

High-Pressure-Mediated Thiourea-Organocatalyzed Asymmetric Michael Addition to (Hetero)aromatic Nitroolefins: Prediction of Reaction Parameters by PCP-SAFT Modelling

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Thiourea-organocatalyzed Michael additions of diethyl malonate to various heteroaromatic nitroolefins (13 examples) have been studied under high-pressure (up to 800 MPa) and ambient pressure conditions. High pressure was conducive to enhanced product yields by a factor of 2–12 at a given reaction time, high reaction rates (reaction times were decreased from 72–24 h down to 4–24 h) and high enantioselectivity. Elucidating the effects of solvents for maximizing reaction rates and yields has been carried out using the Perturbed-Chain Polar Statistical Associating Fluid Theory (PCP-SAFT), allowing for the first time a prediction of the kinetic profiles under high-hydrostatic-pressure conditions.

The efficiency of chemical reactions in terms of their rate, yield and selectivity is influenced by several factors such as temperature, pressure, concentration, and solvent. Therefore, precise information and understanding of these factors are of paramount importance for fine-tuning reaction conditions in order to enhance rates and yields of the desired transformation. Following the first report in 1862 of Berthelot *et al.*,^[1] solvent effects on chemical reactions were correlated with the solvent's polarity and were later explained by the solvation of the reacting agents.^[2] Several groups have studied the effects of solvent on reaction rates and equilibria for chemical reactions^[3]

as well as for biochemical reactions.^[4] The solvent of a reaction has strong effects on molecular interactions that can be quantified by thermodynamic activities. Using thermodynamic models allows for computing activities of the reacting agents in solvent and, thus, predicting solvent effects on reaction. Different models have been proven to correctly predict the influence of solvent on liquid-phase reactions at atmospheric pressure.^[5–7,8] However, the applicability of these computational methods for very-high-pressure conditions in liquid phases (100–800 MPa) has not been validated until today.

The effects of high pressure in solution on the reaction equilibria were first explored by Planck in 1887^[9] and subsequently on reaction rates by Rothmund in 1896.^[10] Since then, many groups explored pressure effects for biochemical^[11] and for chemical reactions,^[12,13] whereas the pioneering study of Matsumoto and Uchida^[14] stands out as the first report of pressure effects on asymmetric organocatalytic reactions. Apart from purely academic interest, high-pressure applications have also gained substantial industrial significance, e.g. in food processing.^[15] High pressure can improve reactions either indirectly by phase transition (especially towards supercritical fluids) or directly by volume effects. The latter typically occur in liquid-phase reactions and are known to depend on solvent. Hence, we set out whether the effects of solvent on reactions are altered at high pressure and whether they can also be predicted by thermodynamic models. Thus, in this study Perturbed-Chain Polar Statistical Associating Fluid Theory (PCP-SAFT) was applied for the first time to an organic reaction at very-high-pressure conditions of up to 800 MPa. PCP-SAFT was chosen for this purpose as it has been successfully applied to compute the reacting agent's interactions in solution under ambient pressure and up to 2 MPa.^[6]


As a model system for this approach, we chose the Michael addition of 1,3-dicarbonyl compounds to nitroolefins, being a well-explored transformation, as the resulting nitroalkanes can easily be transformed into different synthetically useful building blocks harboring a wide variety of functional groups.^[16] In 2003, Takemoto and co-workers^[17,18] developed an efficient method for the highly enantio- and diastereoselective, conjugate addition of 1,3-dicarbonyl compounds to nitroolefins. In the presence of the newly designed bifunctional thiourea catalyst **3**, the transformation proceeds at ambient pressure and room temperature, however, prolonged reaction times and high catalyst loadings (10 mol%, 12–72 h) are required.


