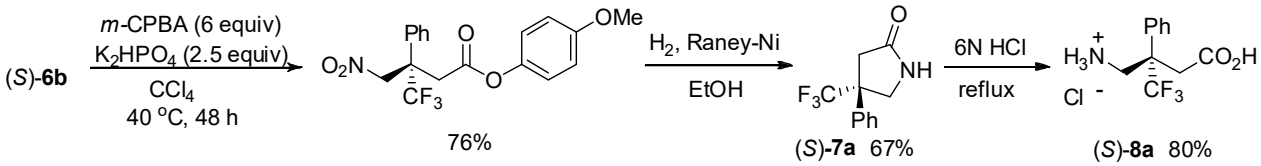



*Scheme 8. Effect of substituents at the β-positions of enones*

We also checked the possibility of using in this reaction enones containing other fluorinated substituents of type $CF_2R$ in β-position. It turned out that $CF_2Cl$ can be successfully introduced there (product **6s**, Scheme 8), but it is much more difficult to carry out such a reaction with perfluoro-*n*-propyl substituent (product **6t,** 52-62%). We observed also that replacing the phenyl substituent with 2-thiazole on the carbonyl group resulted in a significant increase in the enone activity, which allowed to obtain product **6u** in high yield, but unfortunately with a lower enantiomeric excess (74% ee). Nevertheless, it was a very valuable information that we use in current research.

Finally, we presented the possibility of transformation of the adduct **6b** in three steps into γ-amino acid **8a**, which is a trifluoromethylated analog of phenibut (Scheme 9). This is

the first example of enantioselective synthesis of this type of amino acid described in the literature.




*Scheme 9. Synthesis of γ-amino acids with a trifluoromethyl group*

During the preparation of the manuscript for **H3**, a paper describing the addition of nitromethane to trifluoromethyl enones of type **5**, under phase-transfer catalysis conditions using chiral ammonium salts, based on Cinchona alkaloids (20 mol%) and potassium carbonate, appeared in the literature.[44] The method requires the use of a high catalyst loading and the reaction time is 36-72 hours. High yields (80-99%) were obtained with enantiomeric excessess slightly lower (90-93% ee) compared to the high-pressure method we developed. In addition, the range of enones used is limited to derivatives containing phenyl substituents on the carbonyl and in the β-position (no heteroaryl substituents). Moreover, the reaction of the enone with the alkyl substituent instead of the phenyl at the β-position, proceeds with a significant decrease in enantioselectivity (R = Me, 63% ee).[44]

In conclusion, the high-pressure reactions presented in **H3**, works very well with a low catalyst loading (1-3 mol%) for a wide group of β-trifluoromethyl enones, in addition, it is faster, more general and also allows adducts **6** with a slightly higher enantioselectivity in comparison to the method[44] using chiral ammonium salts as catalysts.

In addition, the publication **H3** is the first example of effective enantioselective non-covalent organocatalysis under high-pressure conditions, where the obtained enantiomeric excess exceeds 90%. Previous works on the high-pressure organic catalysis with enantioselectivities over 90% ee was based on covalent activation with formation of enamine[24] or iminium ion[**[H1]**].

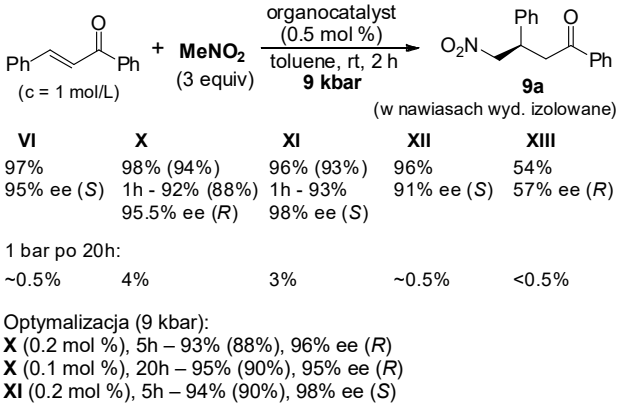
*Publication* **H6**

Closing the topic of nitroalkanes addition, I decided to demonstrate the effect of high pressure on a simple reaction of nitromethane and 2-nitropropane with benzylideneacetophenones (chalcones). Additions of this type, especially with nitromethane, are well known in the literature in the enantioselective organocatalytic variant. Their effective catalysts, among others, are compounds **X** and **XI**,[40,41,43] in quantities of 2-10 mol%, and the required time is at least two days at 50-80 °C. On the other hand, our main goal was to show the influence of pressure on the known reaction variant in the presence of highly enantioselective organocatalysts. In addition, it was also a comparison with the results obtained under high-pressure by Matsumoto.[20a] Our work (**H6**) has rather an illustrative nature, than the practical method for synthesis of these compounds. It demonstrates that the high pressure significantly reduces the catalyst loading as well as a the reaction time, without the need for additional heating.

In preliminary experiments, I decided to investigate the model reaction of chalcone with nitromethane, using among others well-known from the previous work (**H3**), bifunctional alkaloid thioureas **VI**, **X** and squaramide **XI**, as well as the Takemoto catalyst (**XII**) and used by Matsumoto quinidine (**XIII**). The reaction was carried out at a pressure of 9 kbar for 2

[44] H. Kawai, Z. Yuan, T. Kitayama, E. Tokunaga, N. Shibata, *Angew. Chem. Int. Ed.* **2013**, *52*, 5575.

hours in the presence of 0.5 mol% of the mentioned compounds. It turned out that using catalysts **VI**, **X**, **XI** and **XII**, we obtained product **9a** with conversions over 95% and stereoselectivity in the range of 98-91% ee. For comparison, when Soós applied 0.5 mol% of **X** for this reaction, after a week of heating (50 °C), he achieved 82% yield and 94% ee.[40] For further experiments, I selected catalyst **X** and squaramide **XI** that allowed to obtain the opposite enantiomer of product **9a**. Our experiments have shown that with these organocatalysts (0.5 mol% **X** and **XI**), yields exceeding 90% can be obtained after only one hour at a pressure of 9 kbar. In addition, the catalyst loading can be reduced to 0.2 mol% and similar results can be achieved after 5 hours at the same pressure. On a 10 mmole scale, we performed this reaction with only 0.1 mol% of **X**, and after 20 hours, we isolated 90% of product **9a** with 95% ee. Figure 6 illustrates the influence of pressure on this reaction, carried out for 20 hours in the presence of 0.5 mol% of **X**. Under these conditions, approximately 4% of the product is formed at atmospheric pressure, while increasing the pressure to 3 kbar the yield was improve to 65%. The pressure of 6 kbar, which is used to preserve some food products, allows to obtain product **9a** with a yield over 85%. At higher pressures the yield is almost quantitative, and at 8-10 kbar only minimal reduction in enantioselectivity (from 96 to 95%) was observed.




