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Thieme Chemistry Journal Awardees - Where are They Now? Catalytic Transport with an Amine Carrier in a Fluorous Triphasic Reaction

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Abstract

Several aromatic aldehydes are transported by a fluorous amine from one organic phase through a fluorous phase to another organic phase. The derived imines react with phenylhydrazine to immobilize the transported product as a hydrazone and release the amine for reuse. In this way, catalytic transport is accomplished for the first time.

Keywords

triphasic reaction; transport; fluorous chemistry; U-tube; fluorous amine

The production of new organic molecules is typically comprised of a reaction and a separation, and these two stages are almost always conducted separately in space and time. Conducting a reaction and a separation coincidently has the potential to result in a synthesis device (or machine) where starting materials are fed in and products are harvested out continuously. Such devices could potentially be piggybacked to provide for continuous, realtime, multistep reaction and separation.

The separation component of any synthesis device requires some kind of partitioning, and the immiscibility of fluorous and organic liquids offers attractive opportunities.² In 2001, we introduced fluorous triphasic devices for transportative deprotection of fluorous-tagged materials.³ In the example shown in Figure 2, a mixture resulting from enzymatic enantioselective hydrolysis of a racemic fluorous-tagged alcohol was simultaneously separated and detagged.⁴ The mixture was comprised of roughly equal amounts of the free alcohol (*R*)-**1** and its enantiomeric counterpart (*S*)-**2** still bearing the fluorous tag. Three steps are needed to complete the resolution: 1) the alcohol (*R*)-**1** and the ester (*S*)-**2** must be separated; 2) the retrieved ester (*S*)-**2** must be hydrolyzed, and 3) the residual tag must be separated from the resulting alcohol (*S*)-**1**.

The triphasic device in Figure 1, a simple U-tube, accomplishes all three tasks simultaneously. The U-tube contains two organic phases (source and receiving) separated by a fluorous phase that prevents direct contact between these phases and thereby regulates exchange. A mixture of (*R*)-**1** and (*S*)-**2** is added to the source side of the device of sodium methoxide is to the receiving side. Over time, the ester (*S*)-**2** partitions through the fluorous phase over to the

receiving phase, where it is detagged by the base. This strands the resulting alcohol (*S*)-**1** in the receiving phase, while the residual tag (which is now highly fluorous) partitions back to the fluorous phase. The starting alcohol (*R*)-**1** stays put in the source phase. Thus, in an ideal process, there is one product in each of the three phases.

This kind of ‘transportative detagging’ of fluorous-tagged substrates is a potentially general way to remove non-tagged contaminants along with removal of the fluorous tag. But such processes are by definition stoichiometric in the fluorous component (the tag). Herein, we report the first catalytic fluorous triphasic reaction and separation process.

In principle, it should be possible in a fluorous-organic triphasic device to convert an organic substrate to an organic product with the aid of a substoichiometric amount of a fluorous carrier. We set out to prove this principle by transporting an aldehyde from the source phase through the fluorous phase with a fluorous amine carrier via the intermediacy of a fluorous imine. Aldehydes are important raw materials, and their feedstocks can be contaminated with alkenes, alcohols, and other impurities. Thus, their separation with a simultaneous onward reaction has potential value.

The reactions involved in the process are summarized with 4-bromobenzaldehyde (**4**) in Scheme 1. In the source organic phase, **4** reacts with fluorous amine carrier **3** to give fluorous imine **5**. In turn, the imine **5** is transported through the fluorous phase to the receiving organic phase, where it reacts with added phenyl hydrazine **6** to provide hydrazone **7**. The energy released in this reaction drives the separation, and the amine carrier is also released for return through the fluorous phase to the source organic phase.

We expected the rates of both reaction steps to be relatively fast, and thus the rate of the overall reaction and separation process will be limited by the transport rate. Our previous stoichiometric triphasic reactions were also transport-limited, and often took several days to go to completion in standard U-tubes. Reducing the fluorous component to a substoichiometric amount will further slow the process, and accordingly we deemed the U-tube device design unsuitable.

In principle, the transport rate problem can be solved by engineering solutions in which the fluorous phase is circulated between the source and receiving phases. We decided to mimic this engineering solution with serial extractions, as summarized in Figure 2. Thus, the source phase with the aldehyde **5** and the fluorous phase with the amine **3** were vortexed together in a vial to allow reaction and subsequent partitioning of the resulting imine **5**. The phases were then separated and the forward fluorous-phase-containing part of this imine **5** was vortexed with the receiving phase to allow reaction to form the hydrazone **7** with release of the imine **5**. Then the back fluorous phase containing the amine **3** was returned to the source phase and the whole process was repeated in a series of identical cycles.