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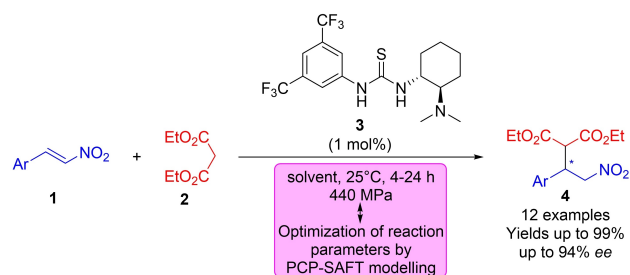
Taking this precedent into account, we investigated whether a rate acceleration can be achieved at high-pressure conditions without erosion of enantioselectivity and moreover, if solvent effects on reaction rate and yield at high pressure can be predicted using Perturbed-Chain Polar Statistical Associating Fluid Theory^[19] (PCP-SAFT, Scheme 1). Michael-type reactions belong to the class of bimolecular addition reactions, which are known to be accelerated by high pressure due to a negative volume of activation (in the range of -5 to -40 cm³ mol⁻¹).^[20,21] The volume of activation is defined as the difference of the volume of the transition state V^\ddagger and the volume of the corresponding reactants V^{A-B} .^[13,20,22]

Aiming to find the optimal solvent for the title reaction, we applied PCP-SAFT to the Michael additions between diethyl malonate (**2**) and *trans*- β -nitrostyrene (**1a**) (Scheme 2). The pure-component thermodynamic data such as vapor pressure, density data, and activity coefficients of the reacting agents were available in the literature,^[23] except for Michael adduct **4a**, which were therefore determined experimentally. Based on these reaction-independent data PCP-SAFT parameters were fitted (see Section 8 in supporting information).

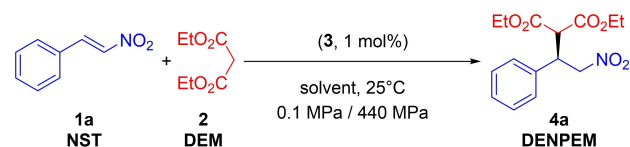
Thermodynamics limits the equilibrium-yield of chemical reactions, depending on the reaction conditions. Further, reaction kinetics depend on the solvent, which can be expressed *via* thermodynamic activities of the reacting agents. These effect of solvent and of pressure on yield and kinetics were investigated for the reaction shown in Scheme 2. The equilibrium constant for this reaction is given by [Equation (1)].

$$K_{th} = \frac{a_{DENPEM}}{a_{NST} \cdot a_{DEM}} \quad (1)$$

[Eq. (1)] is based on thermodynamic activities of the reacting agents **1a**, **2** and **4a**, which are defined as the product of the equilibrium mole fractions and activity coefficients of the



Scheme 1. 1,4-conjugate addition of diethyl malonate (**2**) to *N*-, *S*- and *O*-containing aromatic nitroolefins **1** catalyzed by thiourea derivative **3** at high pressure.



Scheme 2. Model reaction of diethyl malonate (DEM, **2**) and *trans*- β -nitrostyrene (NST, **1a**) in different solvents and at different pressures.

respective component. K_{th} is a function of temperature and pressure, however, it is independent of concentrations and of solvents. Consequently, solvent effects on the reaction-equilibrium concentrations can be predicted for known K_{th} values based on the molecular interactions of the reacting agents with the solvent. Thermodynamic models, e.g. PCP-SAFT, give access to thermodynamic activities and are therefore well-suited tools that allow predicting solvent effects on reaction equilibria.^[5,6]

Reaction kinetics are expressed in [Eq. (2)] as change of the product mole fraction with time.

$$\frac{dx_{DENPEM}}{dt} = k_1 \cdot a_{NST} \cdot a_{DEM} - k_{-1} \cdot a_{DENPEM} \quad (2)$$

Here, k_1 and k_{-1} denote the rate constants of the forth and back reactions, respectively, that are directly linked to the thermodynamic equilibrium constant according to [Eq. (3)].

