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Complete List of Authors:	Leung, Andrew; Imperial College London, Chemical Engineering Hellgardt, Klaus; Imperial College London, Chemical Engineering Hii, King Kuok; Imperial College London, Chemistry

Catalysis in flow: Nickel-catalyzed synthesis of primary amines from alcohols and NH_3

Andrew Yuk Keung Leung[a], Klaus Hellgardt[a,*] and King Kuok (Mimi) Hii[b,*]

[a]Department of Chemical Engineering; and [b]Department of Chemistry

Imperial College London, Exhibition Road, South Kensington, London SW7 2AZ, U.K.

Email: k.hellgardt@imperial.ac.uk; mimi.hii@imperial.ac.uk

Abstract

A highly selective synthesis of primary amines from alcohols and NH_3 was achieved on using a commercially available Ni catalyst, without adding H_2. Using a continuous flow reaction platform, the amination of aliphatic alcohols can be achieved in good yields and selectivities, as the accumulation of water by-product can be removed. Competitive formation of the nitrile side-product was suppressed when the catalyst is pre-reduced. Modes of catalyst deactivation was also briefly examined.

Keywords

Atom-efficient

Continuous flow process

Hydrogen borrowing

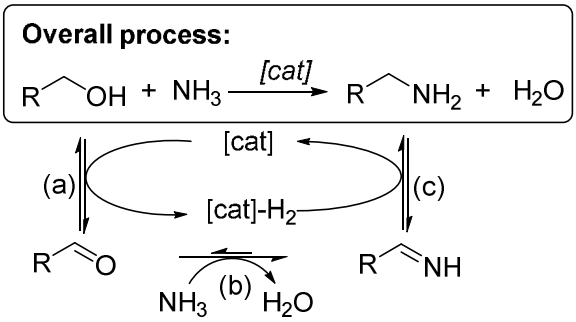
Nickel

Selective

Primary amines

Introduction

Primary amine precursors have a wide range of applications in the chemical and pharmaceutical industries. Higher aliphatic primary amines (containing ≥6 carbon atoms) are a particularly valuable class of compounds with many applications, including the production of personal products, polymers (Nylon), agrochemicals and active pharmaceutical ingredients.[1-2] In principle, primary amines can be prepared from their corresponding alcohols by catalytic alkylation of ammonia *via* a process known as 'hydrogen-borrowing' or 'hydrogen autotransfer'.[3] The reaction involves three key steps (Scheme 1): (a) Dehydrogenation of the alcohol to the aldehyde; (b) condensation with ammonia to the imine; which is then (c) reduced to the amine.



Scheme 1: 'Hydrogen borrowing' cycle: *N*-alkylation of ammonia with an alcohol to form a primary amine.

The overall reaction has excellent environmental credentials as it generates only water as a by-product. The commercial value of the process is further enhanced by the easy availability of alcohol feedstocks, either from natural or petrochemical sources. However, as the amine product is more nucleophilic than NH_3, it could potentially react further with the starting alcohol to produce secondary and tertiary amines as side products.[4] Currently, the hydrogen-borrowing

method is employed industrially to produce volatile amines containing ≤3 carbon atoms (in the gas phase), as the mixture of amine products can be easily separated by distillation. However, the separation of higher molecular weight/involatile amines is much more challenging. As a result, the reaction is rarely used for producing higher-value amines.[2]

As the reaction involves two redox steps (Scheme 1, steps a and c), catalysts known to facilitate dehydrogenation and hydrogenation processes are generally found to be effective for this reaction.[5-6] Homogeneous catalysts include Ir[7-9] and Ru[10] complexes, which can deliver high selectivity for the primary amine products with good tolerance towards the water by-product. However, implementation of such catalysts on an industrial scale can be costly, due to the need to employ ligands or excess base, and the removal (and recovery) of the metal residue from the reaction mixture. For these reasons, heterogeneous catalysts would be more favorable. Previously, supported copper[11] and ruthenium[12] hydroxide catalysts have been reported for the *N*-alkylation of NH_3 by alcohols, displaying selectivity for the higher amines. In comparison, a number of heterogeneous Ni catalysts have been reported to show good selectivity for primary amines.[13-16] In all cases, the reactions were performed in batch reactors.

The aim of our 'Catalysis in Flow' program is to devise practical and scalable solutions to organic synthesis, through the implementation of (multiphasic) catalytic processes in continuous flow. Previously, we have successfully demonstrated that the selective alkylation of primary and secondary amines by alcohols can be performed successfully over a Au/TiO_2 catalyst under continuous flow using liquid feedstocks.[17] In this work, we will extend this approach to the synthesis of primary amines, using ammonia gas as a feedstock and a commercially available Ni catalyst. The performance of the catalyst will be compared using batch and flow reactors. To our

knowledge, this is the first example where the synthesis of primary amines by ammonia monoalkylation with alcohols has been implemented in the liquid phase using a flow reactor.

Experimental

Material

All catalysts and reagents were purchased from commercial supplier (see SI) and were used as received without further purification, unless specified otherwise Solutions were prepared in *o*-xylene and sonicated in a water bath (25 °C) for 2 hours prior to use. Gases (N_2, NH_3, Ar) were purchased (BOC), while H_2 was supplied by a generator (Precision Hydrogen 200).

Methods

Catalyst extrusion preparation:[18] Aqueous acetic acid (3 wt%, 6.0 mL) was added slowly to a stirred mixture of 65wt% $Ni/Al_2O_3/SiO_2$ (2.4 g), bentonite (1.6 g) and methyl cellulose (0.2 g) to form a paste, which was extruded through a 20 mL syringe onto a clean polythene sheet. The extrusions were dried in air at room temperature for 12 hours, before broken into 1 mm fragments, and dried in an oven at 120 °C for 2 hours. The extrusions were found to contain 36%wt. Ni (ICP analysis).

Batch reactions were performed in a 30 mL Teflon-lined SS autoclave reactor, with a sampling port fitted with a filter (25 μm pore size). At the beginning of an experiment, the reactor was charged with the catalyst extradite (100 mg, 36% wt Ni), magnetic stirrer bar, and a benzyl alcohol solution (0.2 M in *o*-xylene, 30 mL, 6.0 mmol). For reactions using aqueous ammonia, 28 wt% NH_3 solution (2.0 g) was also added. Otherwise, the reactor was then sealed and purged with N_2 (3x), followed by NH_3 (3x).

Anhydrous NH_3 was introduced using a condenser tube: This comprises of a SS-316 tubing (¼" O.D., 10 cm) attached to a valve connected to a cylinder of NH_3. The condenser tube was cooled under acetone/ice bath (–10 °C) for 20 minutes, and the amount of condensed NH_3 was determined by the weight difference (0.70 g, 41 mmol). The gas was then introduced into the batch reactor via a charging port, with the aid of a heat gun (150 °C). The condenser tube was then removed and the reactor sealed and heated. Stirring was initiated (1500 rpm) when the solution reached the desired reaction temperature (160 °C) and pressure (12 bar).

Catalyst recovery and reuse (Table 2, Entries 4 & 5): After reactions, the catalyst was recovered by filtration, washed with acetone and dried *in vacuo* for 20 minutes before reuse.

Control reactions were performed to test if leached Ni species could have contributed to the reaction: The procedure described above was repeated without introducing benzyl alcohol to the solution: The mixture of catalyst, xylene and NH_3 was heated at 160 °C for 72 h, cooled and the solution was filtered to remove the solid catalyst. Benzyl alcohol (6.0 mmol) was then added to the filtrate and the solution was heated under and NH_3 at 160 °C for 72 h. No conversion was observed.

