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# Homogeneous Catalysis at its Edge: High-Temperature Ru-Catalysed Amination of Alcohols under Continuous Flow Conditions

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Combining a tubular flow reactor with a robust homogeneous catalyst enabled running the alcohol amination at unique conditions, i.e., very high temperatures at low residence times. Catalytic activities were thus increased to unprecedented values

of  $>900\text{ h}^{-1}$  in the synthesis of tertiary dimethylalkylamines directly from alcohols with excellent selectivities exceeding 99%. Furthermore, several alcohols could be converted to the desired tertiary amines.

Homogeneous catalysts are often associated with decisive advantages, like high activity and selectivity at already mild reaction conditions.<sup>[1]</sup> However, the selectivity of a chemical reaction is not trivial since it has to be distinguished between chemo-, stereo- and regioselectivity. An example of a homogeneously catalyzed reaction is alcohol amination, using the so-called borrowing hydrogen approach (Figure 1).<sup>[2,3]</sup> This reaction is typically characterized by very high chemo-selectivity because side reactions are suppressed since only catalytic concentrations of reactive intermediates are present in the reaction mixture, namely the carbonyl compound, in situ formed from alcohol dehydrogenation (I), and the enamine, formed by the condensation reaction between the carbonyl compound and the respective amine (II).<sup>[4]</sup> Furthermore, the synthesis of, for example, tertiary amines shows the highest selectivities because tertiary amines cannot react further. Moreover, this high activity in synthesizing tertiary *N,N*-dimethyl alkylamines is unique since the heterogeneously catalyzed alcohol amination does not exhibit such high selectivities. In such processes, various side reactions, such as the deaminative coupling of dimethylamine to methylamine and trimethylamine, are catalyzed. Consequently, other methyl dialkyl amines are obtained in further reaction steps.

Hence, the synthesis of *N,N*-dimethyl dodecylamine (DDA), an important tertiary fatty amine for the synthesis of several quaternary cationic surfactants, is industrially produced via

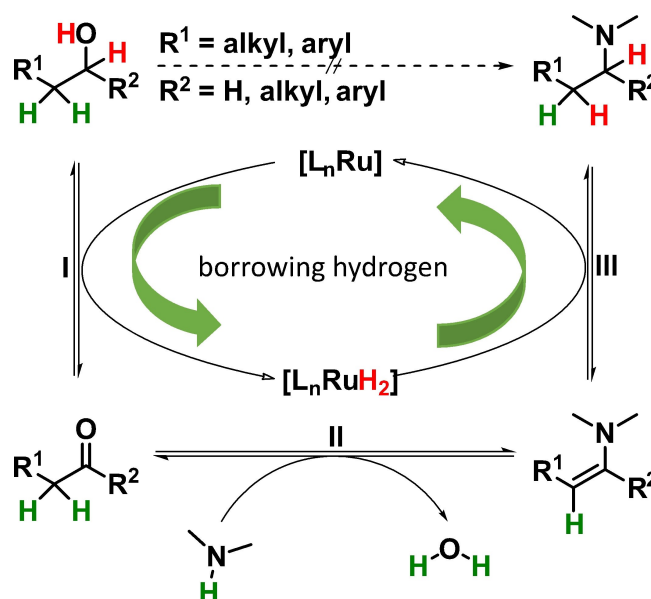


Figure 1. Borrowing hydrogen mechanism for the amination of alcohols with dimethylamine affording dimethylalkylamines.