$$K_{th} = \frac{k_1}{k_{-1}} \quad (3)$$

Owing to the activity-based expressions in [Equations (1) and (2)], also the kinetic constants k_1 and k_{-1} are independent of both, concentrations and solvent. Based on these physical relationships, thermodynamic models can be used to predict solvent effects on reaction kinetics.^[5,7]

The equilibrium constant K_{th} and the kinetic constants k_1 and k_{-1} depend on pressure. These pressure effects on the reaction equilibrium are quantified by the standard volume of reaction $\Delta^R v^0$:

$$\left(\frac{\partial \ln(K_{th})}{\partial p}\right)_T = \frac{-\Delta^R v^0}{R \cdot T} \quad (4)$$

Applying transition-state theory allows quantifying pressure effects on the reaction rate as a function of the volume of activation:

$$\left(\frac{\partial \ln(k)}{\partial p}\right)_T = \frac{-\Delta v^\ddagger}{R \cdot T} \quad (5)$$

In order to determine the equilibrium constant as well as the kinetic constants, the reaction rate and the reaction-equilibrium mole fractions for the addition of diethyl malonate (DEM, **2**) to *trans*- β -nitrostyrene (NST, **1a**) were measured experimentally in the solvent toluene at 0.1 MPa and at 440 MPa. Based on these data, solvent effects on the reaction rate and equilibrium yield were predicted *via* activity coefficients at 0.1 MPa as well as at high-pressure conditions: First, the in-silico solvent screening was performed at 0.1 MPa for solvents covering different solvent classes.

The screening results showed that *n*-hexane had the strongest beneficial effect on the reaction. That is, among the solvents studied, PCP-SAFT predicted that *n*-hexane should lead to the fastest reaction rate and also to the highest product yield at reaction equilibrium. In contrast to that, it was predicted that

dichloromethane would have the most disadvantageous effect on the reaction yield and kinetics (Figure 1, lines).

In order to validate the PCP-SAFT predictions, the kinetic profiles were measured in different solvents (see Figure 1, triangles). Dichloromethane, toluene and a solvent mixture of *n*-hexane/toluene mixture (1:1, %_v) were chosen for this purpose. The latter was necessary due to the insufficient solubility of the reactants in pure *n*-hexane alone as solvent. The experimental results were in excellent agreement with the PCP-SAFT predictions, both with respect to kinetics but also reflected the trend in yield at equilibrium for a given solvent. The data show that PCP-SAFT is a meaningful tool for solvent

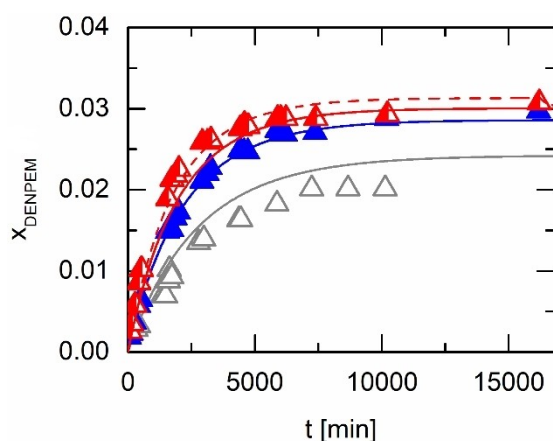


Figure 1. Mole fraction of the reaction product DENPEM plotted against reaction time at 0.1 MPa and 25 °C in different solvents. Symbols: experimental data (gray empty triangles: dichloromethane, blue triangles: toluene, red half-filled triangles: *n*-hexane/toluene). Lines: PCP-SAFT predictions (gray: dichloromethane, blue: toluene, solid red line: *n*-hexane/toluene, dashed red line: *n*-hexane). Reaction conditions: Nitroolefin 1 **a** (1.0 equiv.), diethyl malonate (DEM, **2**) (2.0 equiv.), catalyst **3** (1 mol%) in solvent (0.5 M, with respect to nitroolefin 1 **a**).

