Doctoral Thesis

Aerobic alcohol oxidations mediated by nitric acid

Author(s):
Aellig, Christof

Publication Date:
2013

Permanent Link:
https://doi.org/10.3929/ethz-a-009995236

Rights / License:
In Copyright - Non-Commercial Use Permitted
Aerobic Alcohol Oxidations Mediated by Nitric Acid

A dissertation submitted to

ETH ZÜRICH
for the degree of
DOCTOR OF SCIENCE

Presented by

CHRISTOF AELLIG
MSc Chemical and Bioengineering, ETH Zürich
born on March 22, 1985

citizen of Adelboden (BE)

accepted on the recommendation of

Prof. Dr. Ive Hermans
Prof. Dr. Christophe Copéret

2013
"Wer kämpft, kann verlieren. Wer nicht kämpft, hat schon verloren."

(Berthold Brecht)
Acknowledgements

Firstly, I would like to thank Professor Ive Hermans for the opportunity to do my PhD in his group at the Institute of Chemical and Bioengineering. His excellent supervision, guidance and motivation and outstanding knowledge in the fields of catalysis and chemical engineering were crucial for the successful completion of my PhD.

I would also like to thank Professor Christophe Copéret for the scientific discussions we had, for accepting the task of co-examiner and his competent review of this work.

Not all experiments could be performed with commercially available devices, and therefore I also would like to thank the staff of ETH Zürich for helping me solve technical problems. In particular, the people from the workshop namely Roland Walker, Jean-Pierre Mächler, Roland Mäder, Philippe Trüssel, Markus Kämpfer and Urs Krebs, were especially important. I would also like to give my thanks to Andreas Dutly for helping me out with GC problems, Erol Dedeoglu for helping out with computer problems, Max Wohlwend for solving my electrical problems and Max Haueter for helping me out with administrative issues. Special thanks from my part should be addressed to Ján Kovacovic for his support in the high pressure lab where most of my work was performed. Not only did he help with technical problems, but he also kept the infrastructure of the lab in an excellent condition which resulted in a clean and pleasant working environment.

The completion of this PhD would not have been possible without the help of several undergraduate students. I would like to thank Christophe Girard and Tobias Keller who helped me unravel the mechanism HNO₃ mediated aerobic alcohol oxidations. In addition I would like to extend a very special thanks to David Scholz, whose excellent skills in the lab and outstanding motivation contributed to a large part of my work.
Over the last years the Hermans group made my life at ETH very constructive and enjoyable. Therefore I would like to thank Philipp Mania, Eyal Spier, Natascia Turrá, Martin Schümperli, Patrick Wolf, Sabrina Condrad and Dr. Ceri Hammond. Their input in numerous discussions and seminars brought me a great leap forward in my own research. A special thanks goes to Dr. Ullrich Neuenschwander who was always a mentor and very patient and helpful in the beginning of my PhD.

A thanks also goes to all my friends and acquaintances over the years in Zürich. I would also like to thank all my friends from my hometown who were very helpful in giving diversity to my life, thereby allowing me forget research sometimes in order to return very motivated once more to the university.

Finally I would like to thank my family who all in their own way contributed to this thesis. Their support made my life easier and much more pleasant.
Table of Contents

Acknowledgments ........................................................................................................ iii
Table of Contents ....................................................................................................... v
Summary ..................................................................................................................... vii
Zusammenfassung ....................................................................................................... x

1 Introduction ........................................................................................................... 1
  1.1 Selective Oxidations and Reaction Engineering ............................................. 1
  1.2 Aerobic Alcohol Oxidations on Solid Catalysts ............................................. 2
  1.3 Nitric Acid based Oxidations ........................................................................ 3

2 Aerobic Alcohol Oxidations Mediated by Nitric Acid ........................................ 5
  2.1 Introduction ..................................................................................................... 6
  2.2 Kinetic Analysis of the Oxidation of Benzyl Alcohol .................................... 6
  2.3 Conclusions .................................................................................................. 17
  2.4 Experimental Section .................................................................................. 18

3 Acid-Catalyzed Decomposition of the Benzyl Nitrite Intermediate in HNO₃ Mediated Aerobic Oxidation of Benzyl Alcohol ............................................. 19
  3.1 Introduction ................................................................................................... 20
  3.2 Benzyl Nitrite Decomposition Experiments ................................................ 21
  3.3 Kinetic Isotope Effect and Influence of Electron Donating and
      Withdrawing Substituents on Nitrite Decomposition .................................... 24
  3.4 Oxidation of Substituted Alcohols ................................................................. 27
  3.5 Conclusions .................................................................................................. 29
  3.6 Experimental Section .................................................................................. 29

4 Intensification under Three-Phase Flow Conditions ........................................... 31
  4.1 Introduction ................................................................................................... 32
  4.2 Reactor Set-Up ............................................................................................. 32
Summary

The selective oxyfunctionalization of organic substrates plays a very important role in the chemical industry. Despite its industrial relevance the scientific understanding lags behind the current state-of-the-art. Radical-chain autoxidations are a classical example of large-scale technology which is still not completely understood. Nitric acid based oxidations are another example of poorly understood processes of tremendous industrial importance. The production of adipic acid (3 Mt/year) which is an important building block for the nylon-6,6 synthesis is just one example. One of the intrinsic challenges in this field is the prevention of side or consecutive reactions since the products are most often more reactive than the substrates. Especially the selective oxidation of primary alcohols to the corresponding aldehydes is not an easy task because of the overoxidation to the carboxylic acids. Therefore a profound understanding of the reaction kinetics and thermodynamics are an important prerequisite in order to be able to optimize the selectivity to the desired product.

Chapter 1 presents a mini review of the oxyfunctionalisation of organic substrates, focusing on aerobic alcohol oxidations. Both transition metal based and nitric acid based alcohol oxidations are discussed. Additionally the industrial importance of these transformations is highlighted.

Chapter 2 focuses on the reaction mechanism of the partial aerobic oxidation of benzyl alcohol to benzaldehyde mediated by nitric acid. From this study, it can be concluded that HNO₃ is able to start off a chain oxidation of benzyl alcohol, mediated by (H)NOₓ species; O₂ is however the terminal oxidant. A significant increase in chain length, and hence an improved yield, can be achieved at lower temperature, or upon drying of the gas phase. This chain reaction is catalyzed by the solid acid Amberlyst-15®. Depending on the acid catalyst loading, either the HNO₃ or the nitrite decomposition is rate determining; both steps are acid catalyzed.
In chapter 3 the importance of the acid-catalyzed decomposition of the benzyl nitrite intermediate during the HNO₃-mediated aerobic oxidation of benzyl alcohol is corroborated. Nitrite decomposition is identified as the source of N₂O. A linear Hammett plot with a negative slope is obtained that indicates a transition state with reduced electron density. Kinetic isotope effect studies imply that cleavage of the Cα-H bond is involved in the decisive transition state, and electron withdrawing groups are found to reduce the reactivity of the nitrite significantly. This effect is also reflected in the overall oxidation reaction of the corresponding alcohol, thereby supporting the reaction mechanism.

In chapter 4 a continuous process for the aerobic oxidations of alcohols mediated by HNO₃ was developed. A significant increase in the reaction rate and two orders of magnitude in the space-time-yield could be observed for the aerobic oxidation of benzyl alcohol to benzaldehyde, compared to other reactors. Additionally, the activity of the catalyst was maintained over two weeks making the process attractive compared to transition metal catalyzed systems that very often suffer from deactivation and/or low activities. The increased reaction rate can not only be attributed to a higher catalyst-to-substrate ratio in the flow reactor, but also to a longer HNO chain length, which minimizes both the initial amount of HNO₃ required for efficient oxidation, and the production of N₂O. Furthermore, this increased (H)NOₓ selectivity is also accompanied by an increased carbonyl selectivity, due to the decrease in over-oxidation products and the termination of the oxygen shuttle species. The continuous reaction system could successfully be extended to oxidize several aliphatic and non-aliphatic primary and secondary alcohols always showing a high reaction rate and selectivity.

In chapter 5 The continuous aerobic oxidation of different alcohols using a heterogeneous immobilized TEMPO catalyst was examined. High reaction rates, conversions and selectivities could be obtained. The catalyst remained stable over several hours under mild conditions making the process attractive. Due to the high
reaction rates, only small amounts of HNO$_3$ as co-oxidant have to be used. The system is broadly applicable to a wide range of primary and secondary alcohols, always showing high reaction rates and selectivities. Another advantage of this continuous system is the flexibility of tuning the selectivity in consecutive reactions depending on the application. This can be seen in the case of 5-hydroxymethylfurural oxidation where high yields of either 2,5-diformylfuran or 2,5-furandicarboxylic acid can be obtained, depending on the contact time. Additionally, less stable alcohols like lactic acid or prenols could be smoothly oxidized, due to the moderate conditions of only 55 °C and 5 bar O$_2$. 
Zusammenfassung


In Kapitel 2 wird der Fokus auf den Reaktionsmechanismus von der partiellen aeroben Oxidation von Benzylalkohol zu Benzaldehyd mithilfe von HNO₃ gelegt. Aus dieser Arbeit kann geschlossen werden, dass HNO₃ eine Kettenoxidationsreaktion von Benzylalkohol starten kann, die mithilfe von (H)NOₓ Spezies abläuft, wo aber O₂ das terminale Oxidationsmittel ist. Bei tieferer Temperatur oder wenn die Gasphase getrocknet wird, können die Selektivität und die Ausbeute signifikant erhöht werden. Diese Kettenreaktion wird durch die Feststoffsäure Amberlyst-15® katalysiert. In
Abhängigkeit der Menge an Katalysator, ist in der Reaktion entweder der säurenkatalysierte Zerfall vom Nitritester oder der Zerfall von HNO₃ der geschwindigkeitsbestimmende Schritt.

In Kapitel 3 wird die Wichtigkeit des säurenkatalysierten Zerfalls vom Benzylnitritester in der aeroben Alkoholoxidation von Benzylalkohol mithilfe von HNO₃ näher erläutert. Der Nitritzerfall wird als Quelle der Bildung von N₂O identifiziert. Ein linearer Hammett Graph mit einer negativen Steigung wurde erhalten, was auf einen Übergangszustand mit reduzierter Elektronendichte hindeutet. Die Untersuchung vom kinetischen Isotopeneffekt deutet darauf hin, dass die Trennung der Cₓ-H Bindung im entscheidenden Übergangszustand involviert ist. Elektronegative Gruppen in Paraposition reduzieren die Reaktivität vom Nitrit entscheidend. Dieser Effekt kann auch in der Oxidationsreaktion vom entsprechenden Alkohol beobachtet werden, was den vorgeschlagenen Reaktionsmechanismus stützt.

In Kapitel 4 wird ein kontinuierlicher Prozess für die aerobe Alkoholoxidation mithilfe von HNO₃ entwickelt. Dabei konnte ein signifikanter Anstieg der Reaktionsgeschwindigkeit und der spezifischen Produkteleistung im Vergleich zu anderen Reaktoren beobachtet werden. Zusätzlich blieb die Aktivität des Katalysators über zwei Wochen stabil. Die erhöhte Reaktionsgeschwindigkeit kann dabei nicht nur auf das erhöhte Katalysator- zu Substratverhältnis im kontinuierlichen Flussreaktor zurückgeführt werden, aber auch auf eine Kettenverlängerung der HNOₓ Spezies. Dies führt zu einer Reduktion der N₂O Bildung und der eingesetzten HNO₃ Menge, die für eine effiziente Oxidation gebraucht wird. Diese erhöhte (H)NOₓ Selektivität wird durch eine erhöhte Carbonylselectivität begleitet, was durch eine Verringerung der Überoxidation zu den entsprechenden Carbonsäuren zu erklären ist. Dieses kontinuierliche Reaktionssystem konnte erfolgreich auf andere aliphatische und nicht aliphatische, primäre und sekundäre Alkohole erweitert
werden, dabei wurden immer hohe Reaktionsgeschwindigkeiten und Selektivitäten beobachtet.

1 Introduction

1.1 Selective Oxidations and Reaction Engineering

At the moment coal, natural gas and petroleum cover approximately 96 % of all organic chemicals and 86 % of our energy demand.[1] In future it will be more difficult to meet the growing market demands with the existing petroleum and gas resources. Additionally, stricter legislation concerning CO₂ emissions and environmental pollution encourage both science and industry for the search of sustainable processes. The goals of green chemistry are to efficiently use raw (preferably renewable) materials, eliminating waste streams and the avoidance of toxic or hazardous chemicals and solvents in the manufacture and application of chemical products.[2] In this context oxidation chemistry plays and continues to play a very important role because it’s the tool in the manufacture of a lot of intermediates and monomers for the polymer industry.[3]

In the large domain of oxidation chemistry, oxygenations (i.e. uptake of oxygen) are an important sub-class, apart from other processes like biological oxidation, corrosion of metals or ageing of organic polymers. Oxygenations can be divided into heterolytic and homolytic ones depending on the reaction intermediates. In homolytic oxidation reactions, radicals are formed whereas in heterolytic oxidation reactions an active oxygen compound (peroxy acid, H₂O₂, metal in high valence state) oxidizes the substrate.[4]

The selective oxidative introduction of a functional group for example in alcohols or aldehydes, without over-oxidizing the desired product remains a challenge. In the past oxidants with high molecular weight such as chromates or permanganates have been used producing large amounts of (toxic) waste.[5] To overcome this problem in the design of new selective oxidations processes various parameters should be considered, like the correct choice of the oxidant or the catalyst which are pivotal for the downstream separation of the reaction mixture. But also the knowledge of the
intrinsic chemistry and the activation mechanism are very important parameters.\textsuperscript{[6]} Very often reaction engineering is not considered in chemical literature. Nevertheless, for the optimization of an existing process and to overcome problems like mass transfer limitations, selectivity and energy consumption, the choice and design of an optimal reactor is very important.

Molecular oxygen is the most sustainable of all oxidants. However, there are also safety issues, as it can form explosive mixtures with hydrocarbons. Therefore the use of diluted O\textsubscript{2} sources like air would be ideal. Additionally, the design of good catalysts is very important because the selectivity in direct air oxidations is still a problem.

1.2 Aerobic Alcohol Oxidations on Solid Catalysts

In recent years there has been a growing demand for solid catalysts in the oxidation of alcohols to their corresponding carbonyl compounds. These compounds are used as important intermediates throughout the chemical value chain. Homogeneous catalysis often offers powerful solutions but on an industrial scale problems related to corrosion and plating out on the reactor wall, handling, recovery and reuse of the catalyst pose serious limitations to these processes.\textsuperscript{[7]} In literature a lot of metals like Pt, Pd, Ru, Au, V, Cr or Mo immobilized on different supports have been used for the oxidation of primary and secondary alcohols and polyols.\textsuperscript{[8]} However, even the use of small amounts of transition metals can cause problems like the facile deactivation of the catalyst with oxidation products like acids and the possibility of toxic heavy metal traces in the product mixture. Therefore in many cases the use of metal-free heterogeneous systems is preferred.
1.3 Nitric Acid based Oxidations

Nitric acid is one of the most important chemicals in industry and is produced on a large scale through the Oswald process. First Ammonia is oxidized in two steps to nitrogen dioxide which subsequently is absorbed in water to yield nitric acid. It is mainly used as starting material for nitrogen fertilizers but also as nitrating agent in the preparation of explosives and organic intermediates such as nitroalkanes. Other applications include the use in chemical metallurgy such as etchant and pickling agent for stainless steel or in rocket fuel production.\[9\]

Scheme 1.3.1 Some important applications of HNO₃ based oxidations in the production of adipic acid (1), the production of glyoxylic acid (2) and the manufacture of methanesulfonic acid (3).

Nitric acid based oxidations are of tremendous industrial importance.\[9,10\] The production of adipic acid (3 Mt/year) - a building block for nylon-6,6 - from a mixture of cyclohexanol/cyclohexanone, the synthesis of glyoxylic acid (80 kt/year) - used in the synthesis of vanillin and Amoxicillin - as well as the oxidation of dimethyldisulfide to methanesulfonic acid (30 kt/year) - used in electroplating and detergent formulations - are just a few examples from bulk and commodity chemistry (Scheme 1.3.1).\[3,10,11\] However, oxidations with nitric acid are also extensively used for the
synthesis of fine-chemicals.\cite{12} The reason why HNO$_3$-based oxidations are so valuable is the fact that nitric acid is an inexpensive oxidant that can achieve remarkable selectivities. One disadvantage of this technology is the strongly acidic nature of nitric acid, especially when applied in high concentration. Another disadvantage is the stoichiometric reduction of the HNO$_3$ to NO$_x$ and N$_2$O. In a large-scale process (such as adipic acid synthesis),\cite{13} NO$_x$ and N$_2$O are separated, and the NO$_x$ is recycled into nitric acid. This *ex situ* NO$_x$ recycling however results in large, energy-consuming recycle streams. Moreover, on a smaller scale - such as typically encountered in fine-chemical industry - it usually does not pay off to recycle the NO$_x$. Nitrous oxide, being a severe greenhouse gas, cannot be recycled and should be (catalytically) decomposed prior to emission.\cite{3} More recently, N$_2$O arising from adipic acid production has also been used to oxidize olefins to valuable ketone products (see *e.g.* Scheme 1.3.2 for commercialized examples).\cite{3,14} To date the formation mechanism of N$_2$O in nitric acid based oxidations has not been elucidated, making it a difficult to decrease its formation. One of the key challenges is to lower the HNO$_3$ loading, preferably to catalytic amounts.

![Scheme 1.3.2](image)

*Scheme 1.3.2.* Oxidation of cyclopentadiene to cyclopentanone (1) and oxidation of cyclododecatriene to cyclododecadienone (2) with N$_2$O. Cyclopentanone is used amongst other things as an important intermediate in the formation of pharmaceuticals, crop protection agents and fragrances. Cyclododecatriene is an important intermediate in the manufacture of nylon-12.
2 Aerobic Alcohol Oxidations Mediated by Nitric Acid

Catalytic amounts of HNO₃ can trigger the aerobic oxidation of alcohols in the presence of the solid acid Amberlyst-15®. The desired oxidation cycle, mediated by (H)NOₓ species, is in kinetic competition with the detrimental formation of N₂O by HNO dimerization. In situ water removal in a gas recirculation reactor increases the reaction rate and the end-conversion by minimizing N₂O formation and increasing the (H)NOₓ turnover.
2.1 Introduction

Recently, aerobic oxidation reactions which use substoichiometric amounts of HNO$_3$ have been proposed.$^{[15-17]}$ In those systems, strong acids (such as hydrochloric acid), or carbon-based materials (such as activated carbon), are added to achieve a catalytic turnover in HNO$_3$. Although the reaction mechanism is currently unknown, the idea is very attractive. The final goal would be to develop a process which uses nitric acid as an oxygen carrier in which O$_2$ is the true terminal oxidant. However, the proposed systems suffer from various shortcomings, such as limited turnover. In addition, HCl leads to corrosive reaction conditions and poses recycling issues; highly dispersed carbon-based materials do not seem very appealing as oxidation catalysts from a stability or even safety point of view.

2.2 Kinetic Analysis of the Oxidation of Benzyl Alcohol

Herein, the aerobic oxidation of benzyl alcohol (PhCH$_2$OH) to benzaldehyde (PhCHO), by HNO$_3$, is investigated. This partial oxidation is not only a model reaction of interest to (fine-)chemical synthesis,$^{[18]}$ the selectivity of this reaction is also very sensitive to radical side-reactions which easily cause over-oxidation of PhCHO to benzoic acid (PhCOOH).$^{[19]}$ Selective aerobic alcohol oxidations with catalytic amounts of HNO$_3$ could offer an attractive metal-free alternative to precious-metal-catalyzed systems.

To investigate the HNO$_3$-based PhCH$_2$OH oxidation and to decouple the dual role of HNO$_3$-being both an oxidant and a strong acid sub-stoichiometric amounts of HNO$_3$ were used in the presence of a solid acid as (co-)catalyst. Screening of various solid acids, including most conventional zeolites (e.g., MFI, BEA, FAU, and MOR topologies), revealed the ion-exchange resin Amberlyst-15® in protonic form (4.7 meq g$^{-1}$) as a promising candidate. Actually, zeolites gave disappointing results, probably due to strong sorption of HNO$_3$ and NO$_x$ species, inhibiting the reaction. Our standard
experiments are performed in a bubble column reactor using 25 mL 1,4-dioxane as solvent, \([\text{PhCH}_2\text{OH}]_0 = 500 \text{ mM}, [\text{HNO}_3]_0 = 125 \text{ mM}, 150 \text{ mg of Amberlyst-15}^\circledR (\text{corresponding to} [\text{H}^+]_{\text{Amberlyst-15}} = 28 \text{ mM}), \text{and 1 bar of O}_2 \text{ (bubbling through at 100 mL min}^{-1}). \text{An induction period was observed which could be eliminated by the addition of small amounts of NaNO}_2 \text{ (Figure 2.2.1, curves a-c). This observation - known from the literature}^{[18]} \text{ - points towards the crucial role of HNO}_2, \text{which is formed upon protonation of NO}_2^-. \text{Inhibition of the reaction in the presence of urea - a known HNO}_2\text{ trap}^{[20]} \text{ - is in line with this hypothesis. NO and NO}_2\text{ can alternatively be used to shorten the induction period (see Appendix A.1), pointing towards an efficient interconversion of the nitrogen species}^{[21]}\text{. Interesting to note is that under N}_2\text{ bubbling (1 bar) at 80 °C, the conversion levels off after 6 h to 50 %, leading to a } \Delta[\text{PhCH}_2\text{OH}]/[\text{HNO}_3]_0 \approx 2. \text{ Under the same conditions, but in presence of 1 bar O}_2, \text{ a conversion of 80 % can be achieved in 6 h (see curve b in Figure 2.2.1). Nevertheless, the initial reaction rate is approximately 40 % lower in the presence of O}_2\text{, compared to N}_2 \text{ (see Appendix A.1). These observations indicate that oxygen plays an ambiguous role in this system. On the one hand O}_2\text{ is able to trigger a recycling of the active species and thereby increase the final conversion, on the other hand it reduces the reaction rate. At elevated O}_2\text{ pressures (e.g., 20 bar in a high pressure autoclave) the induction period is significantly longer than at atmospheric pressure, even in presence of initiator (Figure 2.2.1, curves e and d). This elongated induction period is probably caused by a shift of the equilibrated decomposition of HNO}_3\text{ to NO}_2\text{ towards the left-hand-side at higher O}_2\text{ pressure [Eq. (1)]. Indeed, NO}_2\text{ is able to form HNO}_2\text{ by Reaction (2)}^{[22]} \text{, the key oxidizing species in the system, and a shift of the equilibrium in Reaction (1) will hence reduce the HNO}_2\text{ concentration. Note that the Amberlyst-15}^\circledR \text{catalyst accelerates the HNO}_3\text{ decomposition to NO}_2\text{ (see Appendix A.1), thereby speeding up the formation of active species.}

\[
4 \text{HNO}_3 \rightleftharpoons 4 \text{NO}_2 + 2 \text{H}_2\text{O} + \text{O}_2 \quad \text{(1)}
\]

\[
2 \text{NO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{N}_2\text{O}_4 + \text{H}_2\text{O} \rightarrow \text{HNO}_3 + \text{HNO}_2 \quad \text{(2)}
\]
Figure 2.2.1 Effect of the NaNO$_2$ concentration on the PhCH$_2$OH conversion at 80 °C: a-c) at 1 bar O$_2$ (0, 5, and 15 mM NaNO$_2$, respectively); d, e) at 20 bar O$_2$ (0 and 5 mM NaNO$_2$, respectively).

Figure 2.2.2 PhCH$_2$OH conversion vs. time for various amounts of Amberlyst-15®: a-d): 50, 75, 100, and 150 mg (5 mM NaNO$_2$). The insert shows the dependency of the initial rate on the Amberlyst-15® amount.

Gas-liquid mass transfer is found to play an important role for this reaction: when the reaction is performed under a static O$_2$ pressure (in a round-bottom flask with an
oxygen balloon, conventional lab practice), the end-conversion is 20% lower than in a bubble column at the same pressure but with enhanced gas-liquid mass-transfer.

The reaction is quasi first-order in HNO$_3$, although the initial rate is clearly leveling off at increasing [HNO$_3$]$_0$ (see Appendix A.1). This observation points towards an initiating role of nitric acid, rather than a pure stoichiometric reaction. The reaction rate is proportional to the Amberlyst-15$^\circledR$ loading, up to 4 mg mL$^{-1}$ after which it levels off (Figure 2.2.2). Although this could in principle point towards gas-liquid mass-transfer limiting the reaction, an alternative mechanistic explanation is proposed below. Fluid-solid mass-transfer effects can be neglected as 1 mm Amberlyst-15$^\circledR$ beads have the same activity as the powdered catalyst (thus, the activity is independent of the fluid-solid interfacial area). The solid catalyst can be recycled several times without loss in activity.

Overall, the selectivity towards benzaldehyde (PhCHO) is very high, ranging from 95% at 80 °C to 98.5% at 60 °C. The most important by-products are benzyl nitrite, 2-benzyl-1,3-dioxolane (from acetylation of benzaldehyde with 1,2-dihydroxyethane, formed in the acid catalyzed decomposition of 1,4-dioxane$^{[23]}$), and benzoic acid (Figure 2.2.3). Interestingly, benzyl nitrite (PhCH$_2$ONO) can be identified as a reaction intermediate: its concentration initially increases, then decreases. The benzyl nitrite is formed in the equilibrated esterification reaction PhCH$_2$OH + HNO$_2$ ⇌ PhCH$_2$ONO + H$_2$O. Traces of benzyl nitrate, benzyl benzoate, dibenzylether, and benzyl formate (formed out of PhCH$_2$OH and formic acid, a decomposition product of 1,4-dioxane$^{[24]}$) are detected by GC-MS. The most important by-products arise from the use of dioxane as solvent and can be avoided when working in pure PhCH$_2$OH. Note that the maximum benzyl nitrite concentration is significantly higher at lower reaction temperatures (e.g. 34 mM at 60 °C vs. 21 mM at 80 °C); when the reaction is performed with less Amberlyst-15$^\circledR$ (e.g. 50 mg instead of 150 mg), the benzyl nitrite concentration remains below the GC-MS detection limit.
Doubling the initial alcohol concentration barely affects the rate at low Amberlyst-15® loadings, whereas first-order behavior is observed for higher catalyst loadings. Addition of conventional radical trappers, such as 2,4,6-tri-tert-butylphenol, did not significantly affect the reaction rate or selectivity, excluding the involvement of peroxyl or alkoxyl radicals as important reaction intermediates.

Mass spectrometry was used to monitor the evolution of NO (m/z 30) and N₂O (m/z 44) in the gas phase. N₂O was also monitored with transmission IR spectroscopy of the gas phase under static O₂ pressure of 1 bar (Figure 2.2.4; ν₃ vibrational mode), unambiguously assigning the m/z signal of 44 to nitrous oxide. No signal for nitric oxide was observed at 1876 cm⁻¹, probably due to the small dipole-moment change of the NO-stretch. Despite the yellow color of the liquid and the m/z signal of 46 determined in the liquid phase, no NO₂ could be detected in the gas phase, confirming that it is strongly absorbed in the 1,4-dioxane solution. The addition of water to the reaction mixture (in addition to the water already added in the
65% HNO₃ solution) prevents the formation of the yellow color and inhibits the reaction. Presumably, water traps NO₂ in Reaction (2). This observation suggests NO₂ as an important reaction intermediate.

![Image of IR spectra](image)

**Figure 2.2.4** Gas-phase transmission IR spectra from a reaction performed at 80 °C under static O₂ pressure of 1 bar (spectra shown after 0.5, 1, 2, 3, and 5 h; see Appendix A.1): ν₃ vibrational mode of N₂O.

Figure 2.2.5 shows the temperature dependence of the overall oxidation reaction catalyzed by 6 mg Amberlyst-15® per mL. The corresponding Arrhenius activation energy of (12±1) kcal mol⁻¹ excludes mass-transfer limitations as an explanation for the leveling off in reaction rate at higher Amberlyst-15® loadings (see Figure 2.2.2). Using only 2 mg Amberlyst-15® per mL, the activation energy is significantly higher, (33±1) kcal mol⁻¹. This observation, together with a change in reaction order in alcohol (see above), points towards a shift in rate-determining step when going from a low-to-high Amberlyst-15® loading. Interestingly, a higher end-conversion can be achieved at lower temperature.
Figure 2.2.5 Temperature dependency of the PhCH$_2$OH conversion in the presence of 5 mM NaNO$_2$ under standard conditions (a-d: 60, 70, 80, and 90 °C, respectively).

To understand the precise role of the benzyl nitrite ester (PhCH$_2$ONO) - experimentally identified as a reaction intermediate (see above) - we synthesized it according to a literature procedure[25] and studied its acid-catalyzed decomposition (see Appendix A.1). A stoichiometric amount of benzaldehyde is formed, confirming that the nitrite ester is a pivotal intermediate. The reaction is first order in both nitrite and Amberlyst-15$^\text{®}$. In the temperature range 40-70 °C, the rate constant is well described by the Arrhenius expression $(3\pm2) \times 10^6 \exp(-(13\pm1) \text{kcal mol}^{-1}/RT) \text{ M}^{-1} \text{s}^{-1}$.

During the nitrite decomposition-performed under N$_2$ atmosphere N$_2$O formation is detected by IR spectroscopy, identifying this step as the nitrous oxide source. Although the initial nitrite decomposition rate is not affected by the presence of NO$_2$, at higher reaction times, NO$_2$ slightly enhances the decomposition rate, due to the formation of HNO$_3$ and HNO$_2$ in Reaction (2) which increases the proton (i.e. the catalyst) concentration. More important is that approximately 20% less N$_2$O was found in the gas phase when the nitrite decomposition was studied in a dioxane solution saturated with 0.5% NO$_2$ in an He gas flow, prior to the addition of Amberlyst-15$^\text{®}$. Benzyl nitrate (PhCH$_2$ONO$_2$), although being detected with GC-MS
as a trace product, was found to be unreactive at 80 °C for several hours and should hence be considered as a spectator in equilibrium with PhCH₂OH plus HNO₃, rather than a true reaction intermediate.

Note that at high Amberlyst-15® loadings (i.e., 6 mg mL⁻¹), the observed activation energy (i.e. (12±1) kcal mol⁻¹) corresponds with the activation energy of the nitrite decomposition reaction (i.e. (13±1) kcal mol⁻¹, see above). This agreement, together with the observed first-order in alcohol, is an important indication that this acid-catalyzed decomposition of the nitrite ester (formed by PhCH₂OH + HNO₂ ⇌ PhCH₂ONO + H₂O) is the rate-determining-step (RDS) in the overall mechanism, at least at high catalyst loadings. This hypothesis explains why the reaction rate levels off after the nitrite intermediate reaches its maximum concentration (i.e. after 1 h, see curve b in Figure 2.2.1 and Figure 2.2.2). Under the assumption that the nitrite decomposition is rate-determining, the rate constant of this decomposition can be estimated from the overall reaction rate (e.g. 0.26 M h⁻¹ after 0.5 h, see curve b in Figure 2.2.1), the corresponding nitrite and proton concentration stemming from Amberlyst-15® (i.e. [nitrite] = 20 mM, see Figure 2.2.2, and [H⁺]Amberlyst-15® = 28 mM) to be (0.13±0.03) M⁻¹ s⁻¹. This value is in excellent agreement with the value obtained from our nitrite decomposition study (see Appendix A.1), (0.11±0.02) M⁻¹ s⁻¹.

At low Amberlyst-15® loadings (i.e., 2 mg mL⁻¹), HNO₃ decomposition (according to the stoichiometry of Reaction (1)) is likely to be the RDS, explaining the zero order in alcohol. The experimental activation energy in this range (i.e. 33±1 kcal mol⁻¹) is significantly lower than the reported HNO₃ self-decomposition barrier of 38.7 kcal mol⁻¹,[26] pointing towards an Amberlyst-15®-catalyzed decomposition (see Appendix A.1). This shift in RDS also explains why the nitrite ester could not be detected when the reaction is performed with a low Amberlyst-15® loading (see above) as its decomposition is faster than its formation.

All these experimental observations point towards an acid-catalyzed decomposition of the nitrite ester, involving the protonation of the N-atom (Scheme
2.2.1), leading to the formation of HNO. Because the nitrate ester cannot be protonated it is unreactive under similar reaction conditions.

![Scheme 2.2.1.](image)

**Scheme 2.2.1.** Acid-catalyzed decomposition of PhCH$_2$ONO to PhCHO and HNO; PhCH$_2$ONO$_2$ seems unreactive under similar conditions.

HNO is a reactive substance that dimerizes very rapidly to hyponitrous acid (HON=NOH) which decomposes to water and N$_2$O [Eq. (3)].\[^{27}\] The overall rate constant for Reaction (3) can be described by $k_3(T) = 6.9 \times 10^5 \exp(-2.8 \text{ kcal mol}^{-1} / RT) \text{ M}^{-1} \text{ s}^{-1}.\[^{28}\] In the presence of NO$_2$, HNO can be converted into NO (detected by mass spectrometry) by Reaction (4), regenerating HNO$_2$.

\[
\text{HNO} + \text{HNO} \rightarrow \text{HON=NOH} \rightarrow \text{N}_2\text{O} + \text{H}_2\text{O} \tag{3}
\]

\[
\text{HNO} + \text{NO}_2 \rightarrow \text{NO} + \text{HNO}_2 \tag{4}
\]

Reaction (4) is driven by the weak H-NO bond of only 49 kcal mol$^{-1}$, leading to a $k_4(T) = 6 \times 10^8 \exp(-2 \text{ kcal mol}^{-1} / RT) \text{ M}^{-1} \text{ s}^{-1}.\[^{29}\] Kinetic competition between Reactions (3) and (4) explains why less N$_2$O is formed during nitrite decomposition in the presence of NO$_2$ (see above). If water is added to the reaction mixture, NO$_2$ is rapidly trapped by Reaction (2), preventing it from reacting with HNO and the reaction is quenched (see above).

NO can be re-oxidized by O$_2$ to NO$_2$ according to Reaction (5).\[^{28}\] In the absence of O$_2$, NO can probably also react with HNO$_3$,\[^{30}\] regenerating HNO$_2$ and NO$_2$ [Eq. (6)], explaining why even under an inert N$_2$ atmosphere $\Delta[\text{PhCH}_2\text{OH}]/[\text{HNO}_3]_0 \approx 2$
can be achieved. Note that rapid re-oxidation of NO to NO$_2$ is crucial to prevent HNO from dimerizing and forming N$_2$O. This explains why a higher end-conversion can be reached at higher O$_2$ pressure, given a certain temperature (see Figure 2.2.1).

$$2 \text{NO} + \text{O}_2 \rightarrow 2 \text{NO}_2$$  \hspace{1cm} (5)

$$\text{NO} + \text{HNO}_3 \rightarrow \text{NO}_2 + \text{HNO}_2$$  \hspace{1cm} (6)

Note that, although the temperature dependence of HNO consumption by Reactions (3) and (4) are similar, HNO formation (by nitrite decomposition) is more accelerated at higher temperature than NO$_2$ formation by Reaction (5) which actually becomes slower at higher temperature.$^{[28]}$ This hypothesis is confirmed by the lower nitrite ester concentration at higher temperatures. Because of this situation, the [HNO]/[NO$_2$] concentration ratio will increase at increasing temperature, favoring N$_2$O formation (termination) as seen by IR spectroscopy. As an example, at 90 °C, 40% more N$_2$O is found than at 80 °C, both at 60% alcohol conversion. This explains why a higher end-conversion can be achieved at a lower temperature (see Figure 2.2.5).

Scheme 2.2.2 summarizes the mechanistic insights. It shows the NO$_x$ and HNO$_x$ cycling and emphasizes that O$_2$ is the terminal oxidant; HNO$_3$ only triggers an aerobic oxidation cycle.

**Scheme 2.2.2** HNO$_3$ is initiating a NO$_x$/HNO$_x$ mediated oxidation cycle.
As reported above, water has a detrimental effect on the reaction as it traps the NO₂ in Reaction (2) and hence favors the formation of N₂O. We suspect this effect limits the TON in (H)NOₓ under conditions when the nitrite decomposition is rate-determining (i.e., high Amberlyst-15® loadings and hence high reaction rates). Karl-Fischer titration of H₂O in the system shows a gradual increase of the water content from approximately 0.5 w% just after addition of the HNO₃ to 1.8 w% after 6 h (corresponding to 80% conversion).

This observation prompted us to remove water in situ. Addition of molecular sieves to the reaction resulted in inhibition, probably due to strong adsorption of (H)NOₓ, present in the liquid phase. Therefore a gas recirculation reactor was constructed (Figure 2.2.6) in which the gas phase is constantly pumped over a fixed-bed with molecular sieve 4 Å to remove the water via the gas phase.

**Figure 2.2.6** Gas recirculation reactor: a) heated tank-reactor, b) O₂ reservoir connected to reactor by a check-valve, c) jacketed packed column with 4 Å molecular sieves (kept at reaction temperature to avoid solvent condensation), d) condenser, e) condensate recycling, f) dried gas recycling, g) membrane pump, and h) gas disperser.
Using this set-up it is possible to significantly speed up the reaction, while also increasing the end-conversion to 100% (Figure 2.2.7). Karl-Fischer titration confirms that this gas recirculation reactor limits the water content to 0.5 w%. It is important to emphasize that the observed effect is not due to enhanced gas-liquid mass-transfer as increasing the O₂ superficial flow rate in a bubble column reactor, or operating the gas recirculation reactor without molecular sieve, did not lead to an improvement.

![Figure 2.2.7 PhCH₂OH conversion in the presence of 5 mM NaNO₂ at 80 °C vs. time for a reaction performed in a) a bubble column reactor and in the gas recirculation reactor with drying of the gas phase (gas recirculation rate of b) 75 and c) 150 mL min⁻¹).](image)

**2.3 Conclusions**

From this study, it can be concluded that HNO₃ is able to start off a chain oxidation of benzyl alcohol, mediated by (H)NOₓ species; O₂ is however the terminal oxidant. HNO₂ reacts with the alcohol substrate to form a nitrite ester which decomposes, acid catalyzed, to the benzaldehyde product and HNO. The reaction of HNO with NO₂, regenerates HNO₂ and forms NO which is oxidized to NO₂ (propagation reactions). HNO can dimerize and yield N₂O in a termination reaction. A significant increase in chain length, and hence an improved yield, can be achieved at lower temperature, or
upon drying of the gas phase. This chain reaction is catalyzed by the solid acid Amberlyst-15®. Depending on the acid catalyst loading, either the HNO₃ or the nitrite decomposition is rate determining; both steps are acid catalyzed. These mechanistic insights will be used as a starting point to investigate other HNO₃-based oxidation reactions, such as adipic acid synthesis. The present study shows that the reaction of the alcohol substrate with HNO₂ leads to the reactive (H)NOₓ species. Most likely this is the reason why cyclohexanol is needed as a (co-)substrate in the adipic acid synthesis as pure cyclohexanone is rather inert under the same conditions.¹³

2.4 Experimental Section

Standard experiments were carried out in a bubble column reactor using 1,4-dioxane (25 mL; Fluka, p.a. 99.5%) as a solvent, PhCH₂OH (500 mM; Acros, 99%), HNO₃ (125 mM; Merck, p.a. 65%), NaNO₂ (5 mM; Sigma-Aldrich, 99%), and Amberlyst-15® (150 mg; Sigma-Aldrich). Subsequently O₂ was bubbled through the reaction solution at a rate of 100 mL min⁻¹. High-pressure reactions were performed in a 100 mL stainless steel Parr reactor equipped with a glass insert and a polyether ether ketone (PEEK) propeller. Products were quantified using GC (HP-FFAP column, Flame-Ionization-Detector), or in the case of the thermally unstable nitrite with GC-MS with cool-on-column injection (HP-5 column). Transmission IR spectra of the gas phase were taken with a home-made 30 mL quartz cell with CaF₂ windows. The cell was evacuated and flushed with N₂ three times prior to sampling; background measurements were taken with an evacuated empty cell. Spectra are scaled to the C-H stretches of the dioxane solvent (2800 - 3000 cm⁻¹).
3 Acid-Catalyzed Decomposition of the Benzyl Nitrite Intermediate in HNO₃-Mediated Aerobic Oxidation of Benzyl Alcohol

Benzyl nitrite (PhCH₂ONO) was previously identified as the pivotal intermediate in the HNO₃-mediated oxidation of benzyl alcohol. Its acid-catalyzed decomposition yields benzaldehyde and HNO, the precursor of undesirable N₂O. Most likely, an analogous mechanism is responsible for the formation of N₂O during the oxidation of cyclohexanol and cyclohexanone to adipic acid, the largest industrial source of this important greenhouse gas. In this chapter, the decomposition of benzyl nitrite is studied in more detail, allowing the kinetic isotope effect and the influence of substituents to be determined. A linear Evans-Polanyi correlation between the measured Arrhenius activation energies and the computed reaction energies was established. Furthermore, the differences in the reactivities of the substituted benzyl nitrites are reflected in the oxidation of the corresponding alcohols, and also affect the rate-determining step in the overall mechanism. The results of this study corroborate the importance of the nitrite intermediate in HNO₃-based oxidation technology.
3.1 Introduction

In chapter 2, the aerobic oxidation of benzyl alcohol using HNO\textsubscript{3} as an initiator, leading to an (H)NO\textsubscript{x} propagated chain oxidation in which O\textsubscript{2} is the terminal oxidant was examined. The reaction was found to be catalyzed by the ion exchange resin Amberlyst-15® in protonic form.