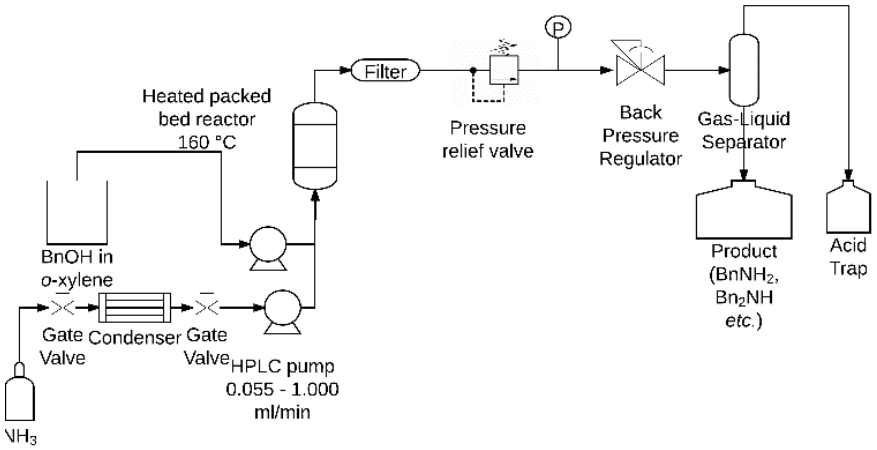


Fig. 1: Schematics of the flow reactor.

Flow reactions were performed using a customized flow reactor system (Fig. 1). Benzyl alcohol solutions (0.10–0.60 M) were prepared. Ammonia was pre-condensed in a condenser (20 mL) at 77 K for 20 minutes, and allowed to warm up for 2 h to room temperature prior to reaction. Two Gilson 305 HPLC pumps were used to deliver the solution of alcohol and liq. NH_3, respectively, with the pressure controlled by a back-pressure regulator (Swagelok K-series). A gas-liquid separator was used to remove NH_3 from the liquid phase at ambient pressure. The exhaust gas was treated by an acid scrubber (0.1 M HCl solution, 1 L) before venting into the gas exhaust, while the liquid eluent was collected in a flask.

The total internal volume of the system was 21 mL. See Supporting Information for details on the reactor set up, and residence time calculations.

In a typical experiment, o-xylene was introduced into the reactor at 160 °C under pressure (60 bar) at 0.5 mL/min for 80 min. Then, BnOH solution and NH_3 were passed at a combined flow of 0.1 mL/min for 5 min. The system was allowed to stabilize, before adjusting the flow rates to that required for the experiment. (*e.g.* 0.009 mL/min NH_3 & 0.491 mL/min 0.1 M BnOH solution, to afford a combined flow rate of 0.5 mL/min with NH_3/BnOH = 7). Analytical samples were collected either after 60 mL of solution had passed through the reactor, or at steady state, as confirmed by 3 consecutive unchanged samples. Subsequent samples were collected every 30 min.

Flow reactions: Pre-reduction procedure. 2.0 g of catalyst extrudates were loaded into a clean reactor SS-316 tube (length = 280 mm, I.D. = 4.6 mm), supported by glass wool plugs. The tube was vertically mounted in a heating block, and heated at 500 °C under a flow of 10% H_2/Ar (40 mL/min) for 2 h. The reactor was cooled to room temperature under flowing N_2 (20 mL/min) before reconfiguring to allow liquid flow.

Analysis: Alcohol conversions and amine selectivities were determined using a GC system fitted with a HP-5 column (25 m x 0.53 mm, 5.00 μm) and a flame ionization detector (FID). Calibration plots for products and reactants were constructed using 4-*tert*-butylphenol as an internal standard. Product mixtures were further analyzed/identified by a GC system fitted with a mass spectrometer detector (GC-MS).

Phase simulation: Aspen plus V8.4 was used for calculations of the NH_3/*o*-xylene phase diagram. The SR-Polar method was selected for the calculation of dew points and bubble points for 0 – 1.0 mole fractions ammonia. Conditions were set at 60 bar, variables were temperature and mole fraction of NH_3.