*Scheme 10. Addition of nitromethane to chalcone*

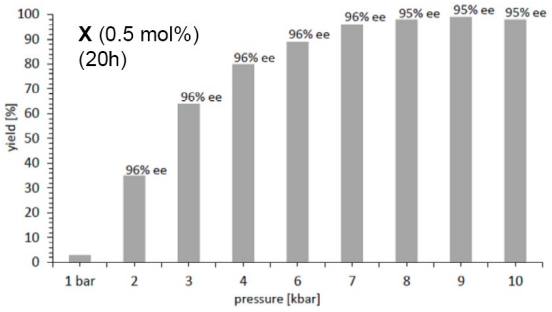
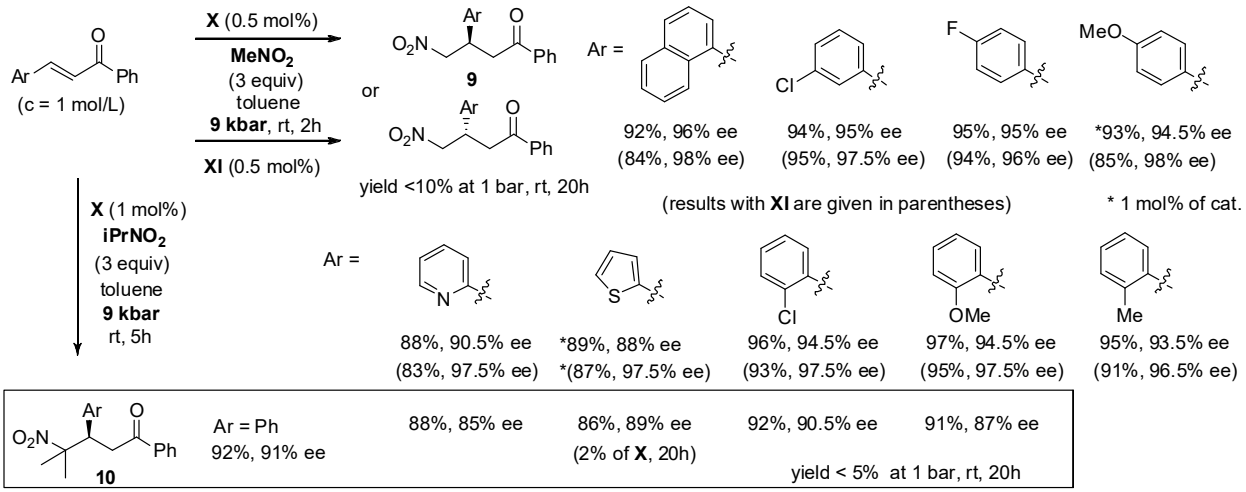



*Figure 6. Effect of pressure on the addition of $MeNO_2$ to chalcone with **X***

The effectiveness of the high-pressure method with the application of catalysts **X** and **XI** (0.5 mol%, 9 kbar, 2h), we also presented in the reaction of nitromethane with other simple enons (Scheme 11). The application of high-pressure allows for substantial reduction of catalyst loading and reaction time. Moreover the enantioselectivity under high-pressure is slightly higher compared with results at atmospheric pressure.[40,41] Furthermore, we examined a more difficult variant of this addition with the use of 2-nitropropane. The appropriate reaction with chalcone under ambient conditions described in the literature required 10 mol% of **X** and 8 days to obtain product **10** with 91% yield and 92% ee.[45] Using a high-pressure approach (9 kbar), practically the same result (92%, 91% ee) can be obtained with 1 mol% of **X** in 5 hours (Scheme 11).

[45] C. G. Oliva, A. M. S. Silva, F. A. A. Paz, J. A. S. Cavaleiro, *Synlett*, **2010**, 1123.




S*cheme 11. High-pressure addition of nitromethane and 2-nitropropane to chalcones*

In conclusion, all three publications (**H1**, **H3** and **H6**) presenting the addition of nitroalkanes to enons, show a very strong pressure effect on the rate of these reactions, often in the presence of a small amount of organocatalyst (0.5-2 mol%). A very important observation is the fact that the high pressure allows to obtain various γ-nitroketones, in particular containing quaternary stereogenic center, with very high enantiomeric excess, both using the so-called covalent and non-covalent organocatalysis. Usually, at higher pressure (about 10 kbar), we observed only a minimal decrease in enantioselectivity (e.g. from 97 to 96% ee), but this does not lower the value of this approach.

## III.b. The influence of high pressure on enantioselective organocatalytic addition of indoles to enones or trifluoromethyl ketones

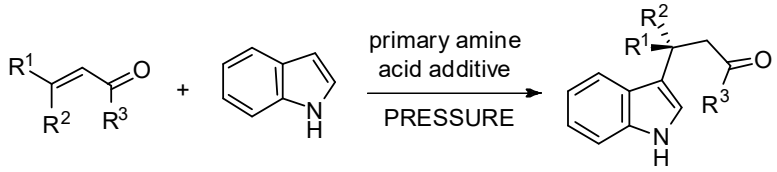
(*Publications* **H2**, **H4** and **H5)**

Indole is a very important representative of heteroaromatic compounds. This structural motif is often found in many natural products, in particular alkaloids, as well as synthetic bioactive substances.[46] The reactive indole ring usually undergo electrophilic substitution in the 3-position. One important reaction in which it can be used is the conjugate addition to various Michael acceptors, which leads very often to chiral products. When we started this project, asymmetric intermolecular reactions of this type described in the literature were limited to examples in which a tertiary stereogenic center was formed.

[46] a) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; b) A. Rahman, A. Basha, *Indole Alkaloids*, Harwood Academic Publishers: Amsterdam, **1998**; c) K. C. Majumdar, S. K. Chattopadhyay, Eds. *Heterocycles in Natural Product Synthesis*, Wiley-VCH: Weinheim, **2011**; d) T. V. Sravanthi, S. L. Manju *Eur. J. Pharm. Sci.* **2016**, *91*, 1.

*Publication* **H2** [47]

In my first project involving indoles, the main goal was to investigate the possibility of carrying out their enantioselective addition to β,β-disubstituted enones (Scheme 12). As I mentioned such reactions were unknown in the literature. However, many examples of corresponding indole reactions with β-monosubstituted Michael acceptors were described.[48] I paid particular attention to the reactions of indoles with simple enones, catalyzed by salts of chiral primary amines of type **V**,[49] in which the carbonyl compound is covalently activated as the result of the formation of the iminium ion.[36] However, these were quite demanding additions in which 20-30 mol% of organocatalyst was used. For this reason, in my initial experiments, I decided to investigate the effect of high pressure on a simple variant of this reaction, with the formation of a tertiary stereogenic center.




*Schemat 12.* Addition of indole to *β,β*- disubstituted enones

I chose the reaction of benzylideneacetone with indole as a model system for preliminary tests (Scheme 13). Chen[49a] using 30 mol% of amine **V** and twice more of trifluoromethanesulfonic acid (TfOH), after three days, obtained the corresponding product in 72% yield and 65% ee. Melchiorre[49b] applied a similar amine based on dihydroquinine (20 mol%) with the addition of *D*-*N*-Boc-phenylglycine (40 mol%) and after one day at 70 ° C the product was isolated in 90% yield and 88% ee.

In our studies, we tested various chiral diamines (5 mol%) with a double excess of benzoic acid, and the reactions were carried out at 10 kbar at 50 °C for 20 hours (Scheme 13). It turned out that under atmospheric pressure the amount of product formed does not exceed 6%, while under pressure of 10 kbar conversions are higher then 70%, and the best results (95% yield and 83% ee) were obtained for the alkaloid derivative **V**. The type of acid used and its amount had a significant influence on the reaction - with the increase of its power increasing the activity of the catalytic system, but often the enantioselectivity drops.

