ChemComm
www.rsc.org/chemcomm

Continuous hydroamination in a liquid–liquid two-phase system†

Volker Neff, Thomas E. Müller* and Johannes A. Lercher
Lehrstuhl für Technische Chemie II, Technische Universität München, Lichtenbergstraße 4, 85747 Garching, Germany. E-mail: Thomas.Mueller@ch.tum.de; Fax: +49 89 28913544; Tel: +49 89 28913538

Received (in Cambridge, UK) 21st December 2001, Accepted 8th March 2002
First published as an Advance Article on the web 26th March 2002

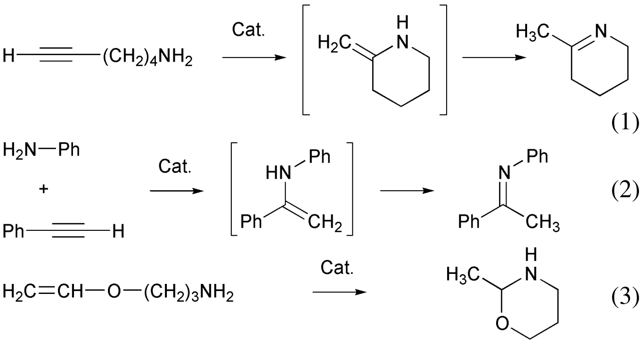
The direct addition of NH across a CC multiple bond (hydroamination) was efficiently catalysed in a liquid–liquid two-phase system. The latter comprised a polar catalyst phase of $Zn(CF_3SO_3)_2$ in the ionic liquid 1-ethyl-3-methylimidazolium trifluoromethanesulfonate and a substrate mixture in heptane. The possibility of catalysing different hydroamination reactions continuously was demonstrated.

The direct reaction of alkenes and alkynes with N–H bonds (hydroamination) is a highly attractive route for the synthesis of nitrogen containing compounds.[1] Currently, several research groups compete to find new and more efficient catalyst systems for this type of reaction. Recently, late transition metals complexes,[2,3] such as $[Pd(Triphos)](CF_3SO_3)_2$, where Triphos = bis(2-diphenylphosphinoethyl)phenylphosphane, were found to be effective homogeneous catalysts. Late transition metal catalysts can be immobilised on a solid support.[4] The possibility of catalysing hydroamination reactions with such catalysts has been demonstrated for Zn^{2+} ion exchanged zeolites in the addition of methylamine to propyne and the cyclisation of 6-aminohex-1-yne.[5] However, neither the homogeneous nor the heterogeneous catalysts have a sufficient activity and stability for a commercial process.

One strategy to achieve higher reaction rates is the use of a high concentration of catalyst, coupled with an efficient separation. This can be realised in liquid–liquid two-phase systems. So far, only one example of hydroamination in a two-phase system has been realised. In the special case of cyclising *o*-ethynylanilines to indoles, the two-phase system comprises a solution of palladium(II)-salts in CH_2Cl_2 and aqueous HCl.[6] The challenge was to develop a new two-phase system, which would allow hydroamination reactions to be performed in a more general manner.

The choice of the solvent pair faces a number of boundary conditions: (i) Most late transition metal catalysts for hydroamination reactions are cationic (*e.g.*, Rh^+, Pd^{2+}, Cu^+, Zn^{2+}).[2] Thus, to dissolve the corresponding salts, a polar solvent is required. (ii) To achieve high reaction rates, the metal center should be only weakly coordinated by the solvent. (iii) The solvent for the catalyst phase has to be immiscible with an appropriate apolar organic solvent over a wide temperature range. (iv) Water can not be used in the addition of RNH_2 to CC triple bonds, as it reacts with the imines formed. Therefore, the ionic liquid 1-ethyl-3-methylimidazolium trifluoromethanesulfonate was chosen as the polar phase.[7] This salt is liquid over the required temperature range (rt to >350 °C) and is chemically relatively inert. The metal salt $Zn(CF_3SO_3)_2$ was chosen as the catalyst. Zinc(II) seemed particularly stable against deactivation as it cannot be reduced to the metal under the reaction conditions. Toluene and heptane were chosen as the apolar phase and solvent for the starting material and product. In the presence of amines, $Zn(CF_3SO_3)_2$ is soluble in small amounts in toluene, which allows a direct comparison with the corresponding homogeneous catalysis. In contrast, the less polar heptane minimises leaching of zinc into the product phase.