Results and Discussion

Preliminary results with Ni and Au in a batch reactor

1 wt% Au/TiO_2 and 65 wt% Ni-Al_2O_3/SiO_2 were initially selected for this study based on previous work and a screening of selected catalysts (Table S1, Supporting information): Very small Au nanoparticles on TiO_2 (Au/TiO_2-VS) had been employed by Cao *et al* to catalyze the alkylation of amines[19] and urea[20] with alcohols in batch reactors. Subsequently, we showed that very high selectivity can also be achieved using commercially-available Au-TiO_2, by utilizing the wider reaction space afforded by the continuous flow platform.[17] The application of a reduced form of Ni/θ-Al_2O_3 for the hydrogen-borrowing reaction was first reported in 2013 by Shimizu and co-workers, subsequently adopted for the alkylation of NH_3.[15] The same group had also reported the catalytic activity of reduced $CaSiO_3$-supported Ni metal nanoparticles.[16] The study concluded that there is strong metal-support interaction (SMSI) in these catalytic systems. Crucially, while both acidic and basic sites are essential for catalytic activity, they are also susceptible to poisoning by acidic and basic moieties present in the alcohol substrates, which

limits the reaction scope.[15] In this work, we have chosen Ni-Al_2O_3/SiO_2 as a catalyst for the following reasons:

1. It is commercially available, thus widely available to the synthetic chemistry community;
2. Silica-alumina contains both acidic and basic sites, which has been shown to be beneficial for catalytic activity;
3. Similar catalysts have been used in the hydrotreatment of heavy oils,[21] leading us to postulate that it may be more resistant to catalyst poisoning; potentially widening the scope of the reaction; and
4. The high loading of Ni (65 wt%) is an attractive feature for its implementation in flow (short residence times).

Table 1. Preliminary batch reactions using Ni and Au catalysts.[a]

Catalyst	**Time (h)**	**Conv./%[d]**	**$BnNH_2$: Bn_2NH : Bu_3N**
65wt% Ni-Al_2O_3/SiO_2[b]	5	44	85:15:0
	24	56	76:24:0
1wt% Au-TiO_2[c]	5	48	0:60:40
	24	78	0:55:45

[a]Conditions: BnOH in o-xylene (0.6 M), 160 °C, 1500 rpm, BnOH/NH_3/H_2O = 1/1/5. [b]BnOH/Ni = 20, [c]BnOH/Au = 100. [d]Consumption of BnOH.

Initially, the experiments were performed in a batch reactor using 28% aq. NH_3 solution: An equimolar mixture of benzyl alcohol (BnOH) and ammonia was subjected to heating at 160 °C in the presence of the Ni or Au catalyst, deployed at 5 and 1 mol% loadings, affording 44 and 48% conversions of the alcohol to amine products, respectively, in 5 h (Table 1). Under these

conditions, the performance of the Ni catalyst was broadly similar to that observed previously using the $CaSiO_3$-supported Ni catalyst, [16, 22] *i.e.* the product mixture contained primary amine as the major product (85%), accompanied by the secondary amine (15%). In contrast, the Au catalyst was more selective towards higher amines, producing a mixture of secondary and tertiary amines in a 3:2 ratio. Notably, the formation of oxidized intermediates (imine and benzaldehyde) was not detected in either of these systems, implying that the reduction (step c, Scheme 1) is reasonably facile under these conditions.

Prolonging the reaction from 5 to 24 hours, however, did not lead to complete consumption of the alcohol. This was attributed to the presence of excess water in the system, which disfavored the thermodynamic equilibrium towards amine formation. Thus, it was decided to replace the aqueous ammonia solution by the anhydrous gaseous reagent.

Improved batch reactor system with ammonia gas

Gaseous ammonia is a toxic, non-ideal gas. As a result, it is rarely deployed in the synthesis lab due to the difficulty in its containment, and control of reaction stoichiometry. In this project, a condenser tube was devised whereby NH_3 can be delivered in weighed amounts into the batch reactor (Experimental Section). To further improve the selectivity for the primary amine product, the concentration of BnOH was reduced to 0.10 M and the ratio of NH_3/BnOH was increased to 7:1, and the reaction was performed at 160 °C under a pressure of 12 bar. Under these conditions, the benzyl amine can be obtained in 92% yield after 12 h, matching that previously recorded by Shimizu *et al*.,[16] *i.e.* the removal of water from the system does have a beneficial effect, both on the yield and selectivity of the process.