In the high-pressure method it is even possible to reduce the loading of the catalyst **V** · 2BzOH to 2 mol% (78%, 84% ee at 10 kbar, Scheme 13). The activity of the catalytic system can be improved by increasing the amount of benzoic acid, however this results in a slight decrease in enantioselectivity (for 2 mol%: **V** · 2.5BzOH: 88%, 83% ee; **V** · 4BzOH: 95% and 78% ee under 10 kbar). The influence of pressure on the course of this reaction is illustrated in more detail in Figure 7, which shows results for two loadings (2 and 5 mol%) of catalyst **V** · 2BzOH. It indicates that the highest enantiomeric excess (88%) was observed at a pressure of 6 kbar with yield up to 75%, while a further increase in pressure improved the yield but at the expense of enantioselectivity (83-84% ee).

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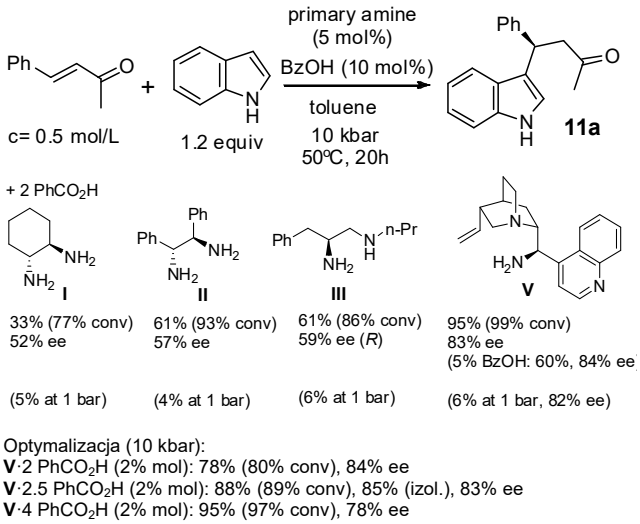
[47] (**H2**) D. Łyżwa, K. Dudziński, P. Kwiatkowski, *Org. Lett.* **2012**, *14*, 1540.

[48] For recent review on asymmetric organocatalytic Friedel-Crafts reactions, see: a) V. Terrasson, R. M. de Figueiredo, J. M. Campagne, *Eur. J. Org. Chem.* **2010**, 2635; b) E. Marques-Lopez, A. Diez-Martinez, P. Merino, R. P. Herrera, *Curr. Org. Chem.* **2009**, *13*, 1585; c) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449.

[49] a) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2007**, *5*, 816; b) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403.




*Scheme 13.* Indole reaction with benzylideneacetone

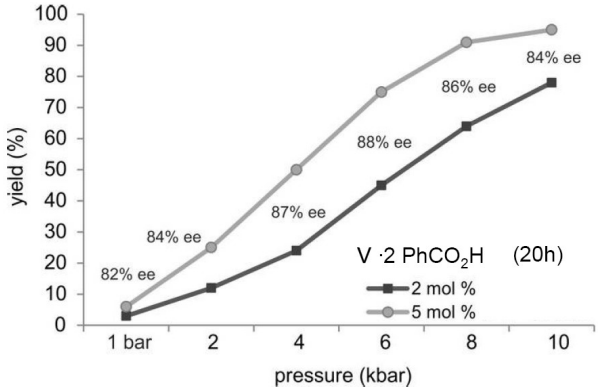



*Figure 7.* The effect of pressure on the reaction of indole with benzylideneacetone

In further studies we showed the applicability of the method with 2 mol% of **V** ·2-2.5 $PhCO_2H$, and in more difficult cases we used 5 mol% of this catalyst, as illustrated in Figure 8. Particularly in more demanding cases, it can be seen that the high-pressure method allows significant improving the yields (products **11c**, **11e**, **11f**) and even the enantiomeric excess, compared to the literature results.[49]

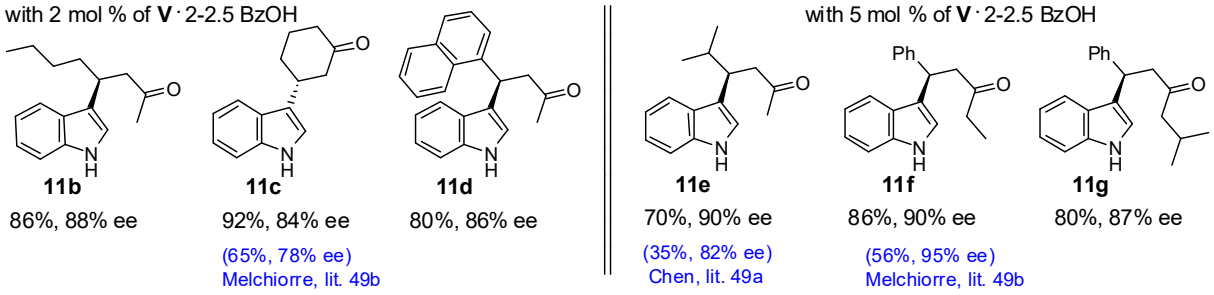
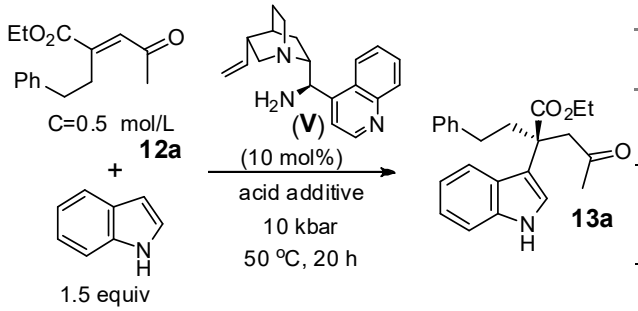



*Figure 8.* Products of indole addition to *β*-monosubstituted enones

After the initial studies, which showed a significant effect of pressure on indole reactions with simple enons, activated by primary amine salts, we switched to the main goal involving β,β-disubstituted enones, and enabling the generation of a quaternary stereogenic center.

For model studies we chose the reaction of indole with acyclic β,β-disubstituted enone (*E*)-**12a** (Scheme 14) containing the electron-withdrawing group in β-position. The previously used amine **V** (10 mol%) with the addition of benzoic acid, acted in moderate yield in this reaction (Table 4, entry 1), therefore it was necessary to screen other acids. The best results were obtained with salicylic acid (20 mol%, entry 4), which allowed to achieve a similar enantioselectivity as benzoic (72-73% ee), but with clearly higher yield (75-78%). The use of a smaller (15 mol%) or higher (30 mol%) amount of salicylic acid resulted in a marked reduction in yield or enantiomeric excess (i.e., entries 8 and 9). A reduction in pressure from 10 kbar to 8 kbar resulted in yield decrease from 78% to 62% and a slight improvement in enantioselectivity. We also checked the (*Z*)-isomer of enone **12a**, but it turned out to be less active, and the reaction proceeded with clearly lower enantioselectivity (44% ee) as well as the opposite enantiomer of **13a** was formed predominantly (entry 10).




*Scheme 14. Model addition of indole to **12a***

*Table 4. Optimization of indole reaction with **12a***

| Lp. | acid (20 mol %) | pressure | yield **13a** (conv) (%) | ee (%) |
|---|---|---|---|---|
| 1 | $PhCO_2H$ | 10 kbar | 34 (51) | 73 |
| 2 | Boc-*D*-Phg-OH | 10 kbar | 54 (69) | 76 |
| 3 | $Cl_3CO_2H$ | 10 kbar | 71 (90) | 19 |
| 4 | salicylic | 10 kbar | 75-78 (88) | 72 (*S*) |
| 5 | salicylic | 8 kbar | 62 (70) | 75 |
| 6 | salicylic | 6 kbar | 45 (57) | 74 |
| 7 | salicylic | 1 bar | < 3 | - |
| 8 | salicylic (15%) | 10 kbar | 55 (70) | 74 |
| 9 | salicylic (30%) | 10 kbar | 87 (97) | 61 |
| 10 | salicylic (*Z*-**12a**) | 10 kbar | 48 (75) | 44 (*R*) |

Conditions: 10% mol **V**, c[**12a**] = 0.5 mol/L

We also examined other substrates in this reaction and similar results to the model system, we obtained mainly in the case of enones that contain one alkoxycarbonyl substituent in the β-position and the other two alkyl groups (products **13b-f**, 68-80% ee, Figure 9). Most of these compounds are solids, which in the case of **13d** allowed to improve the enantiomeric excess (>95%) using crystallization. It is also possible to carry out the reaction with acyclic β,β-dialkyl enones, but with a low enantiomeric excess, which can be explained by their easier isomerization.

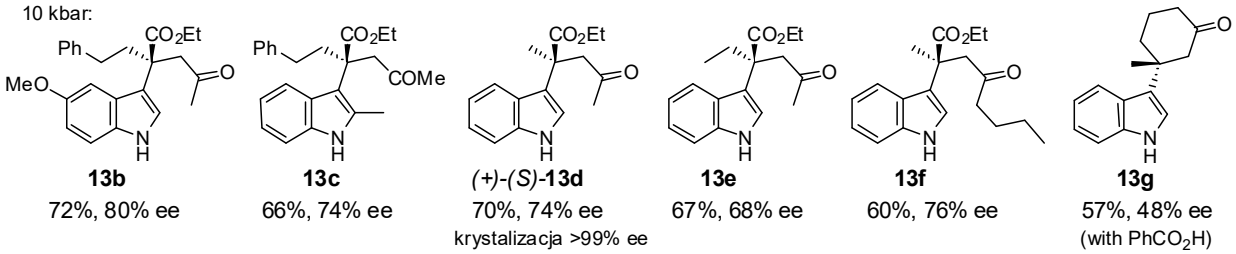
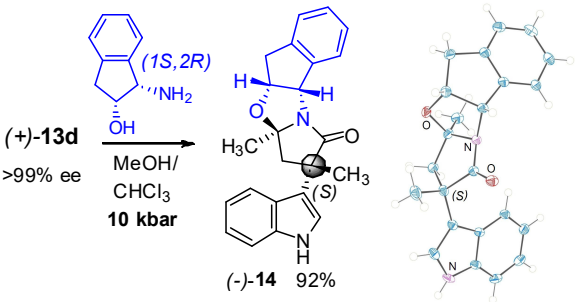



*Figure 9. Products of indole addition to β,β-disubstituted enones*

We have also developed a high-pressure promoted cyclization of γ-ketoesters, such as **13d** with 1,2-aminoalcohol (*cis*-1-amino-2-indanol), to form two five-membered rings (Scheme 15). With (1*S*,2*R*)-*cis*-1-amino-2-indanol, one diastereoisomer **14** was obtained in high yield. This compound was used to determine the absolute configuration of the products **13** by X-ray structural analysis.




*Scheme 15.* Absolute configuration of ***13d***

In conclusion, we have shown that hydrostatic pressure has a significant effect on the rate of organocatalytic alkylation of indoles with enones and yield products with up to 90% ee. The high-pressure approach enabled the use of selected β,β-disubstituted enones in this reaction, which allowed to obtain products containing a quaternary stereogenic center with good yields and enantiomeric excess up to 80%. This is the first example of an enantioselective organocatalytic intermolecular Friedel-Crafts reaction with β,β-disubstituted Michael acceptors.

*Publication* **H5** [50]

Our next project with indoles was focused on their additions to trifluoromethyl ketones, especially trifluoroacetophenones. Trifluoromethyl ketones are much more active in addition reactions to the carbonyl group, compared to the corresponding methyl ketones. However, despite the presence of an activating trifluoromethyl group, still some types of enantioselective reactions (e.g. with indoles) are difficult to carry out.

The enantioselective variant of indole reactions with very reactive trifluoropyruvates, catalyzed with chiral amines, e.g. cinchona alkaloids, is very well described in the literature.[51] However, this type of catalyst does not allow the reaction of indoles with other trifluoromethyl ketones under conventional conditions. The reaction with trifluoroacetophenone is possible in the presence of stronger organic bases, such as achiral guanidine derivatives.[52] Another possible approach is based on Brønsted acids catalysis. The use of chiral phosphoric acids - BINOL derivatives - allows the reaction of indoles with trifluoroacetophenones,[53] but requires to use 5 mol% of expensive catalyst (TRIP) with a high molecular mass.

I decided to study the possibility of enantioselective reaction of indole with trifluoroacetophenone (Scheme 16) in the presence of chiral amines, which would be an alternative and complementary approach to phosphoric acid catalysis.[53] Therefore, we examined a broad group of chiral, usually tertiary amines with additional hydrogen bond donors, and selected examples are shown in Scheme 16. It turned out that under the pressure of 8 kbar this reaction is very efficiently accelerated by only 2 mol% of amines: **VI**, **XII** and **XIV-XIX**, which allowed to obtain product **17a** with 66-90% yield (Scheme 16). For comparison, only trace amounts of this product was detected at atmospheric pressure (≤1%). However, much more challenging was to obtain a high enantioselectivity in this reaction. Finally, cinchonidine (**XIV**) turned out to be the best catalyst in terms of enantioselectivity (80-82% ee) as well as availability and this natural product was used in further optimization studies. In contrast to all the previously discussed studies, in this case under high pressure conditions, the expected product **17a** was formed in a small amount (6% at 8 kbar) without any catalyst.

The key elements necessary for the effective and enantioselective course of this reaction are the presence of the hydrogen bond donor in the basic catalyst and hydrogen on the nitrogen (NH) in the indole ring. The lack of the first element illustrates an example of the use of *O*-benzylated quinidine (**XX**, Scheme 16) as a catalyst, which resulted in very low yield. The use of *N*-methylindole instead of indole also inhibits the reaction and causes loss of enantioselectivity. $^{1}$H NMR experiments confirm importance of catalyst interaction with NH of indole via hydrogen bonding with quinuclidine part. Addition of cinchonidine shifts the indole NH signal to lower field. On the other side, hydroxy group in cinchonidine participates in hydrogen bonding activation of carbonyl in trifluoromethyl ketone. After addition of trifluoroacetophenone to cinchonidine, the signal from OH group at C-9 disappeared in $^{1}$H NMR spectra.

In the next stage of the work, we carried out the optimization of the model reaction using cinchonidine (**XIV**) as an easily accessible catalyst (Table 5 and Figure 10). The effect of pressure on this reaction in the presence of 2 mol% of the alkaloid is shown in the Figure 10. Increasing the pressure to 10 kbar reduces the enantioselectivity to 76% ee. However, the use of 9 kbar, 2 mol% of cinchonidine with 0.5 mol/L concentration of indole is the best

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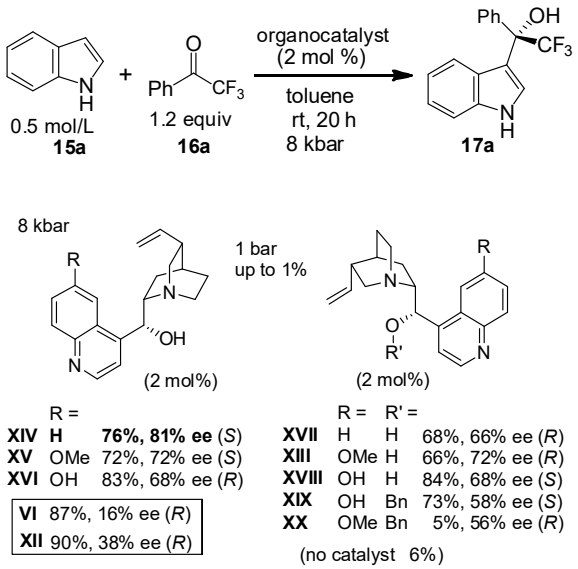
[50] (**H5**) A. Kasztelan, M. Biedrzycki, P. Kwiatkowski, *Adv. Synth. Catal.* **2016**, *358*, 2962.