alternative routes, namely from activated substrates (halides), by reductive amination of the primary dodecylamine with formaldehyde/formic acid or by hydrogenation of the corresponding amides.<sup>[5]</sup> However, when primary amines or even ammonia is used in this type of reaction, a complex network of products is possible due to consecutive reactions and the (chemo)selective synthesis of the desired amines becomes challenging. Besides this, there are also some intrinsic drawbacks using the borrowing hydrogen mechanism: Because the catalyst is needed for both the dehydrogenation of the alcohol (I) and the hydrogenation of the enamine (III), high catalyst loadings are often needed to shorten reaction times to the detriment of catalytic productivity (low turnover numbers, TON). Our research group recently tackled this hurdle by designing an integrated recycling strategy for the homogenous catalyst, resulting in a total turnover number of  $>2300$ .<sup>[2]</sup> However, besides productivity, the catalytic activity is also

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inferior for this kind of reaction (low turnover frequencies, TOF). It typically ranges between 1–100 h<sup>-1</sup>,<sup>[6]</sup> which is relatively low compared to other homogeneously catalyzed reactions.

Considering these points, some basic requirements can be deduced for developing an efficient homogeneously catalyzed alcohol amination by exploiting the full potential of this flexible synthesis towards various amines.

- Increasing the catalytic activity (TOF)
- High (chemo)selectivities at high conversions
- Safe, practical realization

Principally, increasing the temperature is one means of achieving higher activities; however, alcohol amination is already typically carried out at 140–180 °C, which is in the higher temperature range for homogeneously catalyzed reactions. Although chemoselectivity does not limit increased temperatures, at least for the synthesis of tertiary amines, the typically used laboratory equipment (stirred tank autoclaves in batch mode) is. For instance, rupture discs are designed for high pressures, however only at ambient temperatures.

If the reaction temperature is increased to achieve higher catalyst activities in batch operation with a defined reaction start by adding the substrate, this is inevitably associated with an extension of the heating or cooling phase. During this time, the activated catalyst is not in function, but is still exposed to considerable temperature stress (exemplary temperature protocol of alcohol amination in batch at high reaction temperature in the SI).

Furthermore, common organic solvents have high vapor pressures at high temperatures, so the addition of inert gas is needed to keep the reactants and the solvent in the liquid phase. If these disadvantages are summarized, the following requirements result:

- Efficient temperature control, including heating and cooling
- Precise control of the reaction time
- Safe, practical work at high pressures and temperatures

We believe these issues can be solved by combining homogeneous catalysis and reaction engineering, which is why a reactor other than the typical batch reactor was envisaged.

A tubular flow reactor is favored for elevated temperatures due to high surface-to-volume ratios, so efficient heating and cooling are possible, and the catalyst is not stressed at high temperatures for a long time. Furthermore, high pressures permit high temperatures even with low boiling solvents.<sup>[7]</sup> The closed reaction setup makes working with gaseous components in a tubular flow reactor even safer. Ley et al. recently gave an example of the amination of alcohols under continuous flow conditions.<sup>[8]</sup> Dimethylalkylamines were produced with yields up to 93% at high temperatures of 250 °C at a residence time of 15 min resulting in a maximum TOF of 111 h<sup>-1</sup>. Still, high catalyst loadings of 3 mol% ruthenium were used. To the best of our knowledge, this is the highest temperature ever reported for homogeneous transition metal-based catalysts combined with phosphorus ligands. The catalytic productivity was increased slightly, but even under batch conditions, higher TOFs were reported before with lower catalyst loadings. So after all, increasing the catalytic productivity by increasing the temperature still needs to be addressed.

We chose the synthesis of *N,N*-dimethyloctylamine (**2a**) directly from 1-octanol (**1a**) and dimethylamine as the model reaction. Dimethylamine was applied as its CO<sub>2</sub> adduct *N,N*-dimethylammonium *N,N*-dimethylcarbamate (DimCarb, Figure 2), which can be easily and safely handled as a liquid. [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> and Xantphos were chosen as reliable, robust and readily available catalytic system for such amination reactions.<sup>[2,9]</sup>

Tubular flow reactors are commercially available but can also be easily set up in a “do-it-yourself (DIY) approach”. Especially on a simple lab scale, only a pump, an oven, and a backpressure regulator are needed. We used two syringe pumps, a GC-oven, and a back pressure regulator from an HPLC (for pictures of the equipment and the DIY flow setup, see SI).<sup>[10]</sup>

The residence time distribution of the DIY-build reactor (Figure 3) was determined using the step signal method (graph in SI). Its narrow characteristic is essential in alcohol amination: The homogeneous Ru-catalyst must react twice and should therefore flow uniformly through the reactor together with the reactants in an ideal flow with limited back-mixing. Furthermore, possible undesirable consecutive and side reactions can be efficiently suppressed.