The scope of the reaction was subsequently tested with different alcohol substrates (Fig. 2), including substituted benzyl alcohols, 2- & 3- picolyl alcohols, and aliphatic alcohols, represented by 2-octanol and 2-phenylethanol. The reaction with the model substrate (benzyl alcohol substrate) afforded benzylamine in consistently high yield and selectivity, which were maintained with recovered catalysts. The introduction of an electron-releasing methoxy substituent either at the *ortho*- or *para*- positions lowers the reaction yield; nevertheless, the selectivity for the primary benzyl amine remained high (at 99%). The picolyl alcohols contain a Lewis basic pyridyl nitrogen, which is a good probe for the catalyst stability. In these cases, a moderate yield of 3-picolylamine can be obtained with an excellent selectivity (96%). In contrast, 2-picolylamine was obtained in much lower yield (albeit with high selectivity), which is ascribed to the ability of the product to chelate to Ni, causing catalyst deactivation and leaching – evident from the green coloration of the supernatant solution, which was subsequently found to contain 20 ppm of Ni (ICP analysis).

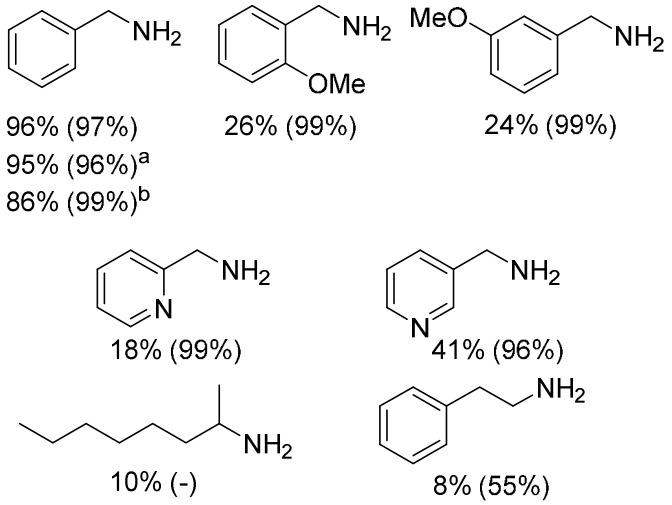


Fig. 2 Ni-catalyzed alkylation of NH_3 by alcohols to primary amines using a batch reactor. Reaction conditions: Alcohol (0.1 M) in o-xylene (30 mL), extruded 36wt% Ni-Al_2O_3/SiO_2, ROH/Ni = 10, NH_3/ROH = 7, 160 °C, 1000 rpm, 72h. 160 °C 12 bar [a]Recycled catalyst (run 1).

[b]Recycled catalyst (run 2). Percentages shown are conversions; selectivities to primary amines are indicated in parenthesis.

Conversions of the aliphatic alcohols in the reaction were even worse in the batch reactor: they proceeded at 10% and 8% conversion for 2-octanol and 2-phenylethanol, respectively. This is particularly interesting, as the reaction with these substrates were previously reported to be much faster than the benzyl alcohols using Ni/θ-Al_2O_3 catalyst.[15] The reason for the opposing trend may be due to the nature of the support, and/or the difference in the sizes of the Ni nanoparticulate, which affect the adsorption of different alcohols containing aliphatic/aromatic moieties.[23]

Continuous flow reactions

Thus far, we have shown that better selectivity for the primary amine can be achieved by using anhydrous NH_3 as a reagent in a batch reactor. However, the turnover remained low for substrates other than benzyl alcohol. Once again, the accumulation of water by-product over the course of the reaction may limit the final conversion as the system reaches equilibrium. Likewise, as the reaction progresses, increasing amount of amine product could also cause catalyst deactivation and leaching. We postulated that these limitations may be overcome by switching to a continuous flow paradigm.