[51] B. Török, M. Abid, G. London, J. Esquibel, M. Török, S. C. Mhadgut, P. Yan, G. K. Surya Prakash, *Angew. Chem. Int. Ed.* **2005**, *44*, 3086.

[52] M. Bandini, R. Sinisi *Org. Lett.* **2009**, *11*, 2093.

[53] J. Nie, G.-W. Zhang, L. Wang, A. Fu, Y. Zheng, J.-A. Ma, *Chem. Commun.* **2009,** 2356.

compromise in terms of yield (87%) and enantioselectivity (up to 80.5% ee, Table 5). The reaction time can be reduced to 8 hours by increasing the catalyst concentration (e.g. up to 4 mol%, entry 6).




*Scheme 16. The model reaction of indole with $ArCOCF_3$*

*Table 5. Optimization of indole reaction with ketone **16a***

| Entry | Catalyst **XIV** (mol %) | Pressure | Indole conc. (mol/L) | yield (isolated) (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | 2 | 8 kbar | 0.5 | 76 (73) | 81 |
| 2 | 2 | 8 kbar | 1.0 | 93 (91) | 77 |
| 3 | 4 | 8 kbar | 0.5 | 85 | 80 |
| 4 | 2 | 9 kbar | 0.5 | 87 (85) | 80.5 |
| 5 | 1 | 9 kbar | 0.5 | 74 | 80.5 |
| 6 | 4 | 9 kbar | 0.5 (8h) | 87 | 80.5 |

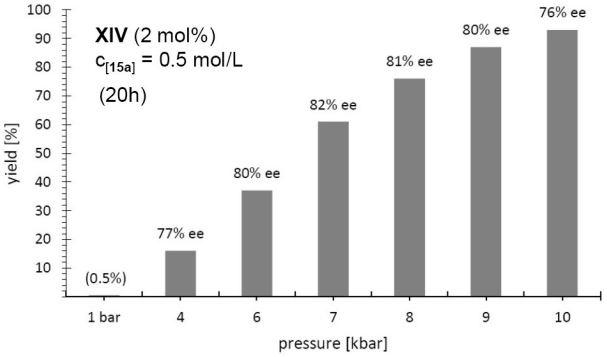
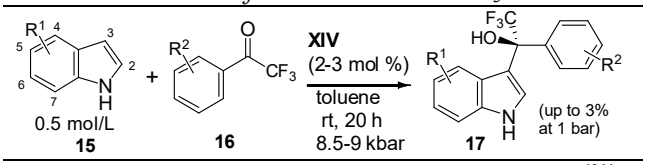



*Figure 10. The influence of pressure on the model reaction*

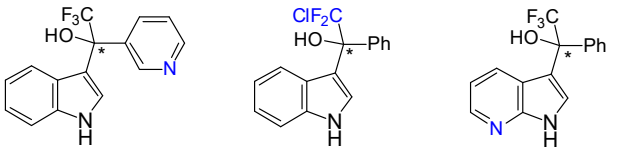
The high-pressure method is quite general and works for a wide range of substrates (Table 6), including indoles having electron-withdrawing substituents ($CO_2Et$, CN in position 5). For reactions of trifluoroacetophenone with different indoles the enantioselectivity was in the range of 71-89% (**17a-i**). In addition, we have found that cinchonidine can also effectively catalyze the reaction of trifluoroacetophenones with 7-azaindole, however the enantioselectivity is slightly lower (**17w**, 63% ee). To my knowledge, this is the first example of the use of 7-azaindoles in the enantioselective addition to carbonyl compounds. For comparison, in control experiments under atmospheric pressure usually traces (<2%) of products were observed.

Then we checked the possibility of using different trifluoromethyl ketones in this reaction at 8-9 kbar. It turned out that various *para*-, *meta*-, *ortho*-substituted trifluoroacetophenones (**17j-r**, 68-95%, 70-86% ee), 2-trifluoroacetylnaphthalene (product **17s**) and 3-trifluoroacetylpyridine

*Table 6 . Addition of indoles to $ArCOCF_3$*




| Lp. | Indole $R^1$ = | Ketone $R^2$ = | Yield (%) | ee (%) |
|---|---|---|---|---|
| **17a** | H | H | 85% | 80% |
| **17b** | 5-OMe | H | 89% | 71% |
| **17c** | 5-Me | H | 81% | 82% |
| **17d** | 5-F | H | 85% | 75% |
| **17e** | 5-Br | H | 81% | 77% |
| **17f** | 5-$CO_2$Me | H | 79% | 76% |
| **17g** | 4-OMe | H | 78% | 89% |
| **17h** | 7-Me | H | 73% | 84% |
| **17i** | 2-Me | H | 80% | 73% |
| **17j** | H | *p*-OMe | 75 | 70 |
| **17k** | H | *p*-Me | 76 | 82 |
| **17l** | H | *p*-F | 76 | 80 |
| **17m** | H | *p*-Cl | 80 | 79 |
| **17n** | H | *o*-MeO | 73 | 83 |
| **17o** | H | *o*-Cl | 68 | 86 |
| **17p** | H | *m*-Br 5% | 95 | 75 |
| **17r** | H | 3,5-di-Me | 74 | 85 |
| **17s** | H | (2-naftyl) | 84 | 85 |



**17t** 71%, 68% ee (8% at 1 bar)



**17u** 76%, 74% ee (5 mol% of **XIV**)



**17w** 84%, 63% ee

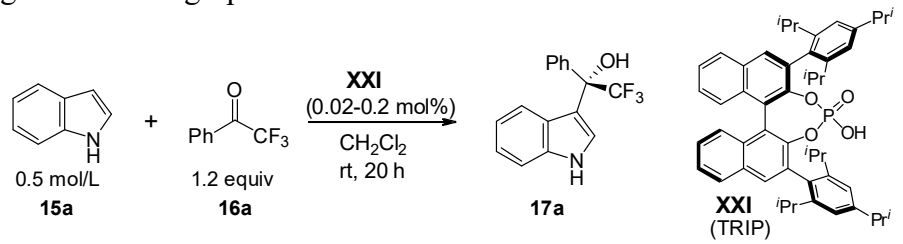
(product **17t**) work generally well. Unfortunately, this approach failed for the addition of indole to trifluoromethyl-alkyl ketones due to their lower activity, side reactions and negligible enantioselectivity.

All studies (**H1-H5**) presented so far have used amines as organocatalysts. One of the important topics we have undertaken was to study the reactions catalysed by chiral Brønsted acids. I was particularly interested in possibility of using BINOL-derived chiral phosphoric acids, which in recent years have found many application in asymmetric catalysis, [8] but have never been used under high pressure conditions.