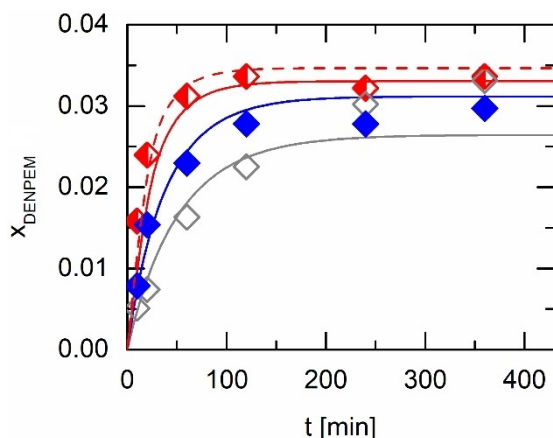


Figure 2. Mole fraction of the reaction product DENPEM plotted against reaction time at 440 MPa and 25 °C in different solvents. Symbols: experimental data (gray empty diamonds: dichloromethane, blue diamonds: toluene, red half-filled diamonds: *n*-hexane/toluene). Lines: PCP-SAFT predictions (gray: dichloromethane, blue: toluene, solid red line: *n*-hexane/toluene, dashed red line: *n*-hexane). Reaction conditions: Nitroolefin 1 **a** (1.0 equiv.), diethyl malonate (DEM, **2**) (2.0 equiv.), catalyst **3** (1 mol%) in solvent (0.5 M, with respect to nitroolefin 1 **a**).

screening using thermodynamic activities as proposed in [Eqs. (1) and (2)].

Subsequently, the in-silico solvent screening was performed at 440 MPa to evaluate if PCP-SAFT can also be used to predict the reactants and product activities in [Eqs. (1) and (2)] at high hydrostatic pressure (Figure 2).

Also under high-pressure conditions, PCP-SAFT again predicts the influence of solvent with respect to kinetics with high accuracy (Figure 2, lines), being in strong agreement with the experimental results (Figure 2, diamonds). Yet, PCP-SAFT slightly underestimates the equilibrium endpoint in dichloromethane.

The approach followed in this study was finally evaluated at even higher pressure (800 MPa), taken the reaction of 1 **a** and 2 in toluene as a representative example (Figure 3). PCP-SAFT predicted a further rate acceleration but no significant change in the equilibrium compared to performing the reaction at 440 MPa, which was again verified by the experimental data obtained.

We next explored the scope of the Michael addition of diethyl malonate (DEM, 2) and various heteroaromatic nitroolefins 1 at 440 MPa.^[24] PCP-SAFT predicted DCM to be an inferior solvent, which was consequently not chosen. Due to solubility reasons, we had to compromise to run all reactions in toluene. The loading of the catalyst 3 was reduced from the typically employed 10 mol%^[17,18] to 1 mol%, and for comparison, ambient pressure reactions under the same conditions were run in parallel. Under these reaction conditions, the corresponding Michael adducts 4b–j (Table 1, entries 1–9) were obtained at ambient pressure as well as at high pressure in a clean reaction: lower yields obtained are the results of an incomplete conversion of the reaction partners. Gratifyingly, the high enantioselectivities obtained at ambient pressures are mirrored at 440 MPa, indicating that pressure is not inducing an uncatalyzed background reaction or altering the catalyst-substrate arrangement necessary for asymmetric induction. The benefit of the high-pressure conditions becomes apparent

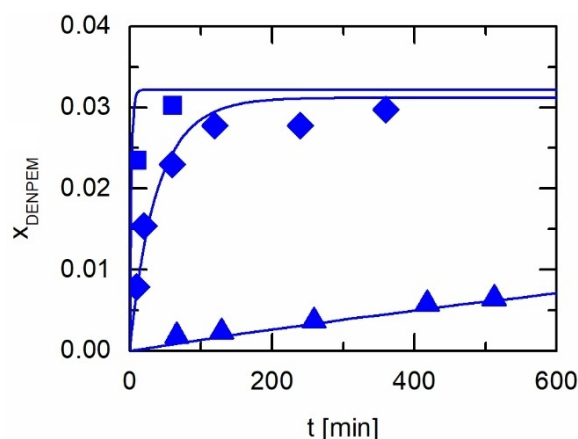


Figure 3. Mole fraction of the reaction product DENPEM plotted against reaction time at 25 °C in toluene. Symbols: experimental data at different pressures (triangles: 0.1 MPa, diamonds: 440 MPa, squares: 800 MPa), lines: PCP-SAFT predictions. Reaction conditions: Nitroolefin 1 **a** (1.0 equiv.), diethyl malonate (DEM, **2**) (2.0 equiv.), catalyst **3** (1 mol%) in solvent (0.5 M, with respect to nitroolefin 1 **a**).

Table 1. Substrate scope of the Michael reaction of diethyl malonate (DEM, 2) to different nitroolefins 1.

| Entry | Ar | P [Mpa] | Time | Solvent | Yield ^[a] | ee ^[b] |
|-------|----|------------|------|---------|------------------------------------|-------------------|
| 1 | | 0.1 440 | 4 h | toluene | 4b , 50% 4b , 99% | 94% 94% |
| 2 | | 0.1 440 | 24 h | toluene | 4c , 20% 4c , 50% | [c] [c] |
| 3 | | 0.1 440 | 24 h | toluene | 4d , 28% 4d , 93% | 92% 93% |
| 4 | | 0.1 440 | 24 h | toluene | 4e , 18% 4e , 67% | 86% 91% |
| 5 | | 0.1 440 | 24 h | toluene | 4f , 22% 4f , 79% | 91% 91% |
| 6 | | 0.1 440 | 24 h | toluene | 4g , 8% 4g , 80% | 85% 85% |
| 7 | | 0.1 440 | 24 h | toluene | 4h , 40% 4h , 83% | 91% 90% |
| 8 | | 0.1 440 | 24 h | toluene | 4i , 25% 4i , 32% | 88% 90% |
| 9 | | 0.1 440 | 24 h | toluene | 4j , 28% 4j , 67% | 87% 87% |
| 10 | | 0.1 440 | 24 h | THF | 4k , 5% 4k , 62% | 60% 60% |
| 11 | | 0.1 440 | 24 h | THF | 4l , 9% 4l , 92% | 70% 70% |
| 12 | | 0.1 440 | 24 h | THF | 4m , 10% 4m , 84% | 69% 69% |

Reaction conditions: Nitroolefin 1 (0.40 mmol, 1.0 equiv.), diethyl malonate (DEM, 2) (0.80 mmol, 2.0 equiv.), catalyst 3 (1 mol%) in solvent (0.8 mL, 0.5 M with respect to nitroolefin 1). [a] Isolated yields, which closely correlate with the conversion of the starting materials [b] Enantiomeric excess was determined by chiral HPLC. [c] HPLC analysis was not possible due to the instability of the product.

when comparing yields at a given reaction time being higher by a factor of 2–12, suggesting that the necessary, but entropically disfavored ternary arrangement of nitroolefin 1, DEM 2 and catalyst 3 in the transition state has a negative volume of activation.

In the case of pyridyl (**4k**) and unprotected indolyl nitroolefins (**4l**, **4m**) the solvent had to be changed to THF (PCP-SAFT simulation see supporting information, Figure S8) due to the lack of solubility for those substrates in less polar solvents. While the reactions again were greatly accelerated under pressure a significant reduction in enantioselectivity (Table 1, entries 10–12) was observed. This can be attributed to the ability of THF to interact with the catalyst 3 via hydrogen

bonding and thereby disrupt the catalyst substrate arrangement necessary for high stereoselection.