To test the scope and suitability of two-phase catalysis, three model reactions were explored (eqn. 1–3). The reactions were performed in the batch mode and the mixtures stirred sufficiently fast to obtain a homogeneous suspension of the two phases. In this case, a large surface area was achieved, enabling fast mass transfer across the phase boundary.



The cyclisation of 6-aminohex-1-yne first generated the enamine 2-methylenepiperidine, which isomerised *in situ* to the corresponding imine 2-methyl-1,2-dehydropiperidine (eqn. 1). In the two-phase system, a quantitative conversion (≥99%) of 6-aminohex-1-yne was achieved within 150 min.† Under equal reaction conditions, the rate of reaction in the two-phase system was higher than in the corresponding homogeneous catalysis using $Zn(CF_3SO_3)_2$ as the catalyst (Fig. 1). Possibly, a polar transition state is stabilised in the presence of 1-ethyl-3-methylimidazolium trifluoromethanesulfonate leading to a higher rate of reaction.[8] In the presence of the ionic liquid, the concentration of zinc ions in the toluene phase (range $0.2–1.2 \times 10^{-3}$ g dm^{-3}) was three orders of magnitude lower than during the homogeneous catalysis (1.3 g dm^{-3}). Thus, the reaction in the two-phase system occurs either in the polar phase or at the phase boundary. Both two-phase and homogeneous reaction followed approximately first order kinetics. Compared to the corresponding heterogeneous (solid–liquid) catalysis using Zn-beta as catalyst, the rate of reaction in the liquid–liquid two-phase system was slightly lower. For this heterogeneous system

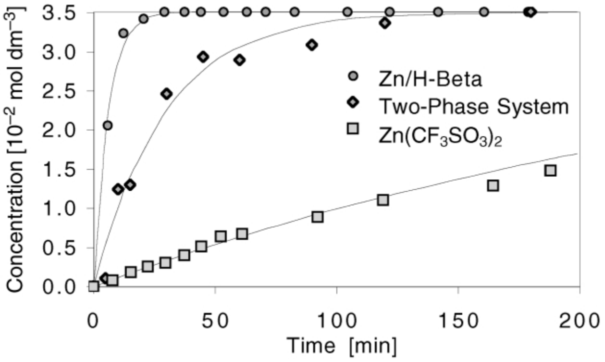


Fig. 1 Time-concentration diagram for the conversion of 6-aminohex-1-yne in a heterogeneous, a two-phase and a homogeneous catalyst system.

---

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b1/b111630d/

DOI: 10.1039/b111630d

This journal is © The Royal Society of Chemistry 2002

it had been shown that the high catalytic activity is due to the presence of protons in the solid material, which function as co-catalyst.[5] In contrast, the two-phase catalysis was performed under neutral conditions. This extends the scope of the reaction to those substrates that have additional acid sensitive functional groups.

The reaction between phenylacetylene and aniline gives phenyl-(1-phenylethylidene)-amine (eqn. 2). This reaction was much slower than the cyclisation of 6-aminohex-1-yne. After 150 min, about 10% conversion was achieved. Whereas the combined concentrations of phenylacetylene and product in the toluene phase added up to the initial concentration of phenylacetylene, about half of the initially added aniline was not found. The missing aniline was probably present in the ionic liquid, and was, therefore, not observed by GC analysis. The unfavourable phase equilibrium for aniline might be the reason for the low rate of reaction. The cyclisation of 3-aminopropyl vinyl ether to tetrahydro-2-methyl-1,3-oxazine was considerably faster (eqn. 3). Quantitative conversion was achieved within 10 min (rate $\geq 1.6 \times 10^{-2}$ mol $(\mathrm{mol}_{\mathrm{Zn}^{2+}}\,\mathrm{s})^{-1}$), which was much faster than in the corresponding homogeneous catalysis with $Zn(CF_3SO_3)_2$ (rate 7.2×10^{4} mol $(\mathrm{mol}_{\mathrm{Zn}^{2+}}\,\mathrm{s})^{-1}$).[2]