*Publication* **H6** [54]

As I mentioned earlier, the enantioselective reaction of indoles with trifluoroacetophenones is possible under ambient conditions in the presence of chiral phosphoric acids - BINOL derivatives (Scheme 17). Ma[53] and co-workers have shown that the most effective in this reaction is derivative with 2,4,6-triisopropylphenyl substituents at the 3,3'-BINOL positions (**XXI**, TRIP). Typical reaction requires 5 mol% of this catalyst and 36-72 hours. In the case of the model reaction (Scheme 17) the product is formed in high yield and 92% ee. However, the use of 1 mol% of TRIP after 120 h allowed to obtain product **17a** with only 40% yield, but without changing the enantioselectivity. Considering the very high cost of this catalyst,[55] as well as demanding synthesis,[56] and high molecular mass (753 g/mol), its application in multi-gram synthesis (~5 mol% loading) can be a serious limitation.

The reason for undertaking high-pressure studies on this reaction with chiral phosphoric acids was to check the possibility of reducing the loading of this expensive catalyst. The second argument was that asymmetric catalysis with phosphoric acids had never been investigated under high-pressure conditions before.




*Scheme 17. The model reaction of indole with trifluoroacetophenone*

Our experiments confirmed that the structure of BINOL-type ligand in phosphoric acid is essential for the activity and enantioselectivity of the catalyst also under hyperbaric condition, and the TRIP (**XXI**) was the most efficient catalyst. High-pressure experiments with 0.2 mol% of **XXI** showed that after 4 hours at 9 bar a product **17a** can be obtained in 82% yield and 91% ee (Table 7, entry 1). When we reduced the catalyst loading to 0.1 mol% and the reaction was conducted under the same pressure for 20 hours we received 91% of the product **17a** with the same enantioselectivity (entry 3). The lowest catalyst loading that allowed to obtain a satisfactory result under these conditions was 0.05 mol% (85% and 91% ee, entry 5). This means that the high-pressure method allows to lower the loading of the catalyst ~100 times compared to the literature method, and actually does not change the enantiomeric excess. Figure 11 shows the effect of pressure and catalyst loading (0.2%, 0.1

[54] (**H6**) M. Biedrzycki, A. Kasztelan, P. Kwiatkowski, *ChemCatChem* **2017**, *9*, 2453.
[55] **XXI** (TRIP) is commercially available, and its price for 100 mg is approx. 500 euro.
[56] M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard, B. List *Synlett* **2010**, 2189.

and 0.05 mol% **XXI**) on the efficiency of the model reaction. It should be emphasized that the enantiomeric excess, regardless of the pressure and the catalyst content, is maintained at high level in a very narrow range of 90-92% ee.

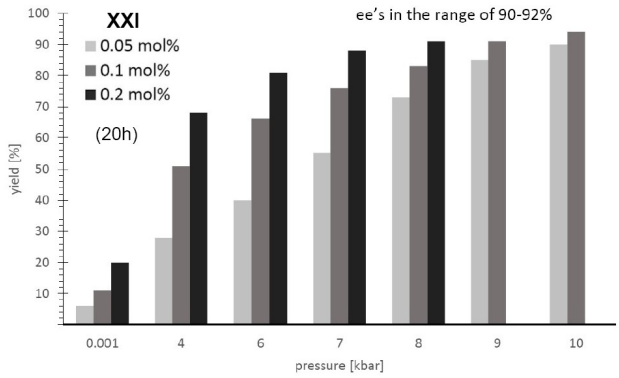



*Figure 11. The effect of pressure and catalyst loading on the reaction of indole with ketone **16a***

*Table 7. Optimization of indole reaction with **16a***

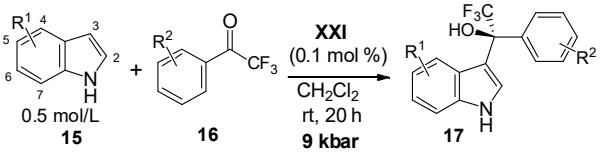
| Entry | **XXI** (mol %) | Time | **1 bar** | **9 kbar** | |
|---|---|---|---|---|---|
| | | | yield (%) | yield (%) | ee (%) |
| 1 | 0.2% | 4h | 6 | 82 | 91 |
| 2 | 0.1% | 8h | 6 | 74 | 92 |
| 3 | 0.1% | 20h | 11 | 91 | 91 |
| 4 | 0.05% | 8h | 3 | 59 | 91 |
| 5 | 0.05% | 20h | 6 | 85 | 91 |
| 6 | 0.02% | 20h | 3 | 52 | 90 |

no catalyst, 8 kbar, 20h: 3%

$c_{[15a]}$= 0.5 mol/L

Then we presented how the high-pressure method works in reactions with other indoles and trifluoromethyl ketones, in the presence of 0.1 mol% of catalyst **XXI** (Table 8). In more difficult cases, we used 0.2% mol% of TRIP. However, this approach has some limitations as compared with the previously developed method with cinchonidine, e.g. it is not effective in the reaction with 7-azaindole and 3-trifluoro-acetylpyridine, which contain in its structure basic motifs.

*Table 8. Addition of indoles to $ArCOCF_3$*




| Lp. | Indole $R^1$ = | Ketone $R^2$ = | Yield at 1 bar / (% ee) | 9 kbar Yield (conv.) (%) | 9 kbar ee (%) |
|---|---|---|---|---|---|
| **17a** | H | H | 11 (91) | 90 (95) | 91 |
| **17b** | 5-OMe | H | 14 (84) | 91 (>99) | 84 |
| **17c** | 5-Me | H | 10 (81) | 75 (99) | 85 |
| **17d** | 5-F | H | 8 (90) | 93 (>99) | 95 |
| **17e** | 5-Br | H | <1 | 89 (>99) | 87 |
| **17g** | 4-OMe | H | 5 | 70 (88) | 95 |
| **17h** | 7-Me | H | 18 (98) | 77 (>99) | 98 |
| **17y** | 5-CN* | H | 0 | 66 (70) | 92 |
| **17k** | H* | 4-Me | 5 | 87 (92) | 89 |
| **17l** | H | 4-F | 3 | 77 (90) | 90 |
| **17m** | H | 4-Cl | 7 | 85 (95) | 86 |
| **17n** | H* | 2-MeO | 5 | 82 (92) | 94 |
| **17r** | H | 3,5-di-Me | 6 | 81 (91) | 87 |
| **17s** | H | (2-naphthyl) | 8 | 83 (92) | 88 |

* 0.2 mol%

To summarize the work presented in **H5** and **H6**, we developed two complementary high-pressure (8-9 kbar) methods for enantioselective synthesis of tertiary α-trifluoromethylated alcohols **17**, obtained from indoles and trifluoromethyl ketones, using small amounts of readily available chiral base (2-4 mol% of cinchonidine) or expensive and less readily available chiral phosphoric acid (0.05-0.2 mol% of TRIP). The use of cinchonidine is a simple and less expensive method, and the main disadvantage of the reaction is lower enantioselectivity. In contrast, the application of phosphoric catalyst **XXI** under pressure of 9 kbar allows for a substantial reduction in the catalyst loading as well as the reaction time, without affecting enantioselectivity.

Publication **H5** shows the first example of the enantioselective reaction of indoles with trifluoroacetophenones, catalysed by chiral bases, and the first enantioselective reaction involving 7-azaindole. In turn, the **H6** publication presents the first studies on the use of chiral phosphoric acids as catalysts under high pressure conditions.

## IV. Summary and Conclusions

The results of my research presented in publications **H1-H6** show that the use of high-pressure can significantly improve the efficiency of selected organocatalytic reactions also with enantioselectivity kept on a very high level. Morever, this approach may help to force reactions which are still beyond the reach of classical organocatalysis.