The reaction mechanism can be summarized by the Reaction Equations (1-7). The reaction is initiated by the acid-catalyzed decomposition of HNO\textsubscript{3} to NO\textsubscript{2} [Eq. (1)]. This equilibrium shifts to the left at higher O\textsubscript{2} pressures, thus leading to a prolonged induction period. However, this induction phase can be reduced, or even eliminated, upon the addition of minute amounts of NaNO\textsubscript{2}, NO or NO\textsubscript{2}.\textsuperscript{[31]} NO\textsubscript{2} is known to react with water to yield a mixture of HNO\textsubscript{3} and HNO\textsubscript{2} [Eq. (2)].\textsuperscript{[22]} and nitrous acid (HNO\textsubscript{2}) can subsequently react, acid-catalyzed, with PhCH\textsubscript{2}OH to form the benzyl nitrite ester, PhCH\textsubscript{2}ONO. It is proposed that this nitrite decomposes, again under the influence of an acid catalyst, to the final product, benzaldehyde, and HNO [Eq. (4)]. NO\textsubscript{2} can react with HNO to yield additional HNO\textsubscript{2} and NO [Eq. (5)], and NO is reoxidized by O\textsubscript{2} [Eq. (6)], thereby recycling the (H)NO\textsubscript{x} species (propagation cycle). Alternatively, HNO can dimerize to hyponitrous acid (HON=NOH), which decomposes to water and N\textsubscript{2}O [Eq. (7), termination].\textsuperscript{[22]}

Therefore, to increase \(\Delta[\text{PhCH}_2\text{OH}]/[\text{HNO}_3]\), one has to kinetically favour Reaction (5) over (7), for instance by maintaining a high NO\textsubscript{2} concentration. \textit{In situ} removal of water also minimizes the importance of Reaction (2) as an NO\textsubscript{2} sink and thereby reduces the formation of N\textsubscript{2}O as shown in chapter 2.

\textbf{Initiation:}

\begin{equation}
4 \text{HNO}_3 \rightleftharpoons 4 \text{NO}_2 + 2 \text{H}_2\text{O} + \text{O}_2 \tag{1}
\end{equation}

\begin{equation}
2 \text{NO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{N}_2\text{O}_4 + \text{H}_2\text{O} \rightarrow \text{HNO}_3 + \text{HNO}_2 \tag{2}
\end{equation}
Propagation:

\[
\text{PhCH}_2\text{OH} + \text{HNO}_2 \rightarrow \text{PhCH}_2\text{ONO} + \text{H}_2\text{O} \quad (3)
\]

\[
\text{PhCH}_2\text{ONO} \rightarrow \text{PhCH}_2\text{O} + \text{HNO} \quad (4)
\]

\[
\text{HNO} + \text{NO}_2 \rightarrow \text{NO} + \text{HNO}_2 \quad (5)
\]

\[
2 \text{NO} + \text{O}_2 \rightarrow 2 \text{NO}_2 \quad (6)
\]

Termination:

\[
\text{HNO} + \text{HNO} \rightarrow \text{HON}=\text{NOH} \rightarrow \text{N}_2\text{O} + \text{H}_2\text{O} \quad (7)
\]

The rate determining step (RDS) in the overall mechanism was found to depend on the Amberlyst-15\textsuperscript{®}-loading. At low to moderate loadings, the Amberlyst-15\textsuperscript{®}-catalyzed decomposition of HNO\textsubscript{3} [Eq. (1)] is rate-limiting. In contrast, the decomposition of the benzyl nitrite intermediate [Eq. (4)] becomes rate-limiting at higher Amberlyst-15\textsuperscript{®} loadings. The activation barriers within these two regimes were experimentally determined to be 33± 1 and 12±1 kcal mol\textsuperscript{-1}, respectively.

We have studied the acid-catalyzed decomposition of (substituted) benzyl nitrites in more detail to further characterize this important rate-controlling reaction step.

### 3.2 Benzyl Nitrite Decomposition Experiments

Benzyl nitrite (PhCH\textsubscript{2}ONO) was synthesized and its acid-catalyzed decomposition subsequently studied under an N\textsubscript{2} atmosphere (see Experimental Section). Figure 3.2.1 shows the time evolution of the benzyl nitrite and benzaldehyde concentrations during a typical experiment at 40 °C, from which the reaction was found to be first order with respect to the benzyl nitrite concentration. These experiments were repeated for various concentrations of Amberlyst-15\textsuperscript{®} and at different temperatures (Figure 3.2.2) to obtain the Arrhenius rate expression:
(3\pm2) \times 10^6 \text{ M}^{-1} \text{s}^{-1} \times \exp(-12.5\pm1 \text{ kcal mol}^{-1} / RT).

Figure 3.2.1 Time evolution of the benzyl nitrite and benzaldehyde concentrations at 40 °C (10 mg mL\(^{-1}\) Amberlyst-15\(^{\circledR}\)).

Figure 3.2.2 Evolution of the pseudo first-order rate constants for nitrite decomposition as a function of the Amberlyst-15\(^{\circledR}\) loading at various temperatures.

Notably, the benzyl nitrate ester is unreactive under the same reaction conditions. Therefore, one has to conclude that PhCH\(_2\)ONO\(_2\) (detected with GC-MS during
PhCH$_2$OH oxidation) is just a spectator, in equilibrium with PhCH$_2$OH and HNO$_3$, and not a real reaction intermediate.

During the catalytic decomposition of benzyl nitrite under N$_2$, N$_2$O formation was followed using IR spectroscopy (Figure 3.2.3). The time evolution of the $\nu_3$ vibrational mode is plotted in Figure 3.2.4 (Curve a) and follows a very similar qualitative trend to that of benzaldehyde formation in Figure 3.2.1. Although the initial nitrite decomposition rate was not affected by the presence of NO$_2$, at longer reaction times, NO$_2$ slightly enhances the decomposition rate, most likely owing to the formation of HNO$_3$ and HNO$_2$ through Reaction (2), which increases the proton (i.e., catalyst) concentration. More importantly, approximately 20% less N$_2$O was observed in the gas phase when the nitrite decomposition was studied in a solution saturated by a flow of NO$_2$ (0.5%) in He, prior to the addition of Amberlyst-15® (Figure 4, Curve b). This is in line with the proposed kinetic competition between Reactions (5) and (7).

![Figure 3.2.3](image-url) Transmission IR spectra of the gas phase during a benzyl nitrite decomposition experiment at 40 °C (10 mg mL$^{-1}$ Amberlyst-15®). Spectra are shown after 0.5, 1, 2 and 3 h and were normalized to the C-H stretches of the dioxane solvent (2800-3000 cm$^{-1}$); peaks indicated with * are from N$_2$O.
Figure 3.2.4 Absorbance of the $\text{N}_2\text{O}$ signal at 2236 cm$^{-1}$ ($\nu_3$ vibrational mode) over time during the decomposition of benzyl nitrite at 40 °C in a) an N$_2$-purged dioxane solution (10 mg mL$^{-1}$ Amberlyst-15®) and b) in a dioxane solution, saturated with NO$_2$ (0.5%) in a He gas flow, prior to the addition of Amberlyst-15®.

3.3 Kinetic Isotope Effect and Influence of Electron Donating and Withdrawing Substituents on Nitrite Decomposition

To further characterize the decomposition of benzyl nitrite, the kinetic isotope effect (KIE) was determined by using PhCD$_2$ONO as a substrate. Between 40 and 70 °C, the temperature dependence of the KIE is well described by Equation (8).

$$\ln(k_H/k_D) = \frac{453}{(T/K)} - 0.99$$

For instance, at 50 °C, the KIE was determined to be 1.5. The estimated $\Delta E_{act}$ of 0.9 kcal mol$^{-1}$, as well as an $A_H/A_D$ value of 0.4, strongly suggests that C-H bond cleavage is involved in the controlling transition state (TS) of nitrite decomposition.

The crucial step in the acid-catalyzed nitrite decomposition is most likely a concerted elimination of HNO and H$^+$ from the protonated nitrite species. In the TS, one can anticipate an anti-periplanar arrangement H-C-O-N (dihedral angle of 180 °)
In the protonated benzyl nitrite, the Lewis structure and Newman projection of which are shown below.

\[
\begin{align*}
\text{Protonated Benzyl Nitrite:} & \quad \text{Lewis Structure:} \\
\end{align*}
\]

In the aldehyde product, the \(\pi_{\text{CO}}^*\) orbital can interact with and be stabilized by an electron donating group (EDG) in the para position by adopting a quinoid mesomeric form (Scheme 3.3.1). The molecule thus adopts a \(C_\text{s}\) symmetry (CHO and Ar in plane) rather than a \(C_\text{2}\) symmetry (CHO and Ar are orthogonal).

\[\text{Scheme 3.3.1 Quinoid mesomeric form of benzaldehyde with an electron donating group (X) in the para position.}\]

Upon populating the \(\pi_{\text{CO}}^*\) orbital, the carbonyl bond is expected to weaken and increase in length, and a corresponding decrease in the Ar-CHO bond length is similarly expected. This is confirmed by the DFT-predicted Ar-CHO bond length in PhCHO (148.0 pm), which is 0.7 pm longer than in p-OMe-PhCHO. The experimental \(\nu(\text{C}=\text{O})\) stretching frequency decreases from 1700 to 1696 cm\(^{-1}\) in the transition from PhCHO to p-NMe\(_2\)-PhCHO, further confirming a weakening of the C=O bond. The TS is affected partially by the quinoid stabilization, owing to the fact that the gap between the HOMO (the delocalized nonbonding orbital from the EDG) and LUMO (the nascent \(\pi_{\text{CO}}^*\) orbital coming from the \(\sigma_{\text{ON}}^*\) orbital) decreases with increasing electron donating character of the substituent (see Appendix A.2).
This mechanistic hypothesis is in line with the experimentally determined Hammett correlation, using $\sigma^+$ parameters for para-substituted benzyl alcohol derivatives (Figure 3.3.1). The negative reaction constant, $\rho (-0.559)$, indicates reduced electron density at the reaction centre during the TS.

![Hammett plot for benzyl nitrite decomposition at 50 °C: log($k_X/k_H$) vs. $\sigma^+$ (reaction constant $\rho = -0.559$).](image)

**Figure 3.3.1** Hammett plot for benzyl nitrite decomposition at 50 °C: log($k_X/k_H$) vs. $\sigma^+$ (reaction constant $\rho = -0.559$).

The temperature dependence of the decomposition rate constants of the various substitute nitrites was subsequently evaluated. A good linear Evans-Polanyi correlation was found between the experimental Arrhenius activation energies and the DFT computed reaction energies [Figure 3.3.2, Eq. (9)]

$$E_{act} = (12.1 \pm 0.1) + (0.15 \pm 0.01) \times \Delta_rE$$  

(9)

Although the benzyl nitrite fragmentation is thermoneutral, or even slightly endothermic, it is kinetically favoured because of the associated entropy gain. Notably, the observed reaction energy dependence (0.15) is somewhat smaller than those observed for radical H atom abstractions (0.25).[35]
Figure 3.3.2 Evans-Polanyi plot of the experimentally measured activation energies $E_{act}$ vs. the computed reaction energy $\Delta E$ (dashed line is the 95% confidence band; $R = 0.98$).\cite{32}

3.4 Oxidation of Substituted Alcohols

In chapter 2, we observed that the initial oxidation rate of benzyl alcohol levelled off at increased Amberlyst-15$^\circledR$ loadings (Figure 3.4.1, Curve a). This effect was attributed to a shift in the rate determining step from the Amberlyst-15$^\circledR$-catalyzed decomposition of HNO$_3$ (initiation) to the Amberlyst-15$^\circledR$-catalyzed decomposition of benzyl nitrite (above 4 mg mL$^{-1}$ Amberlyst-15$^\circledR$). The activation energies in both regimes were experimentally determined to be 33±1 and 12±1 kcal mol$^{-1}$, respectively, thus excluding mass transfer limitations.

During the oxidation of the deactivated p-NO$_2$-PhCH$_2$OH, the reaction rate does not level off as a function of the Amberlyst-15$^\circledR$ loading but continues to increase linearly, albeit at a lower absolute value than for PhCH$_2$OH. Moreover, the activation energy was independent of the catalyst loading and remains constant at 13±1 kcal mol$^{-1}$, that is, exactly the same as the nitrite decomposition energy barrier (13.4 kcal mol$^{-1}$). Apparently, the NO$_2$ group deactivates the nitrite intermediate to such an
extent that even at low Amberlyst-15\textsuperscript{®} concentrations, the nitrite decomposition is rate-determining.

![Graph showing correlation between initial oxidation rate and Amberlyst loading](image)

**Figure 3.4.1** Correlation of the initial oxidation rate with the Amberlyst-15\textsuperscript{®} loading at 80 °C of a) PhCH\textsubscript{2}OH, b) p-NO\textsubscript{2}-PhCH\textsubscript{2}OH and c) p-Me-PhCH\textsubscript{2}OH.

For activated p-Me-PhCH\textsubscript{2}OH, a similar behaviour to that of PhCH\textsubscript{2}OH is observed. At low catalyst loadings, the activation energy is experimentally determined to be 32±1 kcal mol\textsuperscript{-1} (\(T\) range 60-90 °C; 1 mg mL\textsuperscript{-1} Amberlyst-15\textsuperscript{®}), which is similar to the \(T\) dependence of PhCH\textsubscript{2}OH oxidation at similar Amberlyst-15\textsuperscript{®} loadings (\textit{i.e.}, 33±1 kcal mol\textsuperscript{-1}). This implies that the same rate-determining step, that is, HNO\textsubscript{3} decomposition, is in effect. Furthermore, when studying the NO\textsubscript{2} formation rate during the Amberlyst-15\textsuperscript{®}-catalyzed HNO\textsubscript{3} decomposition, an activation energy of 35±2 kcal mol\textsuperscript{-1} was found. This value is significantly lower than the HNO\textsubscript{3} self-decomposition barrier of 38.7 kcal mol\textsuperscript{-1} \cite{26} but supports the hypothesis that at low Amberlyst-15\textsuperscript{®} loadings, HNO\textsubscript{3} decomposition to HNO\textsubscript{2} through NO\textsubscript{2} formation [see Initiation Reaction Eqs. (1) and (2)] is indeed the rate-determining step. At higher Amberlyst-15\textsuperscript{®} loadings (8 mg mL\textsuperscript{-1} Amberlyst-15\textsuperscript{®}), a lower activation energy is
measured (12±1 kcal mol⁻¹), which is in good agreement with the 12.3 kcal mol⁻¹ activation energy observed for p-Me-PhCH₂OH.

3.5 Conclusions

The results of this work corroborate the importance of the acid-catalyzed decomposition of benzyl nitrite during the HNO₃-mediated aerobic oxidation of benzyl alcohol. Nitrite decomposition is identified as the source of N₂O. A good linear Hammett plot with a negative slope is obtained that indicates a transition state with reduced electron density. Kinetic isotope effect studies imply that cleavage of the Cα-H bond is involved in the decisive transition state, and electron withdrawing groups are found to reduce the reactivity of the nitrite significantly. This effect is also reflected in the overall oxidation reaction of the corresponding alcohol, thereby supporting the reaction mechanism.

3.6 Experimental Section

Benzyl nitrite was synthesized according to a literature procedure. A 1,4-dioxane solution (4 mL) containing biphenyl (20 mM) was heated to the desired temperature, as indicated in the text. To this mixture, a benzyl nitrite solution (75 μL) was added to achieve [nitrite] ≈ 200 mM, together with Amberlyst-15® (150 mg). Samples were analyzed and quantified with GC-MS (HP-5 column) with cool-on-column injection to prevent thermal dissociation of the nitrite. Standard oxidation experiments were performed in a bubble column reactor using 1,4-dioxane (25 mL) as solvent, PhCH₂OH (500 mM, 1.29 mL), HNO₃ (125 mM, 220 mL of a 65% aq. solution), NaNO₂ (5 mM, 8.6 mg) and various amounts of Amberlyst-15®. The products were quantified against a biphenyl internal standard using GC (HP-FFAP column, flame ionization detector). Transmission IR spectra of the gas phase were taken with a home-made 30 mL quartz cell with CaF₂ windows. The cell was evacuated and flushed with N₂ three times prior to sampling; background
measurements were taken with an evacuated empty cell. Spectra are scaled to the C-H stretches of the dioxane solvent (2800 - 3000 cm\(^{-1}\)). Quantum chemical calculations were performed with the Gaussian09 software\(^{[33]}\) at the B3LYP/6-311++G(df,pd)//B3LYP/6-31G(d,p) level of theory.\(^{[34]}\) The reported reaction energies (\(\Delta rE\)) were corrected for zero point energy (ZPE) differences.
4 Intensification under Three Phase Flow Conditions

In this chapter we use $O_2$ as terminal oxidant and (H)NO$_x$ species as oxygen shuttle in order to mediate the oxidation of primary and secondary alcohols under the influence of a solid acid catalyst. Process optimization and intensification through the use of a continuous three-phase flow reactor is demonstrated. Space-time-yields were found to increase by two orders of magnitude with respect to batch experiments, along with additional gains in selectivity and a decrease of N$_2$O formation.
4.1 Introduction

The aim of the present contribution is to explore the use of a continuous three-phase flow reactor to further improve the performance of the aerobic oxidation of different primary and secondary alcohols mediated by HNO$_3$.

4.2 Reactor Set-Up

A small scale flow reactor offers considerable advantages over traditional batch reactors. Improved control of the reaction parameters, enhanced heat- and mass transfer, faster mixing of the reactants, shorter reaction times, and smaller reactor volumes are just a few examples.$^{[36,37]}$ Such reactors also offer reaction environments with large interfacial areas between different phases, and thus efficiently promote gas-liquid-solid reactions like the present one.$^{[38]}$

Figure 4.2.1 Experimental set-up: (a) liquid reservoir, (b) O$_2$ reservoir, (c) HPLC pump, (d) pressure reduction valve, (e) mass flow controller, (f) T-mixer, (g) segmented flow, (h) fixed-bed reactor, (i) back-pressure regulator, (k) phase-separator, (l) liquid flow passing through ATR-IR cell and (m) gas-flow passing through transmission IR cell.
Figure 4.2.1 shows an overview of the reactor set-up. The liquid feed (1,4-dioxane, alcohol, HNO₃ and biphenyl standard) is pumped with an HPLC pump and combined with the O₂ flow in a T-mixer, generating a gas-liquid Taylor-flow. It is well known from literature that segmented flow is characterized by an enhanced gas-liquid mass transfer,[39] a feature previously found to be crucial for the present reaction. Subsequently, the gas-liquid mixture enters a tubular reactor, densely packed with Amberlyst-15®. The pressure on the system can be set by a back-pressure regulator. The product flow is sent to a phase separator. Subsequently the liquid fraction flows through an Attenuated Total Reflection Infrared (ATR-IR) cell and is further analyzed by GC (see experimental section). The gas-phase can be analyzed in a transmission IR cell with KBr windows. In order to assure a steady segmented flow, the reactor was operated at 5 bar.

4.3 Benchmarking Experiments with Benzyl Alcohol

In order to compare the performance of the continuous flow reactor with batch and gas-recycle reactors, benzyl alcohol (PhCH₂OH) was taken as a model substrate. Figure 4.3.1 shows the conversion as a function of the residence time of the flow reactor for various temperatures. Interestingly, no induction period could be observed (except at 70 °C), even in absence of initiator (NaNO₂). This can be explained by the fact that the HNO₃ decomposition to NO₂ (reaction 1, see chapter 3) is catalyzed by Amberlyst15®. Since more catalyst per volume of reaction solution is present in the fixed-bed reactor, the (H)NOₓ formation rate is accelerated to such an extent that the induction period is almost eliminated. Furthermore, the selectivity was above 99 % for all samples analyzed, i.e. significantly higher than the results obtained in chapter 2.

In Table 4.3.1, the performance of the flow reactor (Figure 4.2.1) is quantitatively compared to reactors previously used for the same reaction (chapter 2) based on space-time-yield, demonstrating an improvement by two orders-of-magnitude. The
remarkable improvement in rate and space-time-yield is also associated with a complete conversion (see Figure 4.3.1). This points towards a longer HNO chain length ($v_{\text{HNO}} = \text{rate of reaction 5 divided by rate of reaction 7}$, see chapter 3), or in other words, a significantly slower termination (Eq. 7, see chapter 3). In order to investigate this in more detail, the gas and liquid phase of the reactor effluent were monitored with online transmission IR and ATR-IR spectroscopy, respectively.

**Figure 4.3.1** PhCH$_2$OH conversion vs. contact time at various temperatures: (a) 100 °C, (b) 90 °C, (c) 80 °C and (d) 70 °C. (solvent: 1,4-dioxane, [PhCH$_2$OH]$_0 = 500$ mM, [HNO$_3$]$_0 = 125$ mM, 5 bar O$_2$).

<table>
<thead>
<tr>
<th>reactor type</th>
<th>space-time-yield$^{[a]}$ / mol m$^3$ s$^{-1}$ kg$^{-1}$</th>
<th>relative space-time-yield</th>
<th>end-conversion / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>batch</td>
<td>79$^{[b]}$</td>
<td>1.0</td>
<td>60</td>
</tr>
<tr>
<td>bubble column</td>
<td>103$^{[b]}$</td>
<td>1.3</td>
<td>78</td>
</tr>
<tr>
<td>gas-loop</td>
<td>302$^{[b]}$</td>
<td>3.8</td>
<td>100</td>
</tr>
<tr>
<td>flow reactor</td>
<td>18382</td>
<td>232.7</td>
<td>100</td>
</tr>
</tbody>
</table>

$^{[a]}$ Space-time-yields were calculated at maximum conversion as mol substrate converted per m$^3$ reactor volume, per second and per kg of catalyst. $^{[b]}$ Only the liquid volume was used for the reactor volume.
In the liquid phase, the formation of the PhCHO product can be observed by the appearance of a >C=O stretch at 1703 cm\(^{-1}\) (see lower right insert in Figure 4.2.1); as expected this signal is inversely proportional to the PhCH\(_2\)OH conversion as determined by GC.

More important is the \(\nu_3\) vibrational mode of N\(_2\)O that was monitored in the gas phase (see e.g. upper right insert in Figure 4.2.1). Spectra were normalized, relative to the C-H stretches of the 1,4-dioxane solvent (2800-3000 cm\(^{-1}\)). Comparing the evolution of N\(_2\)O during a continuous flow experiment with a traditional batch experiment at the same temperature shows that significantly less N\(_2\)O is formed (Figure 4.3.2). As a comparison, at a conversion of 50 %, 25 % less N\(_2\)O is observed. Interestingly, when the conversion approaches 100 %, the N\(_2\)O signal increases very rapidly to a similar level as observed in the batch case at maximum conversion (viz., 60 %).

**Figure 4.3.2** Intensity of the \(\nu_3\) vibrational mode of N\(_2\)O in the gas phase, normalized to the C-H vibration of the 1,4-dioxane solvent vs. the PhCH\(_2\)OH conversion determined with GC for batch and continuous flow systems. (solvent: 1,4-dioxane, \(T = 90\) °C, [PhCH\(_2\)OH]\(_0\) = 500 mM, [HNO\(_3\)]\(_0\) = 125 mM, batch: 1 bar O\(_2\), fixed-bed: 5 bar O\(_2\)).
The significantly lower rate of N₂O formation can only be explained by the fact that the recycling of (H)NOₓ (Eq. 5 and 6, see chapter 3) is more efficient in the continuous flow than in the batch system. For the recycle of HNO (Eq. 5, see chapter 3), a high NO₂ concentration is crucial. As mentioned above, HNO₃ decomposition to NO₂ is faster in the continuous flow reactor, thus explaining the higher NO₂ amount. In addition to this, it can be expected that the reoxidation of NO (Eq. 6, see chapter 3) is also faster, due to the enhanced gas-liquid mass transfer in the flow reactor. The reduction of the N₂O formation rate (Eq. 7, see chapter 3) makes the use of a flow reactor promising from both an ecological and economical point of view.

In view of the increased HNO chain length, one can reduce the amount of HNO₃ while maintaining full conversion in PhCH₂OH (Figure 4.3.3). This has several advantages such as a higher selectivity towards the desired product, less N₂O formation relative to the product, a less corrosive reaction environment and smaller downstream separation costs of (H)NOₓ species from the reaction solution.

**Figure 4.3.3** PhCH₂OH conversion vs. contact time in the fixed-bed reactor for various HNO₃ loadings: (a) 5 mol%, (b) 10 mol% and (c) 25 mol% (solvent: 1,4-dioxane, T = 100 °C, [PhCH₂OH]₀ = 500 mM, 5 bar O₂).
Next to the increased mass transfer another major advantage of the flow reactor is that it allows the evaluation of the lifetime and stability of a heterogeneous catalytic system. Deactivation of transition metal based catalysts due to leaching is an important but often overlooked problem in heterogeneous catalysis. Interestingly, the catalyst bed could be used for two weeks without any loss of activity. This makes the present system promising compared to state-of-the-art transition metal catalysts.

### 4.4 Expanding the Substrate Scope

In order to extend the substrate scope, several primary and secondary alcohols were tested using 10 mol% of HNO₃. Each of the investigated substrates showed a high reaction rate and selectivity towards the corresponding aldehyde or ketone product. Cyclohexanol is a peculiar substrate as even at 25 mol% HNO₃ loading the conversion levels off around 60 %. It is well-known from literature that cyclohexanol can easily over-oxidize from cyclohexanone to adipic acid.[¹³] During this process, (H)NOₓ species are irreversibly consumed, leading to a significant reduction in the efficiency of the oxygen shuttle and hence a lower overall alcohol conversion. In support of this hypothesis is the observation of trace amounts of adipic acid within the GC-MS spectra – it should not be forgotten that given the sub-stoichiometric quantities of HNO₃, even trace quantities of this by-product are significant.

The use of the flow reactor also simplifies the determination of kinetic parameters.[³⁷] The activation energies of the different substrates could be determined in a very convenient and precise manner (Table 4.4.1 and Figure 4.4.1). In all cases the decomposition of the nitrite intermediate is the overall rate limiting step as determined previously in the case of PhCH₂OH (see chapters 2 and 3). Because the nitrite decomposition is catalyzed by Amberlyst15®, the higher catalyst-to-substrate ratio in the flow reactor provides an additional explanation for the higher reaction rate relative to the batch benchmark. Furthermore the reactivity of the
different substrates corresponds to the Evans-Polanyi correlation for the nitrite decomposition determined earlier. (see chapter 3)

![Graph showing conversion vs. contact time at different temperatures.](image)

**Figure 4.4.1** 2-heptanol conversion vs. contact time at different temperatures in the continuous flow reactor; the insert shows the Arrhenius plot based on the initial rates (solvent: 1,4-dioxane, [2-heptanol]₀ = 500 mM, [HNO₃]₀ = 50 mM, 5 bar O₂).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Time / s[^a]</th>
<th>Conv. / %[^a]</th>
<th>Sel. / %[^a]</th>
<th>Eₐct / kcal mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Substrate 1" /></td>
<td><img src="image" alt="Product 1" /></td>
<td>8</td>
<td>100</td>
<td>99</td>
<td>12.5</td>
</tr>
<tr>
<td><img src="image" alt="Substrate 2" /></td>
<td><img src="image" alt="Product 2" /></td>
<td>4</td>
<td>100</td>
<td>98</td>
<td>12.1</td>
</tr>
<tr>
<td><img src="image" alt="Substrate 3" /></td>
<td><img src="image" alt="Product 3" /></td>
<td>25</td>
<td>100</td>
<td>99</td>
<td>13.4</td>
</tr>
<tr>
<td><img src="image" alt="Substrate 4" /></td>
<td><img src="image" alt="Product 4" /></td>
<td>14</td>
<td>100</td>
<td>98</td>
<td>13.1</td>
</tr>
<tr>
<td><img src="image" alt="Substrate 5" /></td>
<td><img src="image" alt="Product 5" /></td>
<td>12</td>
<td>60</td>
<td>97</td>
<td>13.2</td>
</tr>
<tr>
<td><img src="image" alt="Substrate 6" /></td>
<td><img src="image" alt="Product 6" /></td>
<td>16</td>
<td>100</td>
<td>96</td>
<td>13.3</td>
</tr>
</tbody>
</table>

[^a] Reaction conditions: 1,4-dioxane solvent, [substrate]₀ = 500 mM, [HNO₃]₀ = 50 mM, T = 100 °C, 5 bar O₂.

### 4.5 Conclusions

A metal-free heterogeneously catalyzed continuous process for the aerobic oxidations of alcohols was developed. A significant increase in the reaction rate and
two orders of magnitude in the space-time-yield could be observed for the aerobic oxidation of benzyl alcohol to benzaldehyde, compared to other reactors. Additionally the activity of the catalyst remained stable over two weeks making the process attractive compared to transition metal catalyzed systems that very often suffer from deactivation and/or low activities.

The increased reaction rate can not only be attributed to a higher catalyst-to-substrate ratio in the flow reactor, but also to a longer HNO chain length, which minimizes both the initial amount of HNO\textsubscript{3} required for efficient oxidation, and the production of N\textsubscript{2}O. Furthermore, this increased (H)NO\textsubscript{x} selectivity is also accompanied by an increased carbonyl selectivity, due to the decrease in over-oxidation products and the termination of the oxygen shuttle species.

The continuous reaction system could successfully be extended to oxidize several aliphatic and non-aliphatic primary and secondary alcohols always showing a high reaction rate and selectivity. Overall the present process displays a promising alternative to state-of-the art stoichiometric oxidants or transition metal catalysts for the environmentally benign and economical oxidation of alcohols.

4.6 Experimental Section

The continuous flow reactor (internal diameter 1.65 mm) was packed with presieved Amberlyst-15\textsuperscript{®} particles (0.16 mm < d\textsubscript{p} < 0.24 mm; void fraction of 65%) and connected to the HPLC pump and O\textsubscript{2} mass flow controller as shown in Figure 4.2.1. Before the reaction was started, the packed bed was heated up while pumping ethanol. Afterwards the reaction solution and the oxygen line were connected to the fixed bed reactor. The pressure was set to 5 bar with the back pressure regulator and the reaction was run for 30 minutes before taking a sample. The liquid phase and the gas phase of the reactor effluent could be monitored with IR spectroscopy. Transmission IR spectra of the gas phase were taken with a home-made 30 mL
quartz cell with CaF$_2$ windows. The cell was evacuated and flushed with N$_2$ three times prior to sampling; background measurements were taken with an evacuated empty cell. Spectra are scaled to the C-H stretches of the dioxane solvent (2800 - 3000 cm$^{-1}$). The products of the liquid phase were quantified against a biphenyl internal standard using GC (HP-FFAP column, flame ionization detector).
5 Intensification of TEMPO-Mediated Aerobic Alcohol Oxidations under Three-Phase Flow Conditions

Various homogeneous and heterogeneous catalytic systems based on 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and different (co-)oxidants have been reported for the selective oxidation of alcohols. Herein we report the use of a commercially available silica-immobilized TEMPO catalyst, in combination with catalytic amounts of \( \text{HNO}_3 \) as a \( \text{NO}_x \) source under continuous three-phase flow conditions. First the stability of the catalyst was evaluated with benzyl alcohol and the reaction parameters were optimized. Subsequently different substrates were tested, focusing on the oxidation of renewable substrates like lactic acid and 5-hydroxymethylfurfural.
5.1 Introduction

In chapter 2, 3 and 4 some of us reported on the metal-free oxidation of alcohols using sub-stoichiometric amounts of HNO$_3$ in combination with the ion-exchange resin Amberlyst-15° in protonic form leading to an (H)NO$_x$-propagated chain oxidation with O$_2$ as terminal oxidant. The system was also applied for different primary and secondary alcohols under continuous flow conditions. This application showed a significant increase in the space-time-yield (i.e. the product yield per unit of time and per reactor volume) and a decrease in N$_2$O formation, compared to a conventional batch reactor (chapter 4). However the use of strong acids such as Amberlyst-15° as co-catalyst limits the substrate scope, due to acid-catalyzed dehydration under reaction conditions. Therefore the search of a milder catalytic system is necessary to increase the range of substrates for nitric acid based alcohol oxidations.

![Scheme 5.1.1 Redox-cycle of TEMPO, including TEMPOH and the oxoammonium cation.](image)

The use of the nitroxy radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as catalyst in the oxidation of alcohols has gained much attention in recent years. The redox cycle involves besides TEMPO (I) also hydroxylamine (II) and the oxoammonium cation (III) (Scheme 5.1.1).[40] The oxoammonium cation is supposed to oxidize the alcohol substrate and is thereby converted to TEMPOH. TEMPOH can
be re-oxidized to the oxoammonium ion, closing a catalytic cycle. In literature, different co-oxidants are used for the re-oxidation of TEMPOH. Various inorganic and organic compounds in organic solvents, water or ionic liquids have been reported.\(^{[41]}\) From an ecological and economical point of view, the use of stoichiometric oxidation agents such as chromates or permanganates should be abandoned and replaced by peroxides or, preferably, molecular oxygen.\(^{[5]}\) Therefore the use of catalytic mediators, such as transition metals\(^{[42]}\) or other inorganic compounds,\(^{[43]}\) with O\(_2\) as terminal oxidant is preferred. Nevertheless, even the use of catalytic amounts of transition metals can cause problems like catalyst deactivation and the possibility of metal contamination in the product mixture.

![Scheme 5.1.2 Catalytic cycle of TEMPO using NO\(_x\) as co-oxidant.](image)

Several papers report on the use of catalytic amounts of NO\(_x\) sources such as tert-butyl-nitrite as co-catalyst, and O\(_2\) as terminal oxidant in TEMPO-mediated alcohols oxidations (Scheme 5.1.2).\(^{[44\text{-}46]}\) All of these reactions have been performed in batch mode under relatively mild conditions (room temperature to 80 °C, ambient pressure). That is the reason why these systems very often suffer from limited space-time yields and therefore also require high amounts of TEMPO (typically 10-20 mol%) and a co-catalyst, in order to get acceptable reaction rates. The use of a continuous
plug-flow reactor not only increases the space-time-yield due to a higher catalyst-to-substrate-ratio and enhanced mass-transfer, it also leads to a decrease in the amount of co-oxidant needed in order to reach full conversion. This is an advantage from both an economic and ecological point of view.

In the present work the use of a continuous three-phase flow reactor with commercial available silica-immobilized TEMPO and catalytic amounts of HNO₃ as an inexpensive NOₓ source for the oxidation of different primary and secondary alcohols is examined.

5.2 Reactor Set-Up

A continuous flow reactor on a small scale can offer several advantages compared to a standard batch reactor such as enhanced heat- and mass-transfer, improved control of the reaction parameters, faster mixing of the reactants and shorter reaction times. Enhanced mass transfer between the different phases, due to the generation of large interfacial areas, is indeed important for the present reaction.\[43\]

An HPLC pump is used to pump the liquid phase (solvent, alcohol, HNO₃ and biphenyl standard). It is combined with the O₂ gas flow in a T-mixer, which generates a gas-liquid slug flow as visually verified (see Appendix A.3). Such segmented flows efficiently promote gas-liquid mass transfer.\[39\] Later the gas-liquid feed enters a packed-bed reactor filled with silica immobilized-TEMPO particles. The system pressure is set by a back-pressure regulator. The product mixture coming out of the reactor is sent to a phase separator. The gas phase is analysed by infrared spectroscopy in a transmission cell and the liquid phase is analysed by gas chromatography (GC). The reactor was operated at 5 bar to keep a stable segmented flow.
5.3 Benchmarking Experiments with Benzyl Alcohol

Benzyl alcohol was taken as a model substrate in order to examine the performance of the system and the stability of the catalyst. Screening of different solvents reveals that 1,2-dichloroethane (DCE) gives the best results (Table 5.3.1). The molar vaporization enthalpy of DCE (i.e., 34 kJ mol\(^{-1}\)) is moreover 20% lower than that of water (i.e., 43 kJ mol\(^{-1}\)), leading to a lower energy consumption in the downstream solvent recovery.

<table>
<thead>
<tr>
<th>solvent</th>
<th>vaporization enthalpy / kJ mol(^{-1})</th>
<th>Conv. / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-Dichloroethane</td>
<td>34</td>
<td>98</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>29</td>
<td>85</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>32</td>
<td>73</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>38</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5.3.1 Aerobic oxidation of benzyl alcohol in different solvents mediated by 5 mol% HNO\(_3\) and TEMPO on silica at 55 °C, 5 bar O\(_2\) and a contact time of 0.5 min.

Figure 5.3.1 Conversion vs. time-on-stream for different temperatures, a contact time of 0.5 min. (solvent: DCE, [PhCH\(_2\)OH]_0 = 500 mM, [HNO\(_3\)]_0 = 5 mol%, 5 bar O\(_2\))
Figure 5.3.1 shows the conversion of benzyl alcohol for a contact time of 0.5 minutes against the time-on-stream. A clear deactivation of the catalyst can be observed for temperatures above 55 °C. It is known that the oxoammonium ion of TEMPO can decompose under acidic conditions, forming N₂O, CO₂ and dienes as products (Scheme 5.1.2).[40] This hypothesis is confirmed by the transmission IR spectra of the gas phase (Figure 5.3.2) revealing the presence of N₂O during the decomposition phase of the reaction, pointing towards the degradation of TEMPO species. Additional support for this hypothesis is obtained from the EPR spectra of the TEMPO catalyst, taken before and after 2 hours of reaction (Figure 5.3.3). Clearly, a significant amount of TEMPO is lost during the reaction, explaining the levelling off of the conversion. The catalyst bed is characterized by a pale green colour after exposure to temperatures above 70 °C, in line with the literature indicating different decomposition products of TEMPO.[40] Blank activity of silica gel (i.e., the support) can be excluded since pure silica did not show any activity at temperatures between 55 °C and 80 °C.

![Figure 5.3.2 Gas-phase transmission IR spectra from an oxidation reaction of PhCH₂OH performed at 80 °C, contact time of 0.5 min. and 5 bar O₂; ν₃ vibrational mode of N₂O around 2220 cm⁻¹.](image-url)
No decomposition of the catalyst could be observed at 55 °C for over 8 hours (Figure 5.3.1). Additionally, only traces of N₂O could be observed in the gas phase and the EPR signals have the same magnitude before and after the reaction (see Appendix A.3), pointing towards the fact that at this temperature the catalyst does not decompose. This is the reason why all subsequent reactions were performed at 55 °C. Additionally the reaction was also performed with half the size of the catalyst particles (0.08-0.12 mm) keeping the amount of active sites the same. This clearly showed that the conversion vs. time and the selectivity of the reaction was the same as the standard reaction for benzyl alcohol oxidation, which is a strong indication that intragranular mass transfer is not the rate limiting step in this system.

![EPR spectra](image)

**Figure 5.3.3** EPR spectra of the initial catalyst and of the used catalyst after 2 hours time-on-stream at 80 °C. (solvent: DCE, [PhCH₂OH]₀ = 500 mM, [HNO₃]₀ = 5 mol%, 5 bar O₂)

Although the oxoammonium cation is formed during the catalytic cycle (Scheme 5.1.2), we believe that there is most likely an additional source via the interaction of TEMPO species on the surface at temperatures above 60 °C. This could be possible because the statistical density of active sites is estimated to be 1 TEMPO molecule per nm². Moreover, it is well known that two TEMPO molecules can disproportionate,
acid-catalyzed, to one TEMPOH and one oxoammonium ion (Scheme 5.3.1). This assumption was confirmed by experiments where 0.1 mol L\(^{-1}\) of HCl in dichloroethane was run over the catalyst at 80 °C clearly leading to a red colour of the catalyst bed, indicating the formation of the oxoammonium. Due to the increased concentration of these species, their irreversible acid-catalyzed decomposition is enhanced, especially during the oxidation of less reactive alcohols. This degradation can take place until the distance between the active sites is too large for the disproportionation reaction to take place. This could indeed explain why the conversion always seems to level off, irrespective of the precise reaction conditions (see Figure 5.3.1).

![Scheme 5.3.1](image)

**Scheme 5.3.1** Acid-catalyzed disproportionation of TEMPO species leading to TEMPOH and oxoammonium ion.

![Figure 5.3.4](image)

**Figure 5.3.4** Conversion vs. time-on-stream for benzyl alcohol at 80 °C and a contact time of 0.5 min for different initial amounts of water present in the system (solvent: DCE, [PhCH\(_2\)OH]\(_0\) = 500 mM, [HNO\(_3\)]\(_0\) = 5 mol%, 5 bar O\(_2\) )
The decomposition rate depends on the amount of water initially present in the reaction mixture (Figure 5.3.4). This effect is most likely due to the fact that at higher H$_2$O concentrations more NO$_x$ species are present as HNO$_3$ and HNO$_2$, increasing the rate of irreversible catalyst decomposition.

Table 5.3.2 shows the space-time-yields for the oxidation of benzyl alcohol for different heterogeneous TEMPO catalysts with different NO$_x$ sources as co-oxidant. An excellent performance can be seen with the continuous flow system, featuring three-orders-of-magnitude higher space-time-yields than comparable batch systems.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Catalyst</th>
<th>$T$ / °C</th>
<th>Space-time-yield$^{[a]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>this work</td>
<td>TEMPO on silica$^{[b]}$</td>
<td>55</td>
<td>$4.1 \times 10^5$</td>
</tr>
<tr>
<td>[45]</td>
<td>TEMPO on silica$^{[c]}$</td>
<td>R.T.</td>
<td>$4.4 \times 10^2$</td>
</tr>
<tr>
<td>[46]</td>
<td>TEMPO on magnetic nanoparticles$^{[d]}$</td>
<td>50</td>
<td>$8.3 \times 10^4$</td>
</tr>
</tbody>
</table>

[a] mol PhCH$_2$OH (mol TEMPO)$^{-1}$ h$^{-1}$ (L reactor volume)$^{-1}$, [b] Solvent: DCE, co-oxidant: HNO$_3$, [c] Solvent: DCE, co-oxidant: NO$_x$ absorbed on silica, [d] Solvent: H$_2$O, co-oxidant: tert-butyl-nitrite

5.4 Expanding the Substrate Scope

In order to extend the substrate scope, several primary and secondary alcohols were tested (Table 5.4.1). High reaction rates and selectivities towards the corresponding aldehyde or ketone products were obtained. Over-oxidation to the corresponding acids is limited and selectivities close to 90% can be obtained.

Due to the moderate reaction conditions (viz., 55 °C), alcohols that usually dehydrate under acidic conditions like prenol or isoprenol were smoothly oxidized to the corresponding carboxyls. The liquid phase oxidation of isoprenol offers an interesting alternative to the currently used gas-phase oxidation over a Ag-catalyst, affording 75 % selectivity towards the sum of isoprenal and the thermodynamically more stable prenal (ratio of 4:1). Indeed, for the synthesis of citral, the
isomerization is irrelevant as the crude product is treated with a weak base, isomerizing isoprenal to prenal, during the work-up of the reaction mixture.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>$\tau / \text{min}^{[a]}$</th>
<th>Conv. / %</th>
<th>Sel. / %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5$^{[b]}$</td>
<td>98$^{[b]}$</td>
<td>99$^{[b]}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>67</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>93</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>65</td>
<td>70 (80$^{[c]}$)</td>
</tr>
</tbody>
</table>

$^{[a]}$ Contact time was not optimized for full conversion, $^{[b]}$ 5 mol% HNO$_3$, $^{[c]}$ combined selectivity towards isoprenal and prenal

### 5.5 Renewable Substrates

Sugars are a readily available feedstock from biomass in future biorefineries. Especially 5-hydroxymethylfurfural (HMF) which can be obtained upon dehydration of glucose and fructose, has gained considerable attention as a possible key-intermediate in the manufacturing of chemicals and fuels.$^{[50]}$ One possible application is the selective oxidation of HMF to the corresponding 2,5-diformylfuran (DFF). DFF has been described to be a possible starting material for pharmaceuticals, macrocyclic ligands, monomers for many functional materials and others.$^{[48]}$

The selective oxidation of HMF to DFF was performed with our silica-immobilized TEMPO system at 55 °C, 5 bar O$_2$ and 5 mol% of HNO$_3$. With a contact time of 2 minutes, 97 % conversion in HMF could be achieved with 98 % selectivity towards DFF (Figure 5.5.1). When the contact time is increased, over-oxidation of DFF to 2,5-furandicarboxylic acid (FDCA) can be observed (Figure 5.5.1). FDCA is another interesting building block being a possible replacement for terephtalic acid in the
production of polymers.\textsuperscript{[47]} The present system presents promising results for the manufacturing of both DFF and FDCA, depending on the reaction conditions. However for contact times higher than 6 minutes FDCA starts to crystallize out, due to the low solubility in DCE. This problem could be solved by adding a co-solvent or working in a different solvent. This approach should be further investigated in the future.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure551.png}
\caption{Concentration vs. time-on-stream for HMF at 55 °C and different contact times (solvent: DCE, [HMF]$_0$ = 410 mM, [HNO$_3$]$_0$ = 5 mol\%, 5 bar O$_2$)}
\end{figure}

\textbf{Scheme 5.5.1.} Oxidation of lactic acid to pyruvic acid.

Another interesting renewable substrate is lactic acid which on an industrial scale is mainly produced by fermentation of carbohydrates. Especially lignocellulosics have the potential to become a clean, renewable and low-cost source of lactic acid.\textsuperscript{[51]} The oxidation of lactic acid to pyruvic acid (Scheme 5.5.1) has some difficulties because of the fast decarboxylation of the substrate. Therefore mild conditions and small
amounts of oxidants are a prerequisite. Pyruvic acid is mainly used as intermediate for pharmaceutical applications but it is also used in the production of crop protection agents, polymers, cosmetics and foods.\textsuperscript{[52]} With the present system, the selective oxidation of lactic acid (500 mM) to pyruvic acid was performed at 55 °C, 5 bar O\textsubscript{2} and 5 mol\% of HNO\textsubscript{3}. With a contact time of only 15 seconds 98 % conversion in lactic acid and over 98 % selectivity towards pyruvic acid could be obtained.

5.6 Conclusions

The continuous aerobic oxidation of different alcohols using an heterogeneous immobilized TEMPO catalyst was examined. High reaction rates, conversions and selectivities could be obtained. The catalyst remained stable over several hours under mild conditions making the process attractive, compared to transition metal-catalyzed systems that very often suffer from deactivation and/or low activities. Due to the high reaction rates, only small amounts of HNO\textsubscript{3} as co-oxidant have to be used. Since O\textsubscript{2} is the terminal oxidant the process is attractive both from an economic and ecological point of view.

The system is broadly applicable to a wide range of primary and secondary alcohols, always showing high reaction rates and selectivities. Another advantage of this continuous system is the flexibility of tuning the selectivity in consecutive reactions depending on the application. This can be seen in the case of HMF oxidation where high yields of either DFF or FDCA can be obtained, depending on the contact time. Additionally, less stable alcohols like lactic acid or prenols could be smoothly oxidized, due to the moderate conditions of only 55 °C and 5 bar O\textsubscript{2}.

Overall, the reported system offers a promising alternative to state-of-the-art stoichiometric oxidants or transition metal catalysts for the environmentally benign and economical oxidation of alcohols.
5.7 Experimental Section

The continuous flow reactor (Teflon®, internal diameter 1.65 mm, reactor set-up: see chapter 4) was packed with commercial available TEMPO catalyst attached to a silica support (Sigma-Aldrich, 0.7 mmol/g active sites; particle size 0.16-0.24 mm, void fraction of 65 %) and connected to an HPLC pump and O₂ mass flow controller. When the oil bath reached the desired temperature the packed bed was put inside the oil bath and the reaction was started. For all benzyl alcohol oxidation experiments a liquid flow rate of 0.4 mL min⁻¹ and a gas flow rate of 5 mLn min⁻¹ was chosen. For other contact times the ratio of liquid to gas flow-rate was kept constant. For the rest of the substrates a liquid flow rate of 0.1 mL min⁻¹ and a gas flow rate of 1.3 mLn min⁻¹ was chosen. Segmented flow could be visually verified in the transparent Teflon® tubes (see Appendix A.3, mixing zone and fixed bed reactor). Liquid hold ups in order to determine contact times were calculated with the correlation of Larachi et al.¹⁵³ (see Appendix A.3). The pressure was set to 5 bar with a back pressure regulator and the reaction was run for 30 minutes before taking the first sample. Transmission IR spectra of the gas phase were taken with a home-made 30 mL quartz cell with CaF₂ windows. The cell was evacuated and flushed with N₂ three times prior to sampling; background measurements were taken with an evacuated empty cell. The liquid products were quantified against a biphenyl internal standard using gas chromatography (HP-FFAP column, flame ionization detector). In order to measure EPR both the fresh and the used catalyst was dried on the high vacuum at 100 °C for 3 hours.
Overall Conclusions and Outlook

The selective oxidation of alcohols to the corresponding ketones, aldehydes and carboxylic acids is a very important transformation both in chemical industry and chemical research. Especially the partial oxidation of primary alcohols to their corresponding aldehydes offers a challenge since the product is more activated than the substrate which very often leads to a rapid overoxidation to the corresponding carboxylic acid. This is the reason why in many publications these reactions are performed at higher pH values to prevent catalyst poisoning when transition metal based catalysts are used. Another disadvantage of these traditional catalyst systems is the possibility of metal contamination in the product mixture.

HNO₃-based oxidations offer several advantages compared to transition metal based systems, such as its low price and high achievable selectivities. However, the formation of N₂O, a strong greenhouse gas, is a strong drawback and therefore the amount of HNO₃ used should be kept as low as possible.

In this thesis we have shown that HNO₃ can be used in catalytic quantities as an oxygen shuttle. Within these systems, HNO₃ is able to start off a chain oxidation of alcohols, mediated by (H)NOₓ species, where O₂ is the true terminal oxidant. To begin with, the reaction mechanism was elucidated with the help of benzyl alcohol as a model substrate. Afterwards the reaction was optimized with different reactor set-ups where a continuous flow reactor on a millimeter scale showed the best results. The system could be extended to different primary and secondary alcohols. Since Amberlyst-15®, a strong solid acid, is used as a co-catalyst in these reactions, less stable alcohols tend to dehydrate under reaction conditions.

A possible alternative method for aerobic alcohol oxidation was presented in the final chapter, where silica-immobilized TEMPO was used as a catalyst in combination with HNO₃ as co-oxidant under continuous conditions. Thereby the reaction
temperature and the amount of HNO$_3$ used could be further decreased. Due to the more moderate reaction conditions the substrate scope could be extended.

Amberlyst-15® proved to be a good catalyst for aerobic alcohol oxidations mediated by nitric acid. However, as already mentioned its strong acidity can limit the substrate scope. Therefore less acidic solid Brønsted or Lewis acids should be tested in order to improve the substrate scope.

Another area of immediate research should be the use of silica-immobilized TEMPO with different loadings in order to test whether the surface species can indeed interact with each other and accelerate their decomposition. It is highly probable that less surface species would lead to a higher stability of the TEMPO catalyst at elevated temperatures.
Appendix: Supporting Information

A.1 Supporting Information to Chapter 2

Initiator Influence (100 mL High Pressure Reactor)

PhCH₂OH conversion vs. time at 80 °C: (a): 20 bar O₂, no initiator, (b): 0.03 bar NO₂, 6 bar He, 14 bar O₂, (c) 20 bar O₂, 5 mM NaNO₂, (d) 0.1 bar NO, 2.3 bar He, 17.6 bar O₂. ([PhCH₂OH]₀ = 500 mM, [HNO₃]₀ = 125 mM, 6 mg/mL Amberlyst-15°)

N₂ vs. O₂ (1 bar in Bubble Column)

PhCH₂OH conversion vs. time at 80 °C under N₂ bubbling (a) and under O₂ bubbling (b). ([PhCH₂OH]₀ = 500 mM, [NaNO₂]₀ = 5 mM, [HNO₃]₀ = 125 mM, 6 mg/mL Amberlyst-15°)
PhCH₂OH conversion vs. time at 80 °C for various amounts of HNO₃ (a-e: 31, 62.5, 125, 187 and 250 mM, [PhCH₂OH]₀ = 500 mM, 6 mg/mL Amberlyst-15®)

Initial PhCH₂OH conversion rate at 80 °C vs. [HNO₃]. Notice that the proportional trend is levelling-off, pointing towards the initiating effect of HNO₃, rather than a pure first-order stoichiometric reaction. ([PhCH₂OH]₀ = 500 mM, 6 mg/mL Amberlyst-15®)
Effect of Amberlyst-15® on the Induction Period

PhCH2OH conversion vs. time at 90 °C without Amberlyst-15® (a) and with 6 mg/mL Amberlyst-15® (b). ([PhCH2OH]₀ = 500 mM, [HNO₃]₀ = 125 mM)

The effect of Amberlyst-15® on the decomposition of HNO₃ to NO₂ was studied by monitoring the NO₂ formation with GC-MS (m/z=46) (80 °C, 25 mL 1,4-dioxane, 125 mM HNO₃, various amounts of Amberlyst-15®). Note that only initial rates can be considered, due to the 2 NO₂ + H₂O ⇌ N₂O₄ + H₂O → HNO₃ + HNO₂ equilibrium.

Formation of NO₂ as a function of time, various amounts of Amberlyst-15®: (a)-(e): 0, 50, 75, 150 and 200 mg in 25 mL reaction solution. ([PhCH₂OH]₀ = 500 mM, [HNO₃]₀ = 125 mM)
Initial NO₂ formation rate as a function of the Amberlyst-15® loading at 90 °C.

**Monitoring of NO and N₂O in the Gas Phase with MS**

Time evolution of the N₂O and NO mass spectrometry signals, relative to the N₂ standard, in the gas-phase at 80 °C (static O₂ pressure of 1 bar, [PhCH₂OH] = 500 mM, [HNO₃] = 125 mM, 6 mg/mL Amberlyst-15®).
Monitoring N$_2$O in the Gas Phase with Transmission IR

Transmission IR spectra of the gas phase were taken with a home-made 30 mL quartz cell with CaF$_2$ windows. The cell was evacuated and flushed with N$_2$ 3× prior to sampling; background measurements were taken with an evacuated empty cell. Spectra are scaled to the C-H stretches of the dioxane solvent (2800-3000 cm$^{-1}$).

Transmission IR spectra of the gas phase of a benzyl alcohol oxidation experiment at 80°C under 1 bar of O$_2$ (static pressure, spectra shown after 0.5, 1, 2, 3 and 5 h). Spectra are normalized to the C-H stretches of 1,4-dioxane (2800-3000 cm$^{-1}$); peaks indicated with * are due to N$_2$O. In chapter 2 only the main peak at 2220 cm$^{-1}$ ($v_3$ vibrational mode) is shown. ([PhCH$_2$OH]$_0$ = 500 mM, [HNO$_3$]$_0$ = 125 mM, 6 mg/mL Amberlyst-15$^{\text{®}}$)
A.2 Supporting Information to Chapter 3

Benzyl Nitrite Was Synthesized According to a Literature Procedure:


Benzyl Nitrate Was Synthesized According to a Modified Literature Procedure:


Benzyl bromide (2 mL, 1.4 M) and silver nitrate (2.6 g, 1.3 M) were put together with 10 mL acetonitrile in a 50 mL round bottom flask. The suspension was stirred with a magnetic stirrer for 40 min at room temperature. Afterwards the reaction solution was centrifuged to separate benzyl nitrate, acetonitrile and the remaining benzyl bromide from the solid residue (AgBr). Subsequently the acetonitrile was evaporated with the rotavap.

NMR spectrum of the benzyl nitrite (black) and benzyl nitrate (red).

General Procedure of the Benzyl Nitrite Decomposition:

A solution of biphenyl (0.02 M) in dioxane was prepared. Subsequently 4 mL of this solution were heated to the desired temperature and put together with 75 μL of a
benzyl nitrite solution and a desired amount of Amberlyst-15° in a 5 mL round bottom flask. Afterwards a septum with an N₂-ballon was put on top and the reaction solution was stirred with a magnetic stirrer.

Time evolution of the benzyl nitrite and benzaldehyde signal (relative to the biphenyl standard, monitored with GC-MS with cool-on-column injection); 10 mg Amberlyst-15° per mL, 40 °C. ([PhCH₂ONO]₀ = 200 mM)

Time evolution of the ln of the benzyl nitrite signal, relative to the biphenyl standard; 10 mg Amberlyst-15° per mL, 40 °C. ([PhCH₂ONO]₀ = 200 mM)
Evolution of the pseudo first-order rate constants for nitrite decomposition as a function of the Amberlyst-15\textsuperscript{®} loading at various temperatures. ([PhCH\textsubscript{2}ONO]_0 = 200 mM)

Arrhenius plot for the benzyl nitrite decomposition (R=0.989). ([PhCH\textsubscript{2}ONO]_0 = 200 mM)
A.3 Supporting Information to Chapter 5

The following reactor set-up was used to perform the continuous flow experiments:

![Diagram of reactor set-up]

Experimental set-up: (a) O₂ reservoir, (b) liquid reservoir, (c) pressure reduction valve, (d) mass flow controller, (e) HPLC pump, (g) segmented flow, (h) fixed-bed reactor, (i) back-pressure regulator, (k) phase-separator and (l) gas-flow passing through transmission IR cell.

Transmission IR spectra of the gas phase for a reaction performed at 55 °C indicating that at this temperature only traces of N₂O are formed (viz., the catalyst is stable).
Gas phase transmission IR spectra from an oxidation reaction of benzyl alcohol performed at 55 °C, contact time 0.5 min. for 0.5 and 2 h time-on-stream: $\nu_3$ vibrational mode of N$_2$O around 2220 cm$^{-1}$.

(solvent: DCE, [PhCH$_2$OH]$_0$ = 500 mM, [HNO$_3$] = 5 mol\%, 5 bar O$_2$)

EPR spectra of the catalyst before and after the reaction performed at 55 °C indicate that the decomposition of the catalyst is neglectable at that temperature.

EPR spectra of the initial catalyst and of the used catalyst 2 hours time-on-stream at 55 °C. (solvent: DCE, [PhCH$_2$OH]$_0$ = 500 mM, [HNO$_3$] = 5 mol\%, 5 bar O$_2$)
As mentioned in chapter 5, a slug flow could be observed visually.

Slug flow could be observed in the mixing zone before the reactor but also in the fixed bed reactor itself.

For the calculation of the liquid hold up at elevated pressures, the correlation of Larachi et al (see e.g., V. V. Ranade, R. Chaudhari and P. R. Gunjal, *Trickle Bed Reactors, Reactor Engineering & Applications*, Elsiever B.V., Oxford, 2011) was used:

\[
\log(1 - \beta) = \frac{-1.22 \cdot We_L^{0.15}}{Re_L^{0.2} \cdot X_G^{0.15}}: \quad \beta = 1 - 10 \cdot \frac{-1.22 \cdot We_L^{0.15}}{Re_L^{0.2} \cdot X_G^{0.15}} \tag{1}
\]

\[\beta: \quad \text{liquid saturation} \left( \frac{\text{liquid volume}}{\text{void volume}} \right)\]

\[We_L = \text{Weber number} = \frac{U_L^2 \cdot d \cdot \rho_L}{\sigma_L} \tag{2}\]

\[U_L = \frac{Q_L}{\pi (\frac{d}{2})^2 \cdot \epsilon}: \quad \text{liquid velocity} \left( \frac{m}{s} \right) \tag{3}\]
\( d_p \): particle size \((m)\)

\( \rho_L \): liquid density \(\frac{kg}{m^3}\)

\( \sigma_L \): liquid surface tension \(\frac{N}{m}\)

\( d_r \): reactor diameter \((m)\)

\( Q_L \): liquid volumetric flow rate \(\frac{m^3}{s}\)

\( \varepsilon \): void fraction

\[ Re = \text{Reynolds number} = \frac{\rho_L u_L d_r}{\mu_L} \tag{4} \]

\( \mu_L \): liquid dynamic viscosity \((Pa \cdot s)\)

\[ X_G = \text{Modified Lockhart – Martinelli number} = \left( \frac{u_L}{u_G \sqrt{\rho_L / \rho_G}} \right)^{-1} \tag{5} \]

\[ U_G = \frac{Q_G}{\pi (\frac{d_r}{2})^2 \varepsilon} \]: gas velocity \(\frac{m}{s}\) \(\tag{6}\)

\( Q_L \): gas volumetric flow rate \(\frac{m^3}{s}\)

\[ \rho_G = \frac{p}{R_s T} \tag{7} \]

\( \rho_G \): gas density \(\frac{kg}{m^3}\)

\( R_s \) specific gas constant \((287.058 \ \frac{J}{kg \cdot K})\)

\( T \) reaction temperature \((K)\)
Physical properties of the system (1,2-dichloroethane)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_L$</td>
<td>$6.7 \cdot 10^{-9}$ (0.4 $\frac{mL}{min}$)</td>
</tr>
<tr>
<td>$Q_G$</td>
<td>$1.7 \cdot 10^{-8}$ ($5 \frac{mLn}{min}$ at 5 bar)</td>
</tr>
<tr>
<td>$U_L$</td>
<td>$4.8 \cdot 10^{-3}$</td>
</tr>
<tr>
<td>$U_G$</td>
<td>$1.2 \cdot 10^{-2}$</td>
</tr>
<tr>
<td>$\rho_L$</td>
<td>1250</td>
</tr>
<tr>
<td>$\rho_G$</td>
<td>5.3</td>
</tr>
<tr>
<td>$\sigma_L$</td>
<td>$3.4 \cdot 10^{-2}$</td>
</tr>
<tr>
<td>$\mu_L$</td>
<td>$0.65 \cdot 10^{-3}$</td>
</tr>
<tr>
<td>$d_r$</td>
<td>$1.65 \cdot 10^{-3}$</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>0.65</td>
</tr>
<tr>
<td>$d_p$</td>
<td>$0.2 \cdot 10^{-3}$</td>
</tr>
<tr>
<td>$T$</td>
<td>328</td>
</tr>
<tr>
<td>$We_L$</td>
<td>$1.7 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>$Re$</td>
<td>15.2</td>
</tr>
<tr>
<td>$X_G$</td>
<td>$1.6 \cdot 10^{-1}$</td>
</tr>
</tbody>
</table>
According to equation (1) the liquid hold up is:

$$\beta = 1 - 10^{-0.122 \frac{W}{Re_k^{0.15} \frac{1}{X_G^{0.15}}}} = 0.44$$

(8)

The residence time of the system was calculated in the following way:

$$\tau = \frac{V_r \cdot e \cdot \beta}{Q_l} = \frac{(\frac{d}{2})^2 \pi \cdot e \cdot \beta}{Q_l}$$

(9)

In the case of benzyl alcohol oxidation reactions the reactor length was 0.3 m which corresponds to a residence time of:

$$\tau = 28 \text{ s} \approx 0.5 \text{ min}$$

(10)

Since the reaction was performed in transparent teflon tubes, the residence time of the liquid was visually verified for 30 liquid bubbles with a stop watch under the above mentioned operating conditions, resulting in the following 95 % confidence interval:

$$\tau = 29 \pm 2 \text{ s}$$

(11)

Since the the correlation of Larachi et al is in good agreement with the measured residence time, the correlation was used for all subsequent alcohols and operating conditions.
References


[32] \((\Delta E, E_{act})\) values in kcal mol\(^{-1}\): 4-OMe (1.2, 12.2); 4-Me (2.05, 12.3); 4-Cl (2.2, 12.6); 4-H (2.4, 12.5); 4-NO\(_2\) (8.7, 13.4); 2,3-diF (4.4, 12.8); 2,4-diF (3.6, 12.7); 2,6-diF (7.7, 13.2).


## List of Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>Ångström ($10^{-10}$ m)</td>
</tr>
<tr>
<td>dF</td>
<td>difluoro</td>
</tr>
<tr>
<td>DFT</td>
<td>density functional theory</td>
</tr>
<tr>
<td>$d_p$</td>
<td>particle diameter</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>GC-MS</td>
<td>gas chromatography mass spectrometer</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>i.e.</td>
<td>id est (that is)</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>kcal</td>
<td>kilo-calories ($4.184 \times 10^{-3}$ J)</td>
</tr>
<tr>
<td>kt</td>
<td>kilo-tons</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>M</td>
<td>molar ($\text{mol} \ \text{L}^{-1}$)</td>
</tr>
<tr>
<td>Me-</td>
<td>methyl-</td>
</tr>
<tr>
<td>meq</td>
<td>milli-equiavalents</td>
</tr>
<tr>
<td>mg</td>
<td>milli-gram</td>
</tr>
<tr>
<td>mL</td>
<td>milli-litre</td>
</tr>
</tbody>
</table>
mL\textsubscript{n} milli-litre (normal conditions)

mM milli-molar (mol/L \times 10^{-3})

Mt mega-tons

NMe\textsubscript{2}- mimethyamin-

NO\textsubscript{2}- nitro-

OMe- methoxy-

\( R \) universal gas constant \((8.31 \text{ J mol}^{-1} \text{ K}^{-1})\)

\( T \) temperature (K)

\textit{viz.} videlicet (namely)

\textit{vs.} versus

\( \mu \text{L} \) micro-litre
List of Publications

Publications in Connection with this Thesis

- „Aerobic Alcohol Oxidations Mediated by Nitric Acid”
  (Chapter 2)

- „Acid-Catalyzed Decomposition of the Benzyl-Nitrite Intermediate during the HNO₃-Mediated Aerobic Oxidation of Benzyl Alcohol”
  (Chapter 3)

- „Metall-Free Aerobic Alcohol Oxidation: Intensification under Three-Phase Flow Conditions”
  (Chapter 4)

- „Intensification of TEMPO-mediated Aerobic Alcohol Oxidations under Three-Phase Flow Conditions”
  (Chapter 5)

Other Publications not Included in this Thesis

- „Catalytic Transfer Hydrogenation/Hydrogenolysis for Reductive Upgrading of Furfural and 5-(Hydroxymethyl)furfural”
• „Continuous D-Fructose Dehydration to 5-Hydroxymethylfurfural Under Mild Conditions”
  C. Aellig, I. Hermans, ChemSusChem 2012, 9, 1737 – 1742
• „Understanding Selective Oxidations”
  U. Neuenschwander, N. Turrá, C. Aellig, P. Mania, I. Hermans, Chimia 2010, 64, 225 – 230

Conferences

• „Aerobic Alcohol Oxidations Mediated by Nitric Acid”
  243rd ACS National Meeting, San Diego, USA, April 2012
• „Aerobic Alcohol Oxidations Mediated by Nitric Acid”
  C. Aellig, C. Girard, I. Hermans
  15th International Congress on Catalysis, Munich, Germany, July 2012
• „Aerobic Alcohol Oxidations Mediated by Nitric Acid”
  C. Aellig, C. Girard, D. Scholz, I. Hermans
  SCS Fall Meeting, Zürich, Switzerland, September 2012
• „Continuous D-Fructose Dehydration to 5-Hydroxymethylfurfural under Mild Conditions”
  C. Aellig, I. Hermans
  245th ACS National Meeting, New Orleans, USA, April 2013