For a more detailed exploration of the two-phase system, a custom built autoclave was filled with the catalyst phase (34.5 cm^3) and pure heptane (35.5 cm^3).† Both phases were stirred separately in such a way that the phase boundary (area 3.5 cm^2) remained steady. The reactor was equilibrated with a steady flow of heptane and operated at 40 bar. The reaction was then started by switching to a solution of the substrate in heptane. For a non reactive internal standard (hexadecane) and a flow of 10 cm^3 min^{-1}, an exponential increase in concentration was observed after a dead time of 0.8 min. The residence time distribution (RTD) of the internal standard shows that the hydrodynamic flow pattern of the reactor was close to an ideal continuously operated stirred tank reactor (CSTR). At 10 cm^3 min^{-1} the average residence time was 4.4 min and steady state was reached 13 min after the dead time.

When the experiment was performed with 6-aminohex-1-yne, the sum of the concentrations of starting material and product reproduced that of the internal standard well. This indicates that only little substrate or product diffused into the ionic liquid. At 110 °C and 10 cm^3 min^{-1}, 4% of 6-aminohex-1-yne was converted to 2-methyl-1,2-dehydropiperidine in the steady state, which corresponds to a formal macrokinetic reaction rate of 3.3×10^{-3} mol m^{-3} s^{-1}. This corresponds to a rate of 0.11 mol m^{-3} s^{-1} m_{area}^{-2} when normalised to the area of the interface. No decrease in the rate of reaction was observed over longer periods (6 h) of operation. If run in the batch mode, a quantitative conversion ($\geq$99%) was achieved after 6.5 hours.

The conversion increased exponentially with temperature and linearly with residence time.† From the temperature dependence, an apparent activation energy of 28 ± 8 kJ mol^{-1} was calculated. The linear variation of the conversion with residence time and the equal apparent energy of activation at all residence times strongly implies the absence of external diffusion limitations across the phase boundary. Upon reduction of the reaction area from 3.5 cm^2 to 1.8 cm^2, the conversion dropped by the same factor (flow 2.5–10 cm^3 min^{-1}). The linear correlation between the geometric area of the phase boundary and the reaction rate indicates that the catalytic reaction takes place directly at the interface of the two phases. The zinc ion concentration in the product phase was close to the detection limit of AAS ($\leq$0.07 mg dm^{-3}). This confirms that most of the reaction occurs at the phase boundary. The increase in reaction area is, therefore, the most effective way to increase the conversion with equal residence time.

A model of the elementary steps of the reaction is shown in Fig. 2 based on recent mechanistic studies.[2,9] Once the 6-aminohex-1-yne has diffused from the bulk heptane phase into the layer directly adjacent to the phase boundary, it coordinates to the zinc cations *via* the CC multiple bond. This enables a nucleophilic attack of the amine on the π-system and yields an ammonio alkenyl complex. The latter is energetically unfavourable because of the charge separation. Stabilising this complex, respectively a preceding or succeeding polar transition state, in a highly polar solvent increases the overall rate of reaction. A formal 1,3-hydrogen shift gives the product enamine, which desorbs and isomerises to the corresponding imine. Either the enamine or the imine diffuses back into the bulk heptane phase.