We have shown that under high pressure conditions, asymmetric Michael (**H1**, **H3** and **H6**) and selected Friedel-Crafts type reactions (**H2**, **H4** and **H5**) are efficiently catalyzed. The advantages of the high-pressure method are particularly evident in reactions involving β,β-disubstituted Michael acceptors (**H1**, **H2** and **H3**), in which a quaternary stereogenic center is generated. The most versatile, in the role of organocatalysts in the majority of the high-pressure reactions tested, were primary amines and thioureas based on cinchona alkaloids. Importantly, in many examined reactions the increase in pressure practically does not change the enantioselectivity, which is crucial from the point of view of asymmetric synthesis.

The most important achievement presented in these dissertation is the demonstration that the combination of high-pressure technique with organocatalysis can be a very effective way to accelerate selected, difficult reactions (characterized by a negative volume of activation) with high enantioselectivity and relatively low loading of organic catalyst. It was also important to develop effective and new variants of enantioselective addition reactions of selected *C*-nucleophiles (nitroalkanes and indoles) to β,β-disubstituted enones to form a quaternary stereogenic center. This approach can also significantly reduce the catalyst loading, as well as the reaction time.

In addition, in the presented publications **H1-H6**, we showed in the literature the first examples of:

- enantioselective organocatalytic addition of *CH*-acid (nitromethane) to acyclic β,β-disubstituted enone (**H1**, 3 products),
- enantioselective organocatalytic addition of indoles to β,β-disubstituted Michael acceptors (**H2**),
- enantioselective reaction of indoles with trifluoroacetophenones catalyzed by chiral bases (**H4**),
- enantioselective addition of 7-azaindole to the carbonyl group (**H4**, 3 products),
- enantioselective synthesis of γ-amino acid with a quaternary stereogenic center containing a trifluoromethyl group in the β-position (**H3**),
- studies with the use of chiral phosphoric acids as catalysts under high-pressure conditions (**H6**),
- effective enantioselective covalent organocatalysis with the formation of an iminum ion under high pressure conditions (**H1**),
- effective enantioselective high-pressure organocatalysis based on non-covalent interactions, with enantioselectivity exceeding 90% (**H3**),
- enantioselective organocatalytic high-pressure reaction to form a quaternary stereogenic center (**H1**)

I think that the results we have obtained are encouraging for continuation of this research. Nowadays organocatalysis is a very broad subject, and gives many possibilities resulting from the diversity of reactions, types of organocatalysts and activation modes. However, the research direction using high-pressure presented in this dissertation is still very unique. So far, I have published 6 original papers on this subject, however, further studies on high-pressure organocatalysis are under way in my laboratory, and some of them at the stage of manuscript preparation.

Our research can also influence the further development of catalysis under high-pressure conditions and contribute to greater interest in this way of activating among chemists. This method in my opinion opens up a new possibilities in asymmetric catalysis and could help to develop new effective ways to carry out important reactions, when the classic approach fails. The knowledge about these processes and the benefits of using high-pressure seems to be very important, and in the future may even have application potential, which is also influenced by the progress in the construction of high-pressure reactors.

**5. Other scientific achievements**.

**5. a) Summary**

| | |
|---|---|
| The total number of original publications | 37 |
| Book chapters | 1 |
| Number of publications after receiving PhD degree | 25 |
| Total IF (according to the year of publication) | 138.443 |
| IF publications after receiving PhD degree | 107.54 |
| Total number of citations | 869 |
| Total number of citations without self-citations | 764 |
| The number of citations (without self-citations) of publications after receiving PhD degree | 644 |
| *H*-index | 16 |

*Data were obtained on the basis of Web of Knowledge (18 April 2019)*

**5. b) Publications after receiving the doctoral degree** (from 2006; excluding **H1**-**H7**)

*(the number of citations is given on the basis of the Web of Knowledge, only for publications that obtained at least 15)*

1. Majer, J.; Jurczak, J.; Kwiatkowski, P.*; Cotarca, L.; Jung, M. E.; Caille, J.-C. *„Asymmetric synthesis of (−)-bissetone via a highly enantioselective hetero-Diels–Alder reaction”*
   *Tetrahedron*, **2013**, *69*, 8463-8469.
   $IF_{2013}$ = 2.817, as a corresponding author

2. Dudziński, K.; Pakulska, A. M.; Kwiatkowski, P.* *„An Efficient Organocatalytic Method for Highly Enantioselective Michael Addition of Malonates to Enones Catalyzed by Readily Accessible Primary Amine-Thiourea”*
   *Org. Lett.* **2012**, *14*, 4222–4225.
   (Highlighted in *Organic Chemistry Portal* – http://www.organic-chemistry.org/abstracts/lit3/756.shtm)
   $IF_{2012}$ = 6.142, number of citations: 29, as a corresponding author

3. Kwiatkowski, P.; Beeson, T. D.; Conrad J. C. MacMillan, D. W. C. *„Enantioselective Organocatalytic α-Fluorination of Cyclic Ketones”*
   *J. Am. Chem. Soc.* **2011**, *133*, 1738-1741.
   (Highlighted in *Synfacts* **2011**, 438.)
   $IF_{2011}$ = 9.907, number of citations: 136

4. Majer, J.; Kwiatkowski, P.; Jurczak, J. *„Enantioselective Friedel-Crafts Reaction of Acylpyrroles with Glyoxylates Catalyzed by BINOL-Ti(IV) complexes”*
   *Org. Lett.* **2011**, *13*, 5944–5947.
   $IF_{2012}$ = 5.862, number of citations: 15

5. Mueller, L.; Jakubowski, W.; Matyjaszewski, K.; Pietrasik, J.; Kwiatkowski, P.; Chaladaj, W.; Jurczak, J. *“Synthesis of high molecular weight polystyrene using AGET ATRP under high pressure”*
   *Eur. Polym. J.* **2011**, *47*, 730-734.
   $IF_{2011}$ = 2.739, number of citations: 37

6. Lumbroso, A.; Kwiatkowski, P.; Blonska, A.; Le Grognec, E.; Beaudet, I.; Jurczak, J.; Jarosz, S. Quintard, J.-P. *“Addition of γ-Silyloxyallyltins on Ethyl Glyoxylates: Evaluation of the Influence of the Experimental Conditions on the Stereochemical Course of the Reaction”*
   *Tetrahedron* **2010**, *66*, 1570-1580.
   $IF_{2010}$ = 3.011

7. Majer, J.; Kwiatkowski, P.; J.; Jurczak, J. *„Highly Enantioselective Friedel−Crafts Reaction of Thiophenes with Glyoxylates: Formal Synthesis of Duloxetine”*
   *Org. Lett.* **2009**, *11*, 4636-4639.
   $IF_{2009}$ = 5.420, number of citations: 30

8. Kwiatkowski, P.; Mucha, P.; Mlostoń, G,; Jurczak, J. *„Novel Chiral $C_2$-Symmetric Bis-Imidazole-N-Oxides as Promising Organocatalysts for Enantioselective Allylation of Aromatic Aldehydes”*
   *Synlett* **2009**, 1757-1760.
   $IF_{2009}$ = 2.718, number of citations: 23

9. Kowalczyk. R.; Kwiatkowski, P.; Skarżewski, J.; Jurczak, J. *„Enantioselective Nitroaldol Reaction Catalyzed by Sterically Modified Salen-Chromium Complexes”*
*J. Org. Chem.* **2009**, *74*, 753-756.
$IF_{2009}$ = 4,219, 77 cytowań