If the reactions are rapid and quantitative, and if the partitioning of the fluorous amine/imine into the fluorous phase is also quantitative, then it is possible to transport in each cycle an amount of aldehyde that is equal to the amount of amine added. Control experiments suggested that the two reactions were rapid and quantitative, as expected.⁵

But the partitioning of the amine **3** and imine **5** into the fluorous phase will surely not be quantitative since the fluorine content of these compounds is not nearly high enough.^{6,7} In that case, after a few cycles, a kind of quasi-equilibrium will be reached in which there is unproductive amine **3** in both the source (as imine) and receiving phases and productive amine **3** in the fluorous phase (the imine is present in the forward direction and the free amine in the reverse direction). In this scenario, the amount of aldehyde transported in each cycle will equal the amount of productive amine. Provided that the aldehyde is present in excess, a plot of

transport amount versus time should be linear and should not depend on the aldehyde concentration.

In a typical experiment, 4-bromobenzaldehyde (**4**, 23.2 mmol) and (perfluorooctyl) propylamine (**3**, 0.56 mmol, 25 mol%) in acetonitrile (7 mL) and FC 72 (7 mL) were vortexed in the source vial for one hour. The phases were allowed to separate, and the FC-72 phase was transferred to the receiving vial containing phenylhydrazine (**6**, 2.3 mmol) in acetonitrile (7 mL). This was similarly vortexed for one hour. The FC phase was then returned to source vial to start the second cycle. Cycles were repeated until phenylhydrazine was largely consumed.⁸ The progress of the reaction was followed by GC. We could not detect either imine **5** or aldehyde **4** in the receiving phase. Also, there was no detectable back transport of either the phenylhydrazine (**6**) or the product hydrazone **7** to the source phase.

Figure 3 plots the accumulation of hydrazone **7** in the receiving phase as a function of cycle. As expected, the plot is linear, and about 0.2 mmol of aldehyde **4** is transported from the source phase to the receiving phase in each cycle. This means that about 35% of amine **3** that was added was productive in each cycle.

After the 10th cycle, the yield of phenylhydrazone based on aldehyde was 89%, and the yield based on amine was 350%. This shows the catalytic nature of the transport. The GC analysis showed that the amine **3** was largely intact after the 10th cycle, distributed over the three phases. We conducted a similar experiment with about 10% of the amine catalyst, and about 40% of the phenylhydrazone **7** was produced in the receiving vial after ten cycles (about 4% transport per cycle). This is consistent with the expectations based on the amount of productive amine from the first experiment.

These experiments need to be controlled for direct (passive) transport of the aldehyde through the fluororous phase to the receiving phase. In these first experiments, we did this indirectly by measuring the partition coefficient of the aldehyde between FC-72 and acetonitrile. This was <0.01, so significant passive transport seems unlikely.

We then conducted a second series of cycles with the same procedure mentioned above with 4-fluorobenzaldehyde and 10% amine **3**. This time, we did a parallel series of control cycles with all the same components, but omitting the fluororous amine. The plots of hydrazone yield versus cycle for both experiments are shown in Figure 4. The control experiment, which was stopped after the 4th cycle, shows that the background (passive) transport rate is not zero, but it is rather small (and 1% per cycle). This is presumably due to direct partitioning of the aldehyde into the FC-72.⁹

The results for the transport experiments with 4-fluorobenzaldehyde were similar to those with 4-bromobenzaldehyde. With 10% of the amine **3**, about 40% of the aldehyde was transported to form the hydrazone after the 10th cycle. The initial rate of transport in the experiments with the amine exceeds that rate of the background transport by a factor of about 5. This again demonstrates the effect of the amine/imine on the transport. We did similar experiments with benzaldehyde and 4-trifluoromethylbenzaldehyde with generally similar results (not shown). In each of these case the initial rate of transport in the experiment with the amine exceeded that of the control by a factor of 3.

These experiments demonstrate for the first time that an organic reactant can be transported from one organic phase through a fluororous phase to another organic phase by a substoichiometric amount of a fluororous transport agent. The experiments are prototypes for synthesis devices that accomplish a simultaneous reaction and separation and that are catalytic in the fluororous component. Assuming that the reaction rates are fast, the efficiency of such devices will depend on the efficiency of the transport. This is subject to optimization through

chemistry (changing solvents, catalysts, etc. to alter partition coefficients) and through engineering (for example, by using continuous extractors).

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Biography

Dennis P. Curran received his B.Sc. in 1975 from Boston College. His Ph.D. was granted from the University of Rochester in 1979 where he worked under Professor Andrew S. Kende. After a two year post-doctoral stay with Barry M. Trost at the University of Wisconsin, Dr. Curran joined the faculty of the Chemistry Department at the University of Pittsburgh in 1981. He now holds the ranks of Distinguished Service Professor and Bayer Professor of Chemistry, and is the founder of Fluorous Technologies, Inc. Among other awards, Dr. Curran has received the American Chemical Society Award for Creative Work in Fluorine Chemistry (2008), the University of Pittsburgh Innovator Award (2007), the American Chemical Society Award for Creativity in Organic Synthesis (2000) and the Cope Scholar Award (1988). He is currently an ISI "Highly Cited Researcher". Dr. Curran is well known for his work at the interface of radical chemistry and organic synthesis. More recently, he has made significant contributions to the emerging discipline of fluororous chemistry.

References and Notes

- (1). DPC holds an equity interest in Fