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Turning an Intrinsically Inefficient Reaction Efficient: Homogeneously Catalyzed Continuous-Flow Amination of Alcohols with Ammonia

Authors: Bernd Rienhoff,[1] Dario Nickel,[1] Sidonie Römer,[1] Niclas von Vietinghoff,[1] Dominik Pietschmann,[1] and Thomas Seidensticker,[1,*]

[1]TU Dortmund University, Department for Biochemical and Chemical Engineering, Laboratory of Industrial Chemistry, Emil-Figge-Straße 66, 44227 Dortmund, Germany

*Dr. Thomas Seidensticker, email: thomas.seidensticker@tu-dortmund.de, phone: +49 231 755 2310

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Abstract

Primary amines are key intermediates in pharmaceuticals, agrochemicals, and polymers, and their efficient synthesis from readily available alcohols and ammonia is highly desirable, particularly as water is formed as the sole by-product. However, reduced reaction rates caused by low concentrations of reactive intermediates and the undesired formation of secondary and tertiary amines often impede selective access to the desired product. Herein, we demonstrate that a transformation commonly regarded as intrinsically inefficient and typically requiring high catalyst loadings, can be rendered highly effective through alternative process design. By transferring the reaction to a continuous capillary flow reactor, performance was drastically improved at 280 °C and 70 bar using a homogeneous Ru catalyst at only 1.2 mol%. The optimization and substrate scope focused on pharmaceutically interesting structural motifs, achieving conversions exceeding 99 % and selectivities up to 98 % within 23.3 min. Stable continuous operation over 30 h confirmed robustness of the approach, including successful substrate switching without interrupting production, demonstrating operational flexibility. Furthermore, reliable crystallization enabled facile product isolation with high to excellent purities exceeding 95%, and catalyst recyclability was demonstrated, providing a basis for further process intensification.

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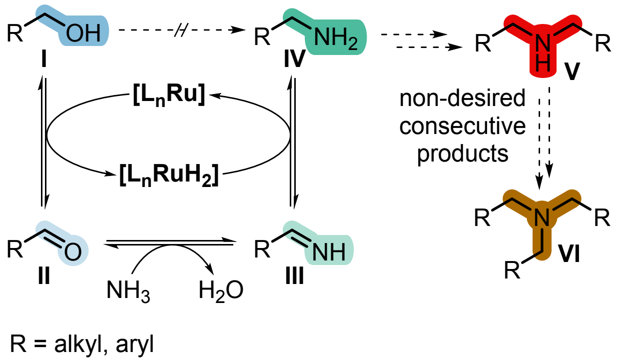
Introduction

Primary amines are vital intermediates in the chemical industry, serving as precursors for numerous applications, including pharmaceuticals, agrochemicals, and polymers.[1–3] On the laboratory scale, a classical approach to their synthesis is the Hofmann alkylation, in which ammonia reacts with activated alkyl halides or triflates to give product mixtures in which the fraction of primary amines is diminished by consecutive alkylation to secondary and tertiary amines.[4] To enhance synthetic efficiency and achieve selective primary amine formation, a variety of non-catalytic strategies have been developed,[5–9] most prominently the Gabriel synthesis.[10] However, despite the improved selectivity of these approaches, the formation of stochiometric amounts of salt and by-products results in considerable waste generation.

From an industrial perspective, attention has increasingly shifted toward the catalytic conversion of abundant feedstocks, minimizing waste-streams. In this context, short-chain alkyl amines are commonly produced via alcohol amination over heterogeneous catalysts with water as the sole by-product.[3] Yet, this method likewise affords mixtures of primary, secondary, and tertiary amines that require energy-intensive rectification for separation. In this regard, homogeneous catalysis presents a particularly attractive alternative, as it combines the utilization of abundant feedstocks with high selectivity toward primary amine formation.[11–21]

The homogeneously catalyzed alcohol amination follows a borrowing hydrogen mechanism (Scheme 1).[11] The substrate alcohol (**I**) is first dehydrogenated by the catalyst, yielding a reactive aldehyde intermediate (**II**). For primary amine synthesis, this intermediate condensates with ammonia to an imine (**III**), which is then reduced through a back-transfer of hydrogen to form the desired primary amine product (**IV**).



Scheme 1: Borrowing hydrogen mechanism for the amination of primary alcohols with ammonia using a homogeneous Ru-catalyst.[14]

The alcohol amination reaction presents an attractive and environmentally benign route to primary amines. However, its application beyond academic laboratories remains scarce, which can be attributed to two inherent mechanistic limitations: restricted reaction rates and

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undesired consecutive alkylation. The latter reduces selectivity and arises from the greater nucleophilicity of primary amines compared to ammonia. To prevent the formation of secondary (**V**) and tertiary amine (**VI**) side products, selective catalysts, a large excess of ammonia, or high substrate dilution have been reported.[11–21]

Additionally, the reaction rate is limited by the low concentrations of the two key intermediates in the catalytic cycle (the aldehyde (**II**) & the imine (**III**)), as well as the catalyst hydride [L_nRuH_2] species. As a result, reported syntheses of primary amines via alcohol amination typically require reaction times exceeding 12 hours,[11–13,15–18,20,21] rendering economic scale-up unattractive. Higher temperatures of 200 °C or above significantly accelerate the transformation, yet such conditions are difficult to implement using conventional laboratory equipment, particularly when applying ammonia. Microwave reactors and capillary flow systems have therefore emerged as enabling platforms for the realization of high-temperature alcohol amination protocols.[22–24]

However, the use of ammonia in the homogeneously catalyzed synthesis of primary amines has not been reported so far, although the continuous flow approach seems particularly advantageous since NH_3 can be fed directly in its liquid form,[25] avoiding dilution effects associated with aqueous solutions. Moreover, excellent heat transfer minimizes thermal fluctuations and eliminates the heating and cooling phases inherent to batch protocols, which reduces overall synthesis time and mitigates potential catalyst degradation.[26] The absence of a gas phase further increases ammonia availability, which potentially enhances selectivity. Moreover, continuous flow reactors also offer clear benefits for scaling and have gained attention in the academic literature for the synthesis of active pharmaceutical ingredients, particularly due to their ability to produce efficiently production-relevant amounts and constant product quality during operation.[27–29]

Until now, these advantages have been exemplified only in the homogeneous catalytic synthesis of tertiary amines by Ley and co-workers and by our group.[23,24] Under capillary flow conditions, turnover frequencies (TOFs) exceeding 900 h^{-1} were achieved at temperatures up to 290 °C, reducing reaction times to 15-20 minutes.[24] By contrast, optimized batch protocols for primary amine synthesis operate at 170 °C with reaction times of 3 to 7 hours and exhibit significantly diminished catalyst activities with TOFs of approximately 60 h^{-1}.[14] Only a single study has addressed continuous primary amine synthesis under capillary flow conditions. Hellgardt and Hii et al. employed a heterogenous Ni-Al_2O_3/SiO_2 (36 wt% Ni) catalyst and achieved quantitative conversion with excellent selectivity exceeding 99% within 47 minutes at 160 °C.[30] Yet, the corresponding turnover frequency of 0.015 h^{-1} is five orders of magnitude

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lower than values reported for homogeneous catalysts in tertiary amine synthesis, highlighting the extent to which the available catalytic potential remains unexploited in this area.

These considerations prompted us to investigate whether homogeneous catalysis under intensified flow conditions could provide a more efficient and selective route to primary amines. Our objective was to develop a continuous protocol capable of overcoming the intrinsic kinetic limitations of the borrowing-hydrogen mechanism while simultaneously maintaining high selectivity (Figure 1). Moreover, to demonstrate the practical value of such an accelerated and time-efficient approach, we focused on small and potentially relevant primary amine motifs for pharmaceutical synthesis as representative target structures in the development and scope (see Figure 5).

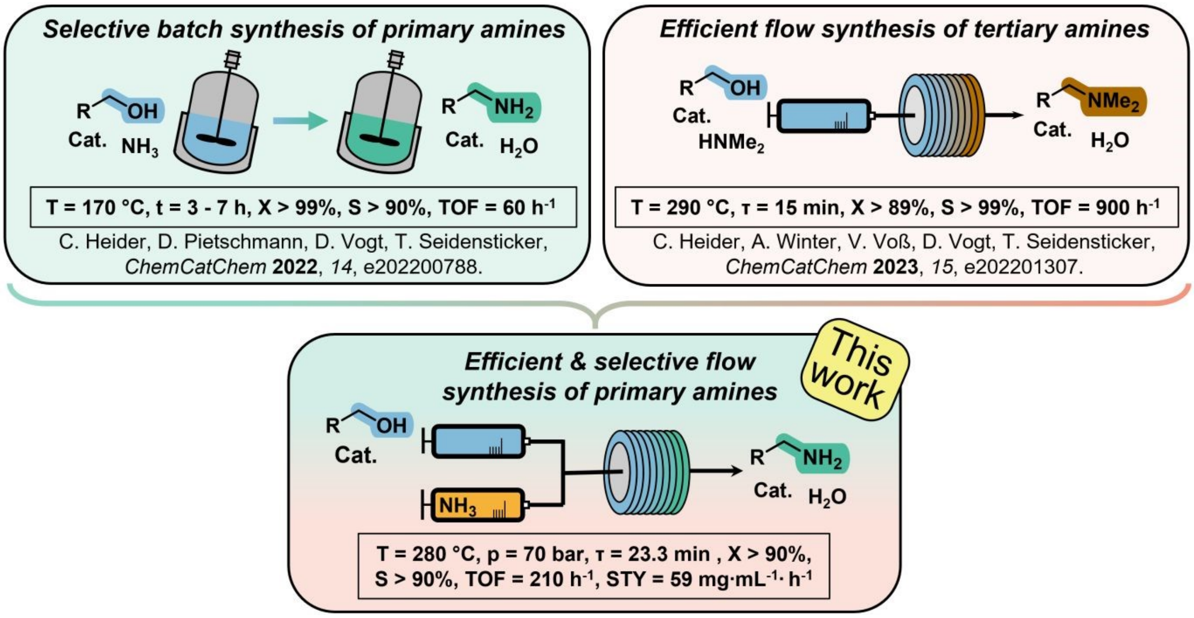

Figure 1: Illustration of the scope of this work to combine selective primary amine synthesis and reaction intensification under continuous flow conditions.[14,24]

Results and discussion

Reactor setup and optimization

In this study, we employed the commercially available catalyst precursor $HRuCl(CO)(PPh_3)_3$ in combination with the Xantphos ligand. This system was previously utilized in highly selective batch investigations,[14] and it has been demonstrated to be recyclable,[31] thereby indicating its stability and suitability for our intended application. To aid understanding, a brief overview of the reaction setup and performance is provided here (Figure 2), while detailed information is given in the Supporting Information (SI).

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The alcohol substrate and catalyst were dissolved in *tert*-amyl alcohol, while ammonia was introduced as a separate liquid stream using syringe pumps. Both streams were merged in a T-fitting, allowing adjustment of substrate ratio and residence time (τ) via the individual flow rates. The reaction mixture was then heated to the desired reaction temperature and subsequently quenched in a temperature-controlled water bath. A back-pressure regulator (BPR) maintained a constant pressure of 70 bar, and samples for GC analysis were taken before the product mixture was collected in a pressurized vessel.

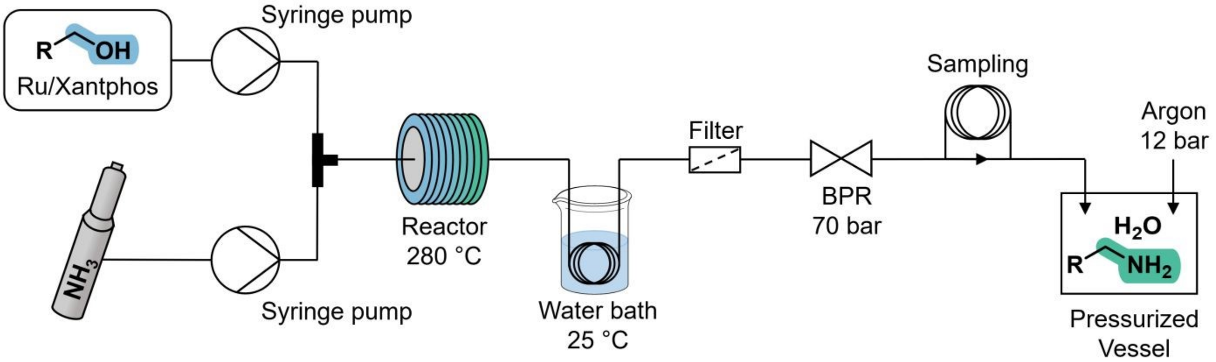

Figure 2: Illustration of the utilized continuous flow setup. The filter unit was only applied during optimization studies.

Benzyl alcohol (**1a**) was selected as a model substrate for the initial investigation, given that the resulting primary benzylamine (**2a**) and its benzylic analogues constitute key structural motifs in numerous active pharmaceutical ingredients (see Figure 5). A first screening of reaction temperature and residence time revealed that temperatures up to 280 °C were accessible before reactor clogging was observed. This was attributed to catalyst deactivation due to ruthenium black formation and was validated by ICP analysis of the precipitated black material collected from the filter unit.

Taking this into account, the system already exhibited highly promising performance at 280 °C with a residence time of 33 minutes. Under these conditions, the transformation proceeded with 96% conversion and afforded a high benzyl amine (**2a**) yield of 80%, corresponding to a selectivity of 84%. These first results already confirmed that the reaction time for primary amine synthesis can be markedly reduced.

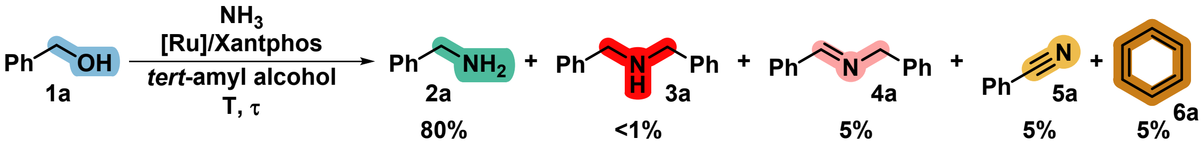

Figure 3: Alcohol amination of benzyl alcohol (**1a**) with ammonia and observed product spectrum with indicated yields. Conditions: Benzyl alcohol (261 mmol·L^{-1}), Ammonia:Alcohol = 34:1 (mmol·mmol^{-1}), $HRuCl(CO)(PPh_3)_3$ (3.2 mmol·L^{-1}), Xantphos (6.4 mmol·L^{-1}), solvent = *tert*-amyl alcohol, p = 70 bar, T = 280 °C, τ = 33 min. Yields determined by GC-FID analysis with dodecane as internal standard. The values shown are mean values from three

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samples. The first sample was taken after 3.5·τ, and the subsequent two samples were taken in 0.5·τ increments. The standard deviation of the shown values is ≤ 1%.

With respect to side-product formation, only trace amounts of <1% of the secondary amine dibenzylamine (**3a**) were detected, while the corresponding intermediate N-dibenzylidenebenzylamine (**4a**) was formed in 5% yield. Benzonitrile (**5a**) and benzene (**6a**) were observed in comparable quantities. The former likely arises from dehydrogenation of the imine intermediate,[32–34] whereas the latter is attributed to decarbonylation of the benzylaldehyde intermediate,[35] in agreement with previous findings from our group.[36] Notably, no tertiary amine product was detected in these initial studies, underscoring the system's high intrinsic selectivity for primary amine formation.

Based on these results, we applied a design of experiments (DoE) methodology to systematically assess the system's performance and operational characteristics. As parameters, the substrate alcohol concentration (14.3 mg·mL^{-1} to 43.0 mg·mL^{-1}), the ammonia-to-alcohol ratio (13.5:1 to 54.1:1), and the residence time (13.3 min to 54.1 min) were investigated. Modde© was used for data evaluation, and a central composite face-centered design with a quadratic model was selected as the experimental framework, yielding a total of 17 experiments. Important results are discussed in the following section (Figure 4), and further details on the product distribution and turnover number (TON) for all reactions are provided in the SI.

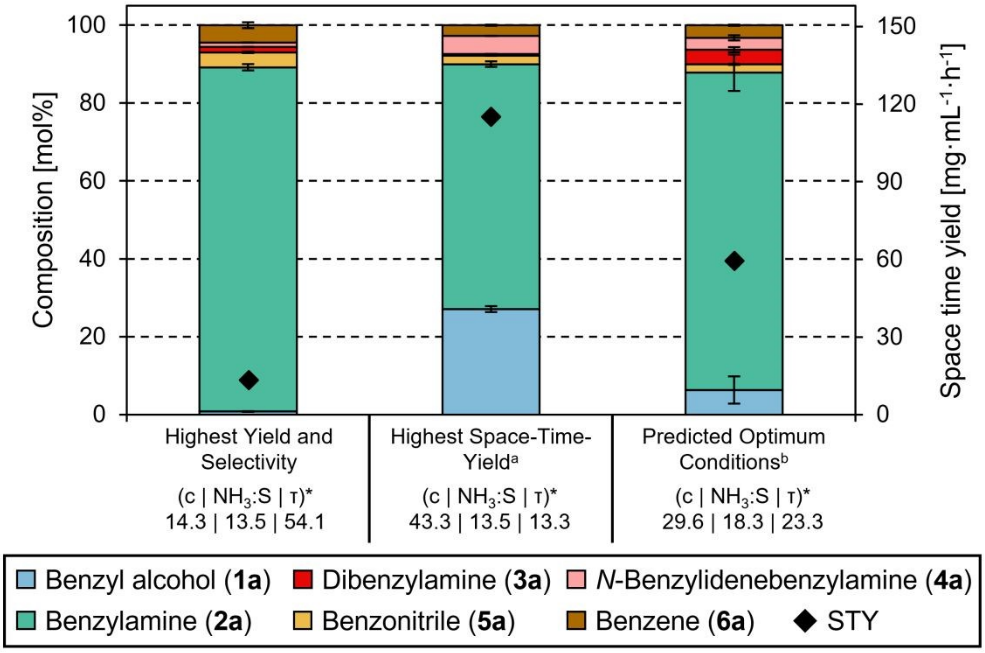

Figure 4: Comparison of selected reactions of the DoE investigation. Reaction conditions: HRuCl(CO)(PPh$_3$)$_3$ (3.2 mmol·L^{-1}), Xantphos (6.4 mmol·L^{-1}), solvent = *tert*-amyl alcohol, T = 280 °C, p = 70 bar, variable parameters as indicated. Product distribution and standard deviation were determined by GC-FID analysis with *n*-dodecane as an internal standard. The values shown are mean values from three samples. The first sample was taken after 3.5·τ, and subsequent samples were taken at 0.5·τ increments. *c = concentration of benzyl alcohol in mg·mL^{-1}, NH$_3$:S = ratio of ammonia to substrate alcohol and τ = residence time in min. a) Pressure not constant and clogging

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of the reactor after sampling. b) Optimum prediction in Modde© was restricted within the range of residence time that allowed continuous operation.

From a laboratory-scale synthesis perspective, quantitative conversion combined with a high overall yield is generally desirable to enable straightforward and efficient product isolation. In contrast, large-scale or economically motivated applications tend to prioritize high productivities, commonly expressed as space-time-yields (STY). Such conditions are often achieved at lower conversions, where increased reaction rates can be exploited and are of particular interest when effective downstream separation strategies are available that enable facile separation of non-converted substrate and product.

Under conditions relevant to laboratory-scale synthesis, our process proved highly effective, delivering nearly quantitative conversion with a benzylamine (**2a**) yield of 85%. Notably, a selectivity of 86% was achieved at an ammonia-to-benzyl alcohol (**1a**) ratio of only 13.5:1, substantially lower than ≥20:1 ratios reported in batch applications of the same catalytic system.[14,16,20] This result indicates improved ammonia availability in the capillary reactor relative to autoclave-based systems. The corresponding STY remained modest at 13 $mg{\cdot}mL^{-1}{\cdot}h^{-1}$. However, this result already exceeds the calculated STY of an optimized 75 mL batch autoclave reaction for benzyl alcohol of 4 $mg{\cdot}mL^{-1}{\cdot}h^{-1}$.[14]

When considering economic criteria, the highest productivity was obtained with an STY of 115 $mg{\cdot}mL^{-1}{\cdot}h^{-1}$, accompanied by a conversion of 74% and a benzylamine (**2a**) yield of 60%. However, pressure monitoring revealed pronounced fluctuations for all experiments at the shortest residence time (13.3 min), which coincided with this elevated STY. This instability ultimately led to reactor clogging through ruthenium black deposition after four to five residence times, rendering such conditions unsuitable for sustained continuous operation.

To identify operating parameters that balance synthetic efficiency and productivity, we employed Modde© to predict an optimum within the residence-time window that would ensure stable performance. This approach proved successful, and under the resulting conditions, the reaction proceeded with 96% conversion, a benzylamine (**2a**) yield of 79%, and an STY of 59 $mg{\cdot}mL^{-1}{\cdot}h^{-1}$. The excellent agreement between experimental data and model predictions (see SI) underscores the robustness of the statistical evaluation and the reliability of the obtained results. Moreover, the STY is nearly 15-fold higher than in the batch process, and the corresponding turnover frequency of 210 h^{-1} represents a substantial enhancement in catalytic activity. It is approximately four times higher than the values obtained for this catalyst system under batch conditions[14] and exceeds previously reported TOFs for heterogeneous primary amine synthesis in capillary reactors by five orders of magnitude.[30] Since TOF values are ideally determined at low conversions (<20%) within the pseudo-first-order regime, the intrinsic catalytic activity is likely even higher.

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Substrate Scope

We next evaluated a small substrate scope to assess the applicability and variability of the developed protocol. Building on the excellent performance obtained for benzyl alcohol (**1a**), structurally related fluorinated benzylic alcohols were examined, motivated by the relevance of their corresponding amine structure motifs in pharmaceutical synthesis (Figure 5, structures **1b**-**1d**). These substrates afforded outstanding selectivities of 94% to 97%, underscoring the capability of the system to provide highly selective primary amine formation at drastically reduced reaction time. Compared to benzyl alcohol (**1a**), the conversions remained at a slightly reduced to similar level of 79%, 92%, and 96%, respectively. Notably, reactor clogging was observed for 2,4-difluorobenzyl alcohol **1d** with its higher degree of fluorination. In contrast to the previously observed clogging associated with ruthenium black formation, this blockage originated from precipitation of the Xantphos ligand, as confirmed by NMR analysis (see SI). For continuous production, a solvent change or higher dilution would likely provide a practical solution to prevent precipitation and ensure stable operation.

For non-benzylic substrates, performance varied. With cyclopropylalcohol (**1e**) no product (**2e**) or non-converted substrate were detectable, most likely due to decomposition of the thermally labile cyclopropyl moiety.[37] In contrast, tetrahydropyran-4-methanol (**1f**), featuring a heterocyclic moiety, showed excellent results with 97% conversion and selectivity. Similarly, the alkyl alcohol substrate octanol (**1g**) reached 97% conversion and 92% selectivity. For the synthesis of the industrially relevant 1,6-hexamethylenediamine (**2h**), the selectivity towards the desired diamine was limited to 40%, due to 11% of remaining aminoalcohol intermediate and the formation of 49% of the cyclic, secondary amine azepane. This result is in accordance with the preference for secondary amine formation which can hardly be prevented due to the intramolecular reaction mechanism. In contrast, the most favorable performance within the studied scope was obtained with tyrosol (**1i**), which was converted into the biogenic tyramine (**2i**) with a conversion exceeding 99% and 98% selectivity.

Product isolation for all amines was carried out by crystallization of ammonium carbamate species followed by thermal recovery of the free amine.[38] This methodology was recently developed by our working group as an efficient strategy for primary amine purification and separation from homogeneous catalysts. Without further optimization of the crystallization parameters, isolated yields of 34% to 89% were achieved (product specific data see SI). The product purities were excellent exceeding 99% (except for **1d**, 95%) and catalyst leaching into the primary amine product remained below 1% (except for **2h**, 3.2%).

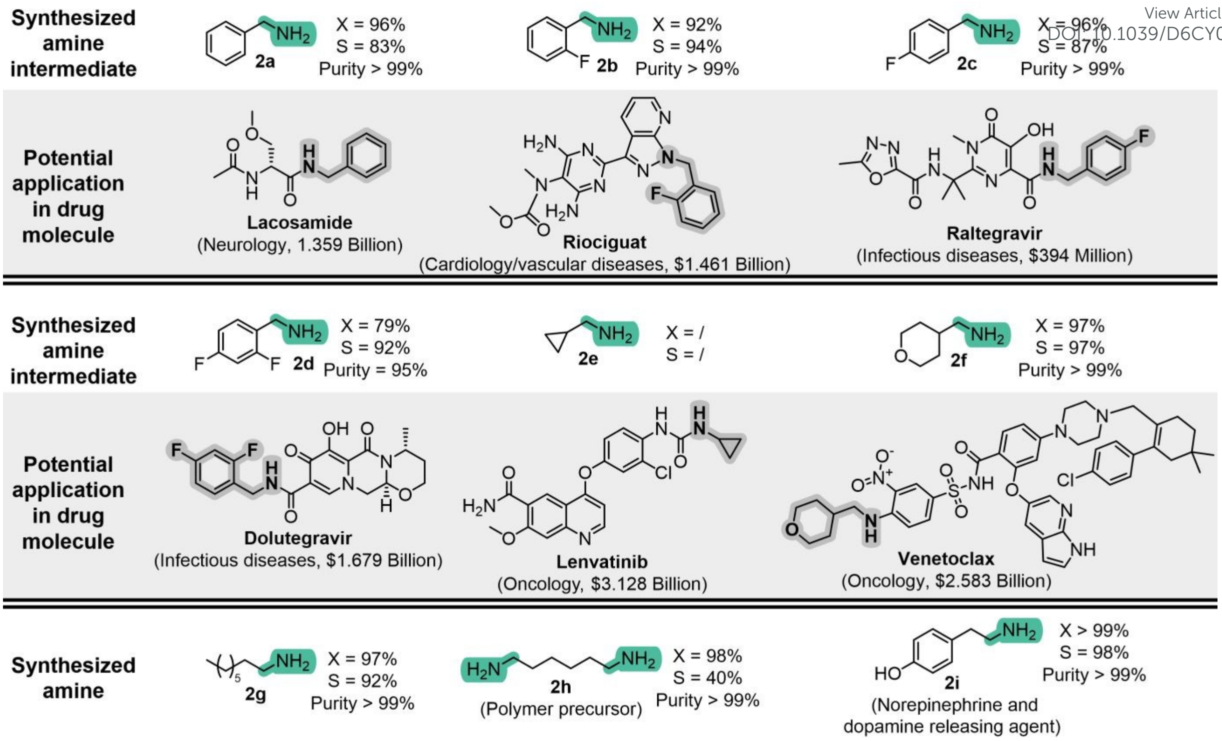

Figure 5: Results of the performed substrate scope, including the chemical structures of commercially available pharmaceuticals. The field of utilization and sales for each drug molecule is indicated in brackets. The figures for Lacosamide are from 2022, all others are from 2024.[39] Reaction conditions: $HRuCl(CO)(PPh_3)_3$ (3.2 mmol·L^{-1}), Xantphos (6.4 mmol·L^{-1}), alcohol (274 mmol·L^{-1}), diol (137 mmol·L^{-1}), Ammonia:Alcohol = 18.3:1 (mmol·mmol^{-1}), solvent = *tert*-amyl alcohol, τ = 23.3 min, T = 280 °C, p = 70 bar. The values for conversion and selectivity are mean values from three samples. The first sample was taken after 3.5·τ, and subsequent samples were taken at 0.5·τ increments. Product purities determined by GC-FID analysis of the isolated product fractions.

Overall, the substrate scope indicated, that thermally labile products and competing side reactions in diamine synthesis conflicted with the employed high reaction temperatures. Despite these predictable constraints, the catalytic protocol proved broadly applicable to various structural motifs, including benzylic, heterocyclic, and alkyl alcohols, highlighting the versatility and potential of the methodology.

Furthermore, comparison of the developed system with reported ruthenium-catalyzed batch processes confirms its high level of performance. Based on the available data for the conversion of benzyl alcohol (**1a**), octanol (**1g**), and 1,6-hexanediol (**1h**) with ammonia, key performance indicators, including conversion, yield, selectivity, and TOF, are comparable to the highest values reported in the literature for both homogeneous and heterogeneous systems (Table 1).

At the same time, operation at elevated temperatures, enabled by the flow setup**,** allows for a substantial reduction in reaction times. In combination with continuous processing, this leads to a significant increase in overall productivity. These findings clearly demonstrate the advantages associated with the transition from batch to flow synthesis and the application of microreactor technology.

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Table 1: Comparison of reaction performance with literature reported ruthenium catalyzed batch processes.

Substrate	Cat.	X [%]	Y [%]	S [%]	t [h]	T [°C]	TOF [h^{-1}]	Source
Benzyl alcohol (**2a**)	Hom.	99	-	93	48	140	-	[11]
		99	87	-	13	110	-	[13]
		99	-	98	5	170	-	[14]
		100	87	-	20	140	-	[16]
		82	-	85	7	150	37.5	[19]
		96	**80**	**83**	**0.4**	**280**	**210**	**This work**
	Het.	-	87	-	2	150	9.0	[40]
		50	49	96	1-24	180	-	[41]
1-Octanol (**2g**)	Hom.	96	-	71	24	140	-	[11]
		99	-	95	12	155	-	[42]
		99	-	>90	4	170	60	[14]
		99	-	96	15	165	-	[17]
		80	-	63	20	130	-	[16]
		97	**89**	**92**	**0.4**	**280**	**214**	**This work**
	Het.	89	80	90	1-24	180	20.9	[41]
		>90	-	92	16	180	100	[43]
		-	78	-	20	110	-	[40]
		96.5	-	96.1	5	180	12.9	[44]
1,6-Hexanediol (**2h**)	Hom.	**98**	**39**	**40**	**0.4**	**280**	**216**	**This work**
	Het.	78.2	-	25.2	5.5	175	-	[45]
		87	-	21	4	190	161	[46]
		100	-	38.4	4.5	220	242	[47]
		72	14	-	2	190	-	[48]
		-	54	-	15	220	-	[49]

TOF was calculated as the overall rate of -OH conversion normalized by the utilized ruthenium amount over the specified time. Cat. = Catalyst, Hom. = Homogeneous, Het. = Heterogeneous.

Long-term performance

To evaluate the practicality and operability of the optimized conditions for continuous operation, the study was concluded with a 30 hours long-term experiment. During the initial 24 h, the established benzyl alcohol (**1a**) model substrate was employed. Subsequently, the feed was switched to tyrosol (**1i**). This procedure was designed to assess not only the

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operational stability of the system but also the feasibility of changing the target amine product on demand without interrupting the continuous production process.

Starting the continuous operation, the reaction exhibited an initial startup phase of approximately 90 min, after which a stable product composition was reached (Figure 6). This behavior is in accordance with our former observation, that approximately 3.5 residence times are required for steady-state conditions. The process achieved an average benzylamine (**2a**) content in the product mixture of 80 ± 3 mol% corresponding to a product yield of 78% ± 2% (8.77 g in 24 h) and a selectivity of 84 ± 2%. These results are identical to those in the previous short-run, thus the applicability of the setup for long-term production was confirmed.

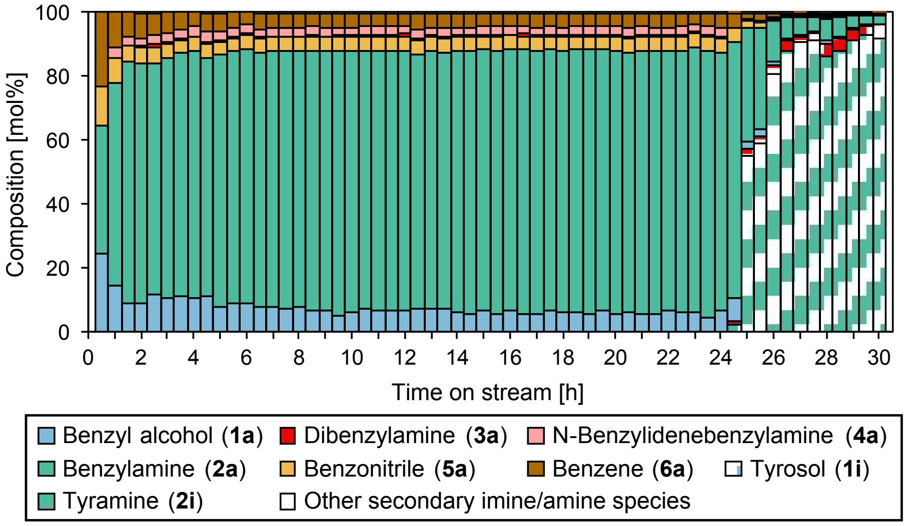

Figure 6: Results of the continuous long-term experiment. Reaction conditions: HRuCl(CO)(PPh$_3$)$_3$ (3.2 mmol·L^{-1}), Xantphos (6.4 mmol·L^{-1}), alcohol (274 mmol·L^{-1}), Ammonia:Alcohol = 18.3:1 (mmol·mmol^{-1}), solvent = *tert*-amyl alcohol, τ = 23.3 min, T = 280 °C, p = 70 bar. After 24 h the substrate alcohol was switched from benzyl alcohol (**1a**) to tyrosol (**1i**). Product distributions determined by GC-FID analysis with dodecane as internal standard.

Furthermore, following the initial phase of the long-term experiment the substrate switch was successfully performed and the benzylamine (**2a**) product fraction was gradually replaced by tyramine (**2i**) in approximately 5 residence times. The reaction achieved even higher reaction performances compared to benzyl alcohol (**1a**) as substrate, with an average tyramine (**2i**) yield and selectivity of 93% ± 2%, respectively. These excellent results underscore the applicability and flexibility of the primary amine synthesis without interruption of the production.

Notably, the remaining benzylamine (**2a**) content of 3 mol% in the product fraction could be attributed to the back-pressure regulator (BPR). Compared to the capillary, the utilized BPR provides a larger inner diameter and volume and potentially presents a buffer tank with alternative flow regimes and dead zones. Focusing on the residence time distribution of the reactor section, the experimentally determined mean residence time of 22.7 min deviated by only 2.6% from the theoretical value of 23.3 min, confirming good agreement (details see SI).

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Furthermore, a Bodenstein number (Bo) of 32 was calculated, which lies between the limits of a stirred tank (Bo ≈ 0) and an ideal plug flow reactor (Bo > 100) and is therefore consistent with the laminar flow regime expected for capillary reactors.

The long-term experiment therefore demonstrated the robustness, efficiency, and flexibility of the developed continuous-flow amination protocol. Stable operation over 24 h was achieved with consistent high yields and selectivities under steady-state conditions, and the successful substrate transition from benzyl alcohol (**1a**) to tyrosol (**1i**) further highlighted the capability to switch primary amine products on demand without interrupting the process. The excellent reaction performances and minimal deviation in residence time, underscore the reliability of the capillary reactor setup.

Catalyst stability and reusability

After demonstrating the operability of the continuous process, we sought to gain insight into catalyst stability and potential reusability to inform future work on catalyst separation and recycling strategies. For this purpose, the ruthenium and phosphorus contents were quantified at six-hour intervals during the long-term experiment. Both elements exhibited stable concentrations throughout the run, corresponding to 97% of the initially applied phosphorus and 67% of the initial ruthenium content (SI).

The observed metal loss is probably not attributable to ruthenium black formation, as neither reactor clogging nor visible black particles were detected. Instead, all samples and product fractions displayed a homogeneous light-yellow color. A plausible explanation is therefore an unobserved deposition of ruthenium within the system. Notably, regular testing for catalytic blind activity remained constantly below 1% and therefore negative (SI).

To evaluate whether complete deactivation had occurred during continuous operation, a portion of the ruthenium-containing product fraction collected between 16.5 and 24 hours was reloaded with fresh substrate and subjected to an additional reaction. Surprisingly, the catalyst solution still showed good performance, achieving a conversion of 77%. The decline compared to the initial reaction is consistent with the reduced metal content and higher dilution resulting from the absence of product removal. Additionally, the selectivity decreased to 75%, which is probably caused by the increased benzylamine (**2a**) concentration in solution, favoring consecutive reactions in line with the borrowing-hydrogen mechanism (comparison of product distributions see SI).

Overall, these results demonstrate that a significant content of the ruthenium species remains catalytically active even under the harsh reaction conditions of 280 °C, which is remarkable for a homogeneous transition-metal catalyst. Preventing metal loss and developing an efficient

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catalyst separation and recycling strategy, therefore, constitute key objectives of ongoing research.

Conclusion

The synthetic performance of the intrinsically inefficient alcohol amination with ammonia for the synthesis of primary amines was drastically increased through the successful transfer into a continuous capillary flow system. Compared to batch operation commonly applied, we increased the performance with a Design of Experiment optimization by a factor of 15 represeted by the STY and TOF of 59 $\text{mg}\cdot\text{mL}^{-1}\cdot\text{h}^{-1}$ and 210 h^{-1}, respectively. Focused on pharmaceutical interesting motifs, the method exhibited broad applicability, converting benzylic, heterocyclic, and aliphatic alcohols in eight examples, with up to 99% conversion and 98% selectivity. Furthermore, long-term operation over 30 h including an integrated substrate switch during continuous production after 24 h confirmed successful the robustness and operational flexibility of the system. Under steady-state conditions benzyl alcohol (**1a**) was converted into benzylamine (**2a**) with 78% ± 2% yield and a selectivity of 84 ± 2%, while the transformation of tyrosol (**1i**) achieved an average tyramine (**2i**) yield and selectivity of 93% ± 2%, respectively. Furthermore, catalyst reuse experimentally verified the persistent activity of the Ru/Xantphos system in solution with 77% conversion and 75% selectivity, which is noteworthy for a homogeneous catalyst under the applied high temperature conditions of 280 °C. Overall, these results establish a practical and efficient continuous protocol for primary amine synthesis and provide a basis for future studies directed toward catalyst recovery and sustainable continuous manufacturing of high value amine intermediates.

Supporting Information

Detailed information is given on the chemicals used, analysis and experimental procedures. Further experimental results are also given.

Conflict of interest statement

The authors declare no conflict of interest.

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In preparing this manuscript, the authors utilized ChatGPT to enhance translation and readability. The authors have reviewed and revised all content to ensure its accuracy and completeness and take full responsibility for the content of the publication.

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Data Availability Statement

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The data supporting this article have been included as part of the Supplementary Information or are available from the corresponding author upon reasonable request.