10. Kwiatkowski, J.; Majer, J., Kwiatkowski, P.; J.; Jurczak, J. *„Simple and Efficient Synthesis of Racemic Substituted Mandelic Acid Esters from Nonactivated Arenes and Ethyl Glyoxylate”*
*Synthesis* **2008**, 3237-3244.
$IF_{2008}$ = 2.447

11. Chaładaj, W.; Kwiatkowski, P.; Jurczak, J. *„Improvement of the reactivity and selectivity of the oxo-Diels-Alder reaction by steric modification of the salen-chromium catalyst”*
*Tetrahedron Lett.* **2008**, *49*, 6810-6811.
$IF_{2008}$ = 2.538

12. Majer, J.; Kwiatkowski, P.; J.; Jurczak, J. *„Highly Enantioselective Synthesis of 2-Furanyl-hydroxyacetates from Furans via the Friedel−Crafts Reaction”*
*Org. Lett.* **2008**, *10*, 2955-2958.
$IF_{2008}$ = 5.128, number of citations: 18

13. Kwiatkowski, P.; Jurczak, J.; Pietrasik, J.; Jakubowski, W.; Mueller, L.; Matyjaszewski, K. *„High Molecular Weight Polymethacrylates by AGET ATRP under High Pressure”*
*Macromolecules* **2008**, *41*, 1067-1069.
$IF_{2008}$ = 4.407, number of citations: 102

14. Chaładaj, W.; Kwiatkowski, P.; Majer, J.; Jurczak, J. *„Enantioselective glyoxylate-ene reaction catalyzed by (salen)chromium(III) complexes”*
*Tetrahedron Lett.* **2007**, *48*, 2405-2408.
$IF_{2007}$ = 2.615, number of citations: 16

15. Kwiatkowski, P.; Kwiatkowski, J.; Majer, J.; Jurczak, J. *„Synthesis of chiral 4-substituted 2-hydroksypent-4-enoic acid derivatives via diastereoselective ene reaction promoted by $ZnBr_2$”*
*Tetrahedron: Asymmetry* **2007**, *18*, 215-223.
$IF_{2007}$ = 2.634

16. Chaładaj, W.; Kwiatkowski, P.; Jurczak, J. *„Sterically Modified Chiral (Salen)Cr(III) Complexes - Efficient Catalysts for the Oxo-Diels-Alder Reaction Between Glyoxylates and Cyclohexa-1,3-diene”*
*Synlett* **2006**, 3263-3266.
(Highlighted in *Synfacts* **2007**, 296.)
$IF_{2006}$ = 2.838

17. Kwiatkowski, P.; Majer, J.; Chaładaj, W.; Jurczak, J. *„Highly Diastereoselective Friedel-Crafts Reaction of Furans with 8-Phenylmenthyl Glyoxylate”*
*Org. Lett.* **2006**, *8*, 5045-5048.
(Highlighted in *Synfacts* **2007**, 71.)
$IF_{2006}$ = 4.659

18. Kwiatkowski, P.; Wojaczyńska, E.; Jurczak, J. *„Asymmetric Friedel-Crafts reaction of furans with alkyl glyoxylates catalyzed by (salen)Co(II) complexes”*
*J. Mol. Catal. A: Chem.* **2006**, *257*, 124-131.
$IF_{2006}$ = 2.511

19. Kwiatkowski, P.; Chaładaj, W.; Jurczak, J. *„Catalytic asymmetric allylation of aldehydes using the chiral (salen)chromium(III) complexes”*
*Tetrahedron* **2006**, *62*, 5116-5125.
$IF_{2006}$ = 2.817, number of citations: 19

## 5. c) Publications before receiving PhD degree (12 papers, 2000-2005):

1. Kwiatkowski, P.; Chaładaj, W.; Jurczak, J. *„A Sterically Modified (Salen)Chromium(III) Complex – An Efficient Catalyst for High-Pressure Asymmetric Allylation of Aldehydes”*
*Synlett* **2005**, 2301-2304.
$IF_{2005}$ = 2.693, number of citations: 17

2. Kwiatkowski, P.; Chaładaj, W.; Malinowska, M.; Asztemborska, M.; Jurczak, J. *„The high-pressure [4+2]cycloaddition of 1-methoxybuta-1,3-diene to the glycolaldehyde-derived heterodienophiles, catalyzed by chiral metallosalen complexes”*
*Tetrahedron: Asymmetry* **2005**, *16*, 2959-2964.
$IF_{2005}$ = 2.429, number of citations: 16

3. Kosior, M.; Kwiatkowski, P.; Asztemborska, M.; Jurczak, J. *„Stereochemistry of the Diels-Alder reaction at high pressure: diastereo- and enantioselective [4+2]cycloaddition of buta-1,3-diene to glyoxylic acid derivatives, catalysed by (salen) chromium(III) complexes”*
*Tetrahedron: Asymmetry* **2005**, *16*, 2897-2900.
$IF_{2005}$ = 2.429

4. Kwiatkowski, P.; Jurczak, J. *„High-pressure enantioselective allylation of aldehydes catalyzed by (salen)chromium(III) complexes”*
*Synlett* **2005**, 227-230.
$IF_{2005}$ = 2.693

5. Kiegiel, K.; Bałakier, T.; Kwiatkowski, P.; Jurczak, J. *„Diastereoselective allylation of N-glyoxyloyl-(2R)-bornane-10,2-sultam and (1R)-8-phenylmenthyl glyoxylate. Synthesis of (2S,4S)-2-hydroxy-4-hydroxymethyl-4-butanolide”*
*Tetrahedron: Asymmetry* **2004**, *15*, 3869-3878.
$IF_{2004}$ = 2.386

6. Kwiatkowski, P.; Asztemborska, M.; Jurczak, J. *„The enantioselective Diels-Alder reaction of 1-methoxybuta-1,3-diene with n-butyl glyoxylate catalyzed by the (salen)Cr(III)Cl and Co(II) complexes”*
*Tetrahedron: Asymmetry* **2004**, *15*, 3189-3194.
$IF_{2004}$ = 2.386, number of citations: 17

7. Malinowska, M.; Kwiatkowski, P.; Jurczak, J. *„The enantioselective high-pressure Diels-Alder reaction of 1-methoxybuta-1,3-diene with tert-butyl-dimethylsilyloxy-acetaldehyde catalyzed by (salen)Co(II) and (salen)Cr(III)Cl complexes”*
*Tetrahedron Lett.* **2004**, *45*, 7693-7696.
$IF_{2004}$ = 2.484, number of citations: 24

8. Kwiatkowski, P.; Asztemborska, M.; Jurczak, J. *„The enantioselective Diels-Alder reaction of 1-methoxybuta-1,3-diene with n-butyl glyoxylate catalyzed by Jacobsen's chromium complexes"*
*Synlett* **2004**, 1755-1758.
$IF_{2004}$ = 2.738, number of citations: 16

9. Kwiatkowski, P.; Chaładaj, W.; Jurczak, J. *„Enantioselective allylation of alkyl glyoxylates catalyzed by (salen)chromium(III) complexes"*
*Tetrahedron Lett.* **2004**, *45*, 5343-5346.
$IF_{2004}$ = 2.484

10. Kwiatkowski, P.; Wojaczyńska, E.; Jurczak, J. *„(Salen)Co(II) complex – an efficient catalyst for the high-pressure Friedel-Crafts reaction of 2-methylfuran with alkyl glyoxylates"*
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