The major hurdle in implementing the reaction in continuous flow is the handling of NH_3. In order to control the stoichiometric ratio of NH_3/BnOH in a liquid phase, Aspen simulation (SR-Polar) was performed to predict the phase behavior of a mixture of NH_3/*o*-xylene when it is subjected to 60 bar of pressure (other methods, such as RKS and other SR, gave fairly similar results). The resultant phase diagram (Fig. 3) shows that at 160 °C, 8% (0.08 mole fraction,

marked by red cross) of NH_3 will be present in an *o*-xylene solution. Hence, we can assume that the catalytic reaction operates as a biphasic system under these conditions, with the reaction occurring at the solid-liquid interface. The absence of gas phase in the system is important as this prevents non-uniform stoichiometry at the catalyst sites.

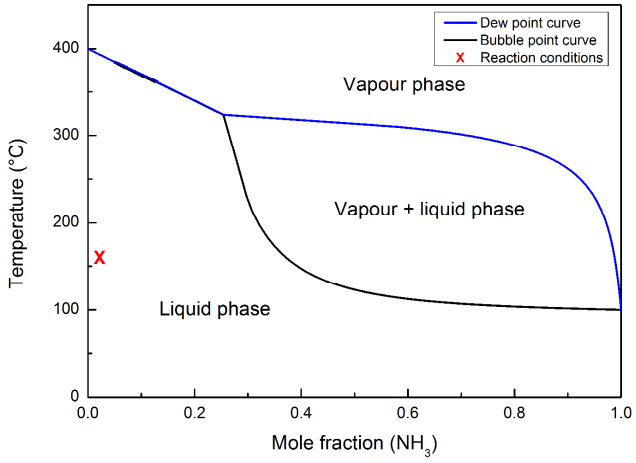


Fig. 3: Aspen simulation: Phase diagram of a NH_3/o-xylene mixture at 60 bar. Black curve = dew point curve; blue curve = bubble point curve. These curves separate the liquid and vapor phases. Red cross = operating conditions.

A continuous flow reactor system was subsequently constructed (Fig. 1), whereby a solution of the alcohol in *o*-xylene and NH_3 were delivered separately *via* HPLC pumps to the catalyst at 60 bar. To prevent excessive pressure drop, the catalyst particles were embedded in an inert material (bentonite) and extruded into 1 mm pallets. In the preliminary experiment, a solution of benzyl alcohol in xylene (0.6 M) and liquid NH_3 were mixed in a 1:7 ratio, and the resultant mixture was passed through the Ni catalyst bed at 0.2 mL/min (residence time, τ = 14 min). The output stream was collected in fractions such that the catalyst performance can be monitored over time. Steady-state conversion to the benzyl amine (25%) can be obtained after 2 h under these

conditions. However, side products were observed, including the secondary aldimine (PhCH=NBn) and benzonitrile (PhCN) intermediates. The formation of the latter appears to be transient: reaching a maximum of <20% yield after 1 h, before subsiding (Fig. 4, red squares).

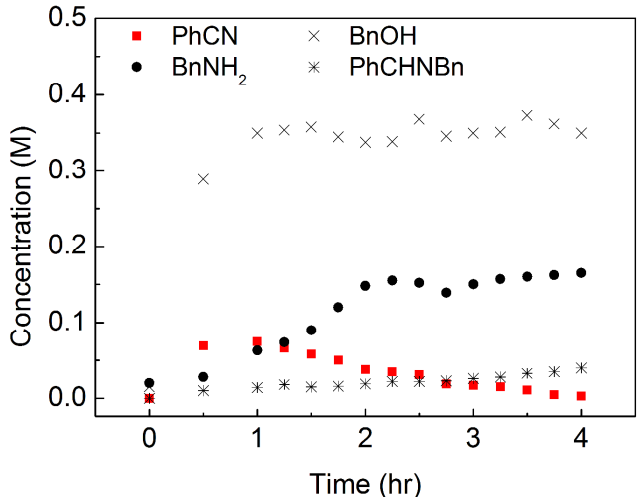


Fig. 4: Data collected from flow reaction. Conditions: 160 °C, 0.2 mL/min, 2.0 g extruded 36wt% Ni-Al_2O_3/SiO_2, NH_3/BnOH = 7, initial BnOH = 0.6 M, τ = 14 min.

Subsequently, we found that the formation of benzonitrile can be suppressed by pre-treating the catalyst with H_2, which suggests that its formation is due to the presence of NiO species on the catalyst surface. Accordingly, all subsequent studies were performed using pre-reduced catalysts.

Flow rate dependence

To control the selectivity of the process towards the primary amine and to minimize catalyst deactivation by the amine product, the initial concentration of the BnOH solution was reduced to 0.10 M. Experiments were conducted at different flow rates between 0.06-1 mL/min (Fig. 5A). As expected, the single-pass conversion of benzyl alcohol decreased with increasing flow rate/decreasing residence time. The corresponding TOF vs flow rate graph (Fig. 5B) shows that the TOF is essentially unchanged, *i.e.* the catalysis is operating under kinetic control within these

flow rates. Gratifyingly, the selectivity for the primary benzyl amine remained at 100% regardless of flow rate, demonstrating the formation of higher amines can indeed be eliminated by good residence time control.

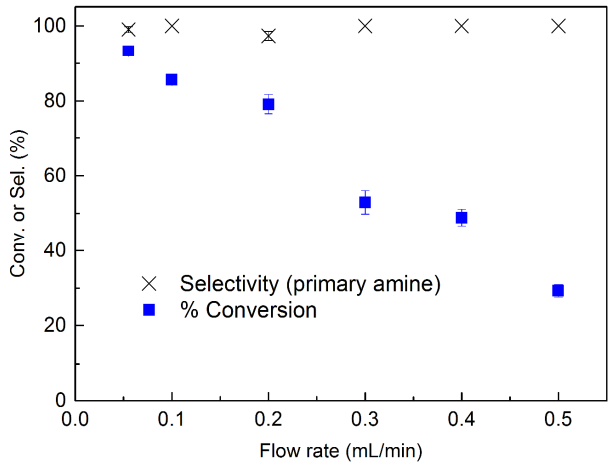


Figure 5A: Single-pass conversion of BnOH to $BnNH_2$. Flow rates = 0.06 – 0.5 mL/min. BnOH in *o*-xylene (0.1 M), 2.0 g extruded 36wt% Ni-Al_2O_3/SiO_2, NH_3/BnOH = 7, τ = 5.6 – 46.7 min, 60 bar.

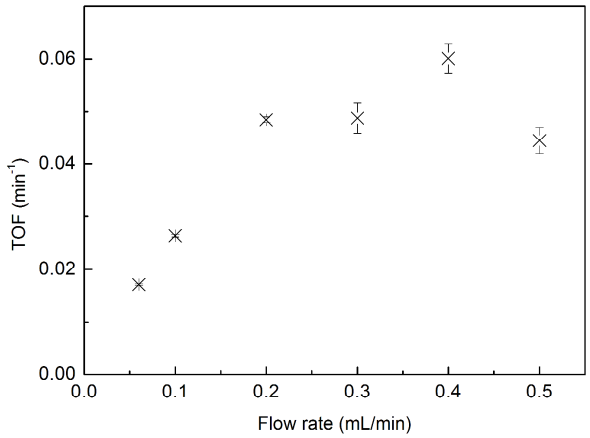
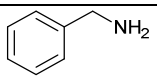
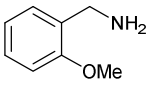
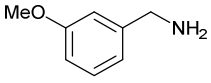
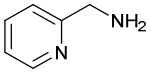
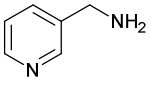
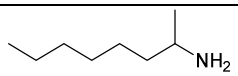
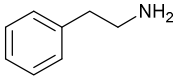


Fig. 5B: Single-pass TOF recorded over flow rates 0.06–1 mL/min. BnOH in *o*-xylene (0.6 M), 2.0 g extruded 36wt% Ni-Al_2O_3/SiO_2, NH_3/BnOH = 7, τ = 5.6 – 46.7 min, 60 bar. TOF = [$BnNH_2$]*flow rates/[Ni]

Substrate scope under continuous flow conditions. Reactions with alcohol substrates (Fig. 2) were re-examined under continuous flow conditions (Table 2). Pleasingly, in all cases, very good single-pass conversions and selectivities can be obtained. Notably, reactions with the benzyl alcohols (entries 1-3) and picolyl alcohols (entries 4-5) can be obtained with exclusive selectivity for the primary amines. The conversions for the picolyl alcohol substrates, once again, were lower due to leaching of the Ni catalyst (green coloration of the collected eluent was observed). The result obtained from the amination of aliphatic alcohols were also encouraging (entries 6 and 7). In these cases, very good conversions can be obtained by reducing the flow rate to increase the residence time.

Table 2. Amination of alcohols under continuous flow conditions.[a]

Entry	Product	Conversion[b]/%	Selectivity/%	TOF[c]/ x10^{-4} min^{-1}
1		100	100	2.5
2		86	100	2.1
3		100	100	2.5
4		51	100	1.3
5		67	100	1.6

6[d]		89	94[e]	1.0
7[d]		78	90[f]	0.86

[a]Conditions: 0.10 M ROH in o-xylene, NH_3/ROH = 7, 2.0 g extruded 36wt% Ni-Al_2O_3/SiO_2, flow rate = 0.06 mL/min, residence time (τ) = 46.7 min; [b]Steady-state conversion achieved after 15 x τ and maintained for 3 x τ. [c]TOF at steady-state (3 x τ) calculated by RNH_2 (mmol/min)/(mmol/Ni). [d]flow rate = 0.03 mL/min, τ = 93 min. [e]Ketone detected. [f]Secondary amine detected.

Catalyst deactivation and leaching. The industrial viability of a catalyst is dependent on its long-term stability. Invariably, catalyst activity degrades due to the loss of active sites, either by the loss of nickel content (leaching), or the active sites being blocked (poisoning). In the present system, the steady-state conversion of benzyl alcohol to benzyl amine decreases slowly over a period of time (>72 h), signifying catalyst deactivation. In this part of the work, the spent catalysts from flow or batch reactions were examined using ICP and TGA.

The absence of Ni content in all liquid phases (ICP analysis, <0.5 mg/L), suggested that catalyst leaching is not a significant issue in the absence of a Lewis basic group (such as a pyridyl group in the picolyl substrates, as described above). Instead, TGA-MS experiments performed with the recovered catalysts showed the liberation of volatile compounds as carbon dioxide (*m/z* = 44) at 300 °C, indicating that the catalyst deactivation was a result of carbonaceous deposition of the catalyst material by organic compounds. The C:H ratio of the gaseous thermal product was 1:1.2, suggesting a form of aromatic oligomer has been formed, possibly catalyzed by bentonite.[24]

Conclusions

Selective alkylation of ammonia with alcohols to primary amines has been achieved using a commercially available catalyst (65 wt% Ni-Al_2O_3/SiO_2). The reaction outcome was dramatically improved by using anhydrous NH_3 under continuous flow conditions to avoid the accumulation of water and amine products that can inhibit the catalyst. As a result, a number of primary alcohol substrates can be converted into their corresponding primary amines in very high single pass conversion and selectivity.

Catalyst deactivation of the Ni system can occur in two ways: the presence of a Lewis basic substrate (pyridyl group) and/or the deposit of carbonaceous deposits. Further work will focus on the design of more robust catalysts, and the assessment of their application to a wider range of alcohol substrates, for example diols and triols.

Supporting information. Flow reactor set up; Residence time calculations; Preliminary experiments with commercial catalysts and compare with other papers; Temperature study with anhydrous ammonia in batch system; TOF calculations; Time course graph for table 2, entry 1; Catalyst characterization.

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Synopsis: A high pressure continuous flow system has been designed to facilitate a Ni-catalyzed monoalkylation of ammonia by alcohols with high selectivities.