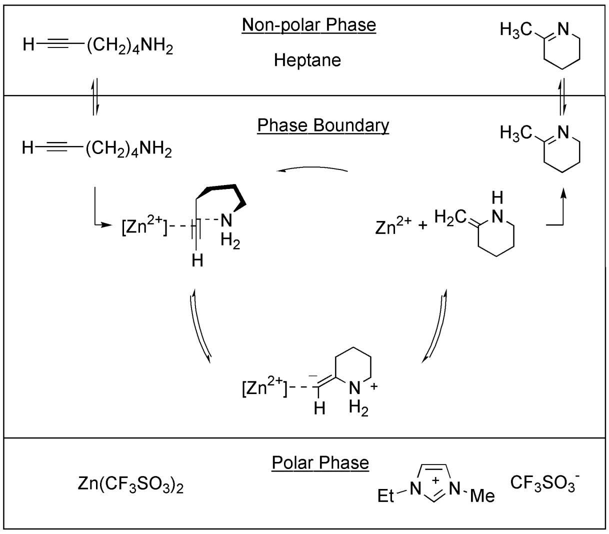


Fig. 2 Model for the two-phase catalysis of hydroamination reactions.

In summary, it was shown that hydroamination reactions can be efficiently catalysed in a liquid–liquid two-phase system. For the first time, an ionic liquid (1-ethyl-3-methylimidazolium trifluoromethanesulfonate) was employed successfully as a polar solvent in this type of reaction. The catalyst $Zn(CF_3SO_3)_2$ was fixed efficiently in the ionic liquid, whereas the product phase was readily separated. It is particularly noteworthy that the presence of a highly polar solvent led to a higher intrinsic rate of reaction compared to the corresponding homogeneous catalysis. We speculate that this is induced by the better stabilisation of the polar transition state at the ionic liquid interface. The CSTR used in the experiments proved well suited for determining the reaction rate. For an efficient two-phase catalysis of hydroamination, such as the cyclisation of 6-aminohex-1-yne, the reactor needs to be designed such that the area of the interface is maximised.

The support of *Deutsche Forschungsgemeinschaft* and *Dr-Ing Leonhard-Lorenz-Stiftung* is acknowledged. Dr L. Callanan and Dr E. Bratz are thanked for proof-reading the manuscript.

Notes and references

1 T. E. Müller and M. Beller, *Chem. Rev.*, 1998, **98**, 675.

2 T. E. Müller, M. Berger, M. Grosche, E. Herdtweck and M. F. P. Schmidtchen, *Organometallics*, 2001, **20**, 4384; R. Q. Su and T. E. Müller, *Tetrahedron*, 2001, **57**, 6027; T. E. Müller and A.-K. Pleier, *J. Chem. Soc., Dalton Trans.*, 1998, **4**, 583.

3 See also, *e.g.*, M. Kawatsura and M. J. F. Hartwig, *Organometallics*, 2001, **20**, 1960; C. G. Hartung, A. Tillack, H. Trauthwein and M. Beller, *J. Org. Chem.*, 2001, **66**, 6339.

4 M. K. Richmond, S. L. Scott and M. H. Alper, *J. Am. Chem. Soc.*, 2001, **123**, 10521.

5 J. Penzien, T. E. Müller and M. J. A. Lercher, *Microporous Mesoporous Mater.*, 2001, **48**, 285; R. S. Neale, L. Elek and R. E. Malz, *J. Catal.*, 1972, **27**, 432.

6 S. Cacchi, V. Carnicelli and M. F. Marinelli, *J. Organomet. Chem.*, 1994, **475**, 289.

7 For reviews on ionic liquids see: R. Sheldon, *Chem. Commun.*, 2001, 2399; Charles M. Gordon, *Appl. Cat. A*, 2001, **222**, 101; J. F. Brennecke and E. J. Maginn, *AIChE Journal*, 2001, **47(11)**, 2384.

8 See Y. Marcus, *The Properties of Solvents*, ed. P. G. T. Fogg, John Wiley & Sons, Chichester, 1999, **vol. 4**, p. 187.

9 H. M. Senn, P. E. Blöchl and M. A. Togni, *J. Am. Chem. Soc.*, 2000, **122**, 4098.