In conclusion, it is demonstrated for the first time that thermodynamic-based PCP-SAFT screening can be applied at high hydrostatic pressures (up to 800 MPa) in liquid phase to predict solvent effects relevant for the reaction outcome with respect to kinetics and yield. Thus, the asymmetric Michael addition reaction of diethylmalonate to various heteroaromatic nitroolefins was significantly enhanced with respect to catalyst loading (from 10 down to 1 mol%) and reaction time (from 24–72 h down to 4–24 h). No erosion of enantioselectivity is observed, proving that the application of pressure did not induce an uncatalyzed background reaction. The obtained products are valuable for the synthesis of analogs of Baclofen, a pharmaceutical agent used to treat spastic movement disorders such as multiple sclerosis, as demonstrated with the conversion of **4l** (see supporting information). The combination of PCP-SAFT and high hydrostatic pressure appears to be promising for improving on the major drawbacks of sluggish process cycles generally encountered in organocatalyzed reactions.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: high-pressure chemistry · kinetics · Michael addition · organocatalysis · thermodynamics

- [1] M. Berthelot, P. De Saint-Gilles, *Recherches sur les affinités de la formation et de la décomposition des éthers*, Mallet-Bachelier, 1862.
- [2] a) S. Brownstein, *Can. J. Chem.* **1960**, *38*, 1590–1596; b) O. Tapia, J. Bertrán, *Solvent Effects and Chemical Reactivity*, Vol. 17, Springer, 1996; c) C. Reichardt, T. Welton, *Solvents and solvent effects in organic chemistry*, Wiley-VCH, Weinheim, Germany, 2011.
- [3] a) A. Behr, J. Leschinski, C. Awungacha, S. Simic, T. Knoth, *ChemSusChem* **2009**, *2*, 71–76; b) A. Behr, N. Tenhumberg, A. Wintzer, *RSC Adv.* **2013**, *3*, 172–180; c) S. Grob, H. Hasse, *J. Chem. Eng. Data* **2005**, *50*, 92–101; d) H. Struebing, Z. Ganase, P. G. Karamertzanis, E. Sioungkrou, P. Haycock, P. M. Piccione, A. Armstrong, A. Galindo, C. S. Adjiman, *Nat. Chem.* **2013**, *5*, 952–957.
- [4] a) A. Wangler, R. Loll, T. Greinert, G. Sadowski, C. Held, *J. Chem. Thermodyn.* **2019**, *128*, 275–282; b) A. Wangler, A. Hüser, G. Sadowski, C. Held, *ACS Omega* **2019**, *4*, 6264–6272; c) A. Wangler, R. Canales, C. Held, T. Q. Luong, R. Winter, D. H. Zaitsau, S. P. Verevkin, G. Sadowski, *Phys. Chem. Chem. Phys.* **2018**, *20*, 11317–11326; d) M. Voges, R. Abu, M. T. Gundersen, C. Held, J. M. Woodley, G. Sadowski, *Org. Process Res. Dev.* **2017**, *21*, 976–986; e) M. Voges, C. Fischer, D. Wolff, C. Held, *Org. Process Res. Dev.* **2017**, *21*, 1059–1068; f) M. Voges, F. Fischer, M. Neuhaus, G. Sadowski, C. Held, *Ind. Eng. Chem. Res.* **2017**, *56*, 5535–5546; g) A. E. M. Janssen, B. J. Sijursnes, A. V. Vakurov, P. J. Halling, *Enzyme Microb.*

