Universität Rostock — Traditio et Innovatio

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Switchable-Hydrophilicity Solvents for Product Isolation and Catalyst Recycling in Organocatalysis

Julia Großeheilmann,[a] Jesse R. Vanderveen,[b] Philip G. Jessop[b] and Udo Kragl[a]

Introduction

Switchable-Hydrophilicity solvents (SHS) are solvents that can switch reversibly between a water-miscible state that forms a biphasic mixture with water. In this study, SHSs have been studied for easy product/catalyst separation. A series of tertiary amine SHSs (Figure 1) have been identified for the extraction of an enantiopure compound from an organocatalyzed HENRY reaction. These amines form biphasic mixtures with water in the absence of CO_2. Protonation of the amines by carbonic acid results in water-soluble bicarbonate salts.

$$NR_3 + CO_2 + H_2O \leftrightarrows [NR_3H^+][HCO_3^-]$$

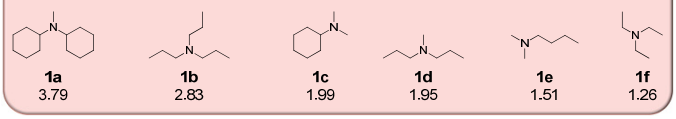


Figure 1. The amines used in this study. The number in plain font is the predicted log K_{OW} whereas the number in bold font is the compound number.

Results & Discussion

Preparation of switchable-hydrophilicity solvents

Table 1. Amounts of water and CO_2 bubbling times to merge into a single phase.

Entry	1	2	3	4	5	6
Amine	1a	1b	1c	1d	1e	1f
Amine/water ratio[a]	1:10	1:5	1:2	1:2	1:2	1:2
pH value[b]	6.7	7.6	8.1	8.4	8.0	n.d.
Time / min	40	35	20	20	20	10

[a] *v/v* solution of amine and water, for gas input, 1 bar was used with a gas dispersion tube. [b] pH value was measured from the aqueous phase.

Obtaining monophase depends on:

- Amine/water ratio
- Sample size
- Method of CO_2 addition
- pH value

⇨ with increasing hydrophobicity of the amine, more water is needed and time increases

Extraction efficiency of carbonated SHS solutions

Ability to extract product/catalyst depends on:

- Hydrophobicity of the amine
- Polarity of SHS
- Water/amine ratio
- Ionic strength
- pH value

⇨ best result was obtained with amine **1e**

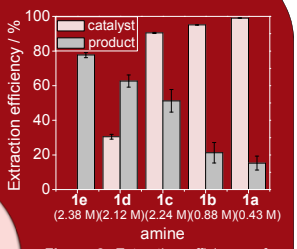
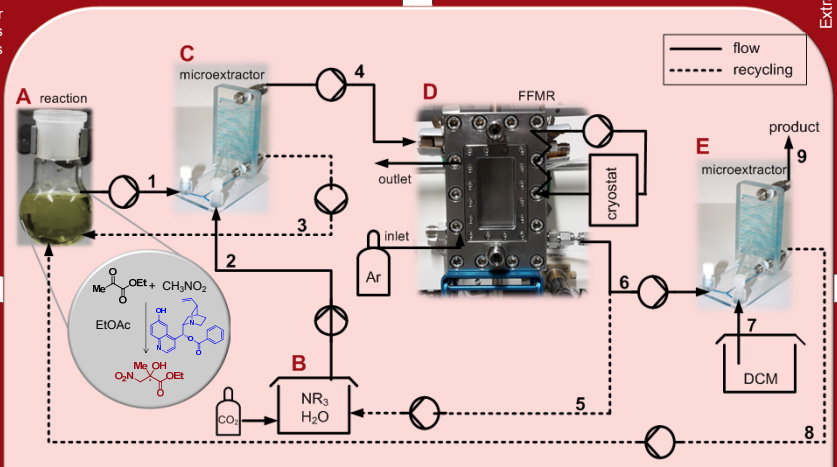


Figure 2. Extraction efficiency of carbonated amine/water solutions for the extraction of product and catalyst from EtOAc postreaction mixture. Cond. 10 mL SHS (ratios are the same as in Table 1, values in parentheses are the concentration of the amine) and 10 mL postreaction mixture (1 M product and 2.5 mM catalyst).



Scheme 1. Schematic setup for recycling experiments. **A** – Reaction performed in a reaction vessel; **B** – Preparation of SHS as extraction solvent, **C** – Extraction of prod. **D** – Removing CO_2.; **E** – Extraction of prod. **1** – Postreaction stream containing cat., prod. and EtOAc; **2** – protonated hydrophilic SHS stream; **3** – Recycling of cat. in EtOAc; **4** – SHS stream enriched with prod.; **5** – Recycling of amine; **6** – Aqueous stream enriched with prod.; **7** - DCM as extraction solvent; **8** – Recycling the aqueous phase; **9** – prod. In DCM.

CO_2 Removal

Working with falling-film microreactor yield in:

- 99% time saving
- Low mass loss of only 9%
- No formation of racemate
- Continuous process
- Ambient conditions

Catalyst Recycling

Downstream processing is simplified to a large extent:

- High product isolation (84%)
- Full catalyst recycling (99%)
- High catalyst activity (91% *ee*)
- High product purity (98%)
- Effective recycling (4 cycles)

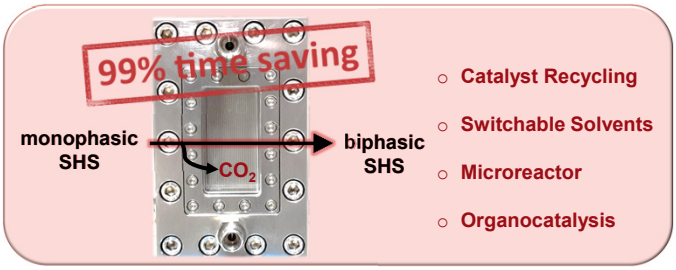
Table 2. Comparison of different methods for removing CO_2.

Method	Time / h	Phase split	Mass loss / %	ee / %
gas dispersion tube	4	no	n.d.	n.d.
heating (40 °C)	6	yes	48	68
heating (70 °C)	3	yes	53	43
sonicator	4	yes	62	41
FFMR	0.25	yes	9	89

Table 3. Results for the catalyst recycling experiments.

Batch	ee / %	Yield / %	Recycled cat. / %	Extraction prod. / %
1	90	90	>99	81.
2	91	99	>99	79
3	90	99	>99	78
4	90	99	>99	78

Summary



The combination of SHSs with microstructured devices has been introduced as an ecofriendly and sustainable alternative to existing methods for product and catalyst separation. With this study, we demonstrate the separation of homogeneously soluble organocatalyst from the postreaction mixture without any loss of activity. Here, we compensated the disadvantage of the high catalyst loadings required for organocatalytic reactions by decoupling the residence time of the reactants and catalyst. Furthermore, the isolation of the product and the catalyst removal using this technique could be completed in a reasonable amount of time.

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DFG

[a] Institute of Chemistry | University of Rostock | Albert-Einstein-Str. 3a | 18059 Rostock | Germany
[b] Department of Chemistry| Queen`s University | 90 Bader Lane, Chernoff Hall | Kingston, Ontario, K7L 3N6 | Canada

References:

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