The first reaction was performed using conditions from batch reactions at a residence time of 10 minutes and an internal pressure of 70 bar. The conversion *X* of **1a** was 56% at 170 °C and 85% at 200 °C, respectively, corresponding to a TOF (determined after the residence time for all following reactions) of 168 and 254 h<sup>-1</sup>. As expected, an excellent chemoselectivity *S* of 99% was maintained, and no by-products were formed (*X* and *S* were determined by GC-FID with *n*-dodecane as internal standard).

To explore the limits of this catalytic system, we successively increased the reaction temperature. From gas chromatographic measurements, we knew that Xantphos degrades at a temperature of about 320 °C. Indeed, performing a reaction at 320 °C ended in clogging of the reactor and without conversion of **1a**

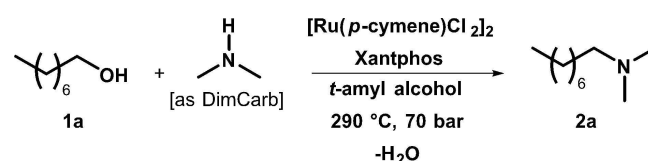


Figure 2. Homogeneous, Ru-catalysed amination of 1-octanol with DimCarb as dimethylamine source.

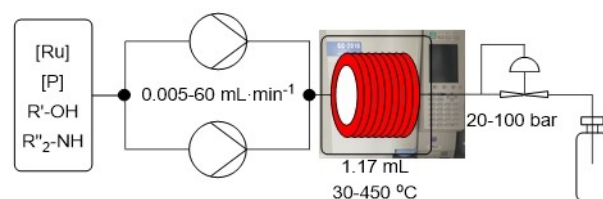


Figure 3. Simplified set-up of the self-built tubular reactor from a syringe pump, a GC-oven, and a backpressure regulator.

(pressure profile in the SI). Next, the reaction temperature was set to 290 °C at a residence time of 7.5 minutes. Under these conditions, a conversion of 96 % was obtained with a selectivity of >99%. The TOF increased to 384 h<sup>-1</sup>. We excluded the ligand in a blank experiment to immediately rule out the possibility of ligand degradation, where 'naked' Ru species might be responsible for catalysis. Under these conditions, a yield of only 15 % was obtained, indicating that the ligand is crucial for the active species. 31P-NMRs were measured after the catalyst was treated at 290 °C for 15 minutes (no substrate, for NMR, see SI). No free Xantphos was detected, but two signals appeared: One at 25.7 ppm, which is like other active Ru-phosphine complexes,<sup>[11]</sup> the other signal at -22.1 ppm can be attributed to a fragment of Xantphos, as an excess of Xantphos is used.

As additional evidence for the catalytic activity, the catalyst was reused after a reaction at 290 °C (*X* > 99%). To do so, fresh 1-octanol (**1 a**) and DimCarb were added to the reaction mixture and re-inserted into the tubular reactor. Again, 95 % conversion and excellent chemoselectivity were obtained even at the higher dilution caused by the product. This reuse of the catalyst shows that it remains active, so studies for an effective recycling of the active catalyst are part of current research. Due to this increased activity, we systematically decreased the amount of ruthenium from 2 to 0.125 mol% (Table 1).