- Technol. **1999**, *24*, 463–470; h) A. E. M. Janssen, A. M. Vaidya, P. J. Halling, *Enzyme Microb. Technol.* **1996**, *18*, 340–346.
- [5] M. Lemberg, R. Schomäcker, G. Sadowski, *Chem. Eng. Sci.* **2018**, *176*, 264–269.
- [6] M. Lemberg, G. Sadowski, M. Gerlach, E. Kohls, M. Stein, C. Hamel, A. Seidel-Morgenstern, *AIChE J.* **2017**, *63*, 4576–4585.
- [7] M. Lemberg, G. Sadowski, *ChemPhysChem* **2017**, *18*, 1977–1980.
- [8] a) O. Riechert, M. Husham, G. Sadowski, T. Zeiner, *AIChE J.* **2015**, *61*, 3000–3011; b) R. Rönnback, T. Salmi, A. Vuori, H. Haario, J. Lehtonen, A. Sundqvist, E. Tirronen, *Chem. Eng. Sci.* **1997**, *52*, 3369–3381; c) H. Teo, B. Saha, *J. Catal.* **2004**, *228*, 174–182; d) V. K. S. Pappu, A. J. Yanez, L. Peereboom, E. Muller, C. T. Lira, D. J. Miller, *Bioresour. Technol.* **2011**, *102*, 4270–4272; e) Y. Qu, S. Peng, S. Wang, Z. Zhang, J. Wang, *Chin. J. Chem. Eng.* **2009**, *17*, 773–780; f) M. T. Sanz, R. Murga, S. Beltrán, J. L. Cabezas, J. Coca, *Ind. Eng. Chem. Res.* **2002**, *41*, 512–517; g) P. Kiviranta-Pääkkönen, L. Struckmann, A. O. I. Krause, *Chem. Eng. Technol.* **1998**, *21*, 321; h) P. Delgado, M. T. Sanz, S. Beltrán, *Chem. Eng. J.* **2007**, *126*, 111–118; i) P. Patidar, S. M. Mahajani, *Chem. Eng. J.* **2012**, *207–208*, 377–387; j) A. K. Kolah, N. S. Asthana, D. T. Vu, C. T. Lira, D. J. Miller, *Ind. Eng. Chem. Res.* **2007**, *46*, 3180–3187; k) J. Gangadwala, S. Mankar, S. Mahajani, A. Kienle, E. Stein, *Ind. Eng. Chem. Res.* **2003**, *42*, 2146–2155; l) L. K. Rihko, P. K. Kiviranta-Pääkkönen, A. O. I. Krause, *Ind. Eng. Chem. Res.* **1997**, *36*, 614–621; m) T. Pöpken, L. Götze, J. Gmehling, *Ind. Eng. Chem. Res.* **2000**, *39*, 2601–2611; n) A. Orjuela, A. J. Yanez, A. Santhanakrishnan, C. T. Lira, D. J. Miller, *Chem. Eng. J.* **2012**, *188*, 98–107; o) W.-T. Liu, C.-S. Tan, *Ind. Eng. Chem. Res.* **2001**, *40*, 3281–3286.
- [9] M. Planck, *Ann. Phys. Chem.* **1887**, *268*, 462–503.
- [10] V. Rothmund, *Z. Phys. Chem.* **1896**, *20 U*.
- [11] a) R. Winter, D. Lopes, S. Grudzielanek, K. Vogtt, *J. Non-Equilib. Thermodyn.* **2007**, *32*, 367; b) T. Q. Luong, S. Kapoor, R. Winter, *ChemPhysChem* **2015**, *16*, 3555–3571.
- [12] a) S. W. Benson, J. A. Berson, *J. Am. Chem. Soc.* **1962**, *84*, 152–158; b) E. Whalley, *Ber. Bunsen-Ges.* **1996**, *70*, 958–968; c) J. H. Espenson, *Chemical kinetics and reaction mechanisms, Vol. 102*, Citeseer, **1995**; d) H. Tiltcher, H. Hofmann, *Chem. Eng. Sci.* **1987**, *42*, 959–977; e) D. G. Peck, A. J. Mehta, K. P. Johnston, *J. Phys. Chem.* **1989**, *93*, 4297–4304; f) G. Jenner, *J. Phys. Org. Chem.* **2002**, *15*, 1–13; g) F.-G. Klärner, F. Wurche, *J. Prakt. Chem.* **2000**, *342*, 609–636; h) R. van Eldik, *Angew. Chem. Int. Ed.* **1986**, *25*, 673–682; *Angew. Chem.* **1986**, *98*, 671–680; i) G. Jenner, *Angew. Chem. Int. Ed.* **1975**, *14*, 137–143; *Angew. Chem.* **1975**, *87*, 186–194; j) A. Cholewiak, K. Adamczyk, M. Kopyt, A. Kasztelan, P. Kwiatkowski, *Org. Biomol. Chem.* **2018**, *16*, 4365–4371; k) H. Kotsuki, M. Moritaka, K. Nakano, *Heterocycles* **2013**, *87*, 2351; l) P. Kwiatkowski, A. Cholewiak, A. Kasztelan, *Org. Lett.* **2014**, *16*, 5930–5933; m) P. Kwiatkowski, K. Dudziński, D. Łyżwa, *Org. Lett.* **2011**, *13*, 3624–3627; n) N. Miyamae, N. Watanabe, M. Moritaka, K. Nakano, Y. Ichikawa, H. Kotsuki, *Org. Biomol. Chem.* **2014**, *12*, 5847–5855.
- [13] P. Kwiatkowski, K. Dudziński, D. Łyżwa in *Comprehensive Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2013**, pp. 579–615.
- [14] K. Matsumoto, T. Uchida, *Chem. Lett.* **1981**, *10*, 1673–1676.
- [15] a) M. E. G. Hendrickx, D. Knorr, L. Ludikhuyze, A. Loey, V. Heinz, *Ultra High Pressure Treatments of Foods*, Springer, US, **2012**; b) P. C. K. Cheung, B. M. Mehta (Eds.) *Handbook of food chemistry*, Springer Reference, Heidelberg, New York, Dordrecht, London, **2015**.
- [16] a) Y.-H. Li, P. S. Akula, B.-C. Hong, C.-H. Peng, G.-H. Lee, *Org. Lett.* **2019**, *21*, 7750–7754; b) N. Ono, H. Feuer (Eds.) *Wiley Series in Organic Nitro Chemistry*, John Wiley & Sons, Inc, New York, USA, **2001**; c) S. Z. Zard, *Helv. Chim. Acta* **2012**, *95*, 1730–1757.
- [17] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
- [18] T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125.
- [19] a) J. Gross, G. Sadowski, *Ind. Eng. Chem. Res.* **2001**, *40*, 1244–1260; b) J. Gross, J. Vrabec, *AIChE J.* **2006**, *52*, 1194–1204.
- [20] G. Jenner, *Tetrahedron* **2002**, *58*, 5185–5202.
- [21] T. Weinbender, M. Hofmann, O. Reiser, *Biophys. Chem.* **2019**, 106280.
- [22] a) O. Reiser, *Top. Catal.* **1998**, *5*, 105–112; b) B. Chen, R. Hoffmann, R. Cammi, *Angew. Chem. Int. Ed.* **2017**, *56*, 11126–11142; *Angew. Chem.* **2017**, *129*, 11278–11295.
- [23] a) A. Brozena, J. H. Buchanan, R. W. Miles, B. R. Williams, M. S. Hulet, *J. Chem. Eng. Data* **2014**, *59*, 2649–2659; b) J. A. Riddick, W. B. Bunger, T. K. Sakano, *Organic Solvents: Physical Properties and Methods of Purification*, Wiley, **1986**; c) S. L. Oswal, P. Oswal, P. S. Modi, J. P. Dave, R. L. Gardas, *Thermochim. Acta* **2004**, *410*, 1–14; d) C. L. Yaws, *Chemical properties handbook. Physical, thermodynamic, environmental, transport, safety, and health related properties for organic and inorganic chemicals*, Knovel, Norwich, NY, **2001**.
- [24] For reactions on preparative scale, we could not go beyond 440 MPa with the pressure equipment available to us.

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