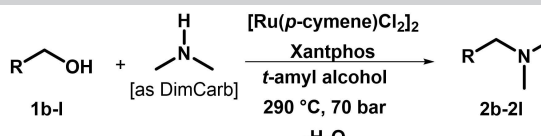
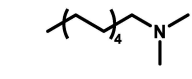

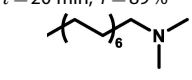
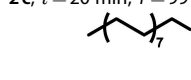
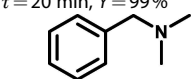
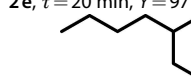
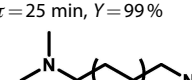
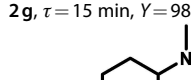
At 0.5 mol% Ru, 1-octanol **1 a** is fully converted after only 15 minutes, corresponding to a TOF of > 750 h<sup>-1</sup>. A maximum TOF of > 900 h<sup>-1</sup> was observed at limited conversion. To the best of our knowledge, this represents the highest TOF ever reported for a homogeneously catalyzed alcohol amination. The inherent activity of the catalyst is probably much higher as it should be determined at conversions where the reaction still follows a pseudo first order regime (e.g., 20%, TOF<sub>20</sub>) and not at complete conversion.

Next, we explored, whether also other alcohols (**1 b–1 i**) can be converted with dimethylamine under those conditions and still obtain high activity and selectivity (Table 2). Several

Ru [mol %]	$\tau$ [min]	<i>X</i> [%]	TOF [h <sup>-1</sup> ]
2	7.5	96	384
1	10	96	576
	15	97	388
	20	98	294
0.5	10	76	912
	15	97	776
	20	97	582
0.25	20	11	132
	25	89	854
0.125	20	14	336
	30	28	448
	45	29	309
	60	40	320

Conditions: 1-octanol (**1 a**, 7.68 mmol, 1.0 eq), DimCarb (5.76 mmol, 0.75 eq), [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (0.0625–1 mol%), Xantphos (0.25–1 mol%), [Ru]:Xantphos = 1:2, *T* = 290 °C, *p* = 70 bar und  $\tau$  = 7.5–60 minutes. Conversion (*X*) and selectivity (*S*) determined via GC-FID with *n*-dodecane as internal standard. Selectivity (*S*) for all reactions > 99%.

**Table 2.** Results from the substrate screening in the continuous amination of several alcohols with dimethylamine.

$\text{R-OH} + \text{N(CH}_3)_3 \xrightarrow[\text{-H}_2\text{O}]{\text{[Ru}(p\text{-cymene)Cl}_2)_2, \text{Xantphos, } t\text{-amyl alcohol, 290 }^\circ\text{C, 70 bar}} \text{R-N(CH}_3)_2$	
	
 <b>2 b</b> , $\tau$ = 20 min, <i>Y</i> = 89 %	 <b>2 c</b> , $\tau$ = 20 min, <i>Y</i> = 99 %
 <b>2 d</b> , $\tau$ = 20 min, <i>Y</i> = 99 %	 <b>2 e</b> , $\tau$ = 20 min, <i>Y</i> = 97 %
 <b>2 f</b> , $\tau$ = 25 min, <i>Y</i> = 99 %	 <b>2 g</b> , $\tau$ = 15 min, <i>Y</i> = 98 %
 <b>2 h</b> , $\tau$ = 30 min, <i>Y</i> = 99 %	 <b>2 i</b> , $\tau$ = 15 min, <i>Y</i> = 50 %

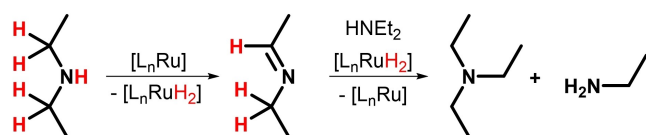
Conditions: alcohol **1 a–1 i** (7.68 mmol, 1.0 eq), DimCarb (5.76 mmol, 0.75 eq), [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (0.25 mol%), Xantphos (1 mol%), [Ru]:Xantphos = 1:2, *T* = 290 °C, *p* = 70 bar und  $\tau$  = 15–30 minutes. Conversion (*X*) and selectivity (*S*) determined via GC-FID with *n*-dodecane as internal standard. Selectivity (*S*) for all reactions > 99%.

aliphatic, cyclic, as well as primary and secondary alcohols were tested.

For all fatty alcohols (**1 b–1 e**), excellent conversions were reached at only 20 minutes residence time. 2-Ethyl-1-hexanol (**1 g**) was fully converted after only 15 minutes. The other primary alcohols, dodecane diol (**1 h**) and benzyl alcohol (**1 f**), needed 30 and 25 minutes, respectively, for excellent conversion exceeding 90%. As expected, the conversion of the cyclic, secondary alcohols cyclohexanol (**1 j**) was 50% after 15 minutes. The lower conversion is caused by the generally lower reactivity of cyclic, secondary alcohols compared to aliphatic, primary ones.<sup>[5,12]</sup>

To demonstrate the substrate scope, also other amines were applied. However, applying higher dialkylamines than dimethylamine in the Ru-catalysed alcohol amination is not trivial and has thus never been reported. Both catalytic activity and selectivity are limited: In a batch experiment of 1-octanol (**1 a**) with diethylamine using our recently published conditions, only 80% conversion at 170 °C was achieved after more than 24 hours (8 times longer compared to dimethylamine in batch). Moreover, diethylamine can also react via the borrowing hydrogen mechanism (Figure 1) intermolecularly in a so-called deaminative coupling (Figure 4), resulting in selectivity issues. With dimethylamine, this side reaction is not limiting selectivity since the  $\alpha$ -protons cannot be abstracted, generally leading to the highest activity and selectivity in the alcohol amination with this particular amine.

To demonstrate the benefits of the tubular flow reactor compared to batch conditions, the more challenging reaction



**Figure 4.** Deaminative coupling of 2 mols diethylamine to triethylamine and ethylamine.

of **1a** with diethylamine was carried out at  $T=290^{\circ}\text{C}$ , leading to a conversion of 77% at a residence time of only  $\tau=35$  min. The overall TOF could be increased to  $528\text{ h}^{-1}$ , corresponding to a factor of 40 compared to batch. Furthermore, based on this success, in combination with the recently published results from the alcohol amination with ammonia,<sup>[12]</sup> the first homogeneously catalyzed syntheses of primary amines under flow conditions were carried out. Also, the catalytic activity can be significantly increased, and reaction times of less than 30 minutes can be achieved. Detailed investigations are part of our current research.

In conclusion, we presented the synthesis of tertiary amines under continuous flow conditions, achieving high catalyst productivity and high selectivity by combining homogeneous catalysis with reaction engineering. We increased the TOF of the Ru-catalysed alcohol amination to  $>900\text{ h}^{-1}$ , representing the highest ever reported activity in this reaction. Such high activities were achieved by pushing the boundaries of homogeneous catalysis: In a simple home-made continuous tubular flow reactor, the reaction temperature was increased to unprecedented values of  $290^{\circ}\text{C}$  at very short residence times. The Ru/Xantphos catalyst maintained activity, proving its robustness under these unique conditions, so far not accessible under typical batch conditions. Furthermore, several fatty and other primary alcohols could be converted to the desired tertiary amines with residence times less than 30 minutes, with excellent yields exceeding 90%. Aliphatic secondary alcohols and cyclic secondary alcohols could be converted with yields up to 98%. Finally, also more challenging amine substrates like diethylamine and ammonia were shown to greatly benefit from our new approach in alcohol amination reactions. The reaction time has already been reduced by a factor of 40. Currently, in-depth investigation of amination reactions with ammonia and more complex reaction systems are ongoing.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords:** Homogeneous Catalysis · Flow Chemistry · Amine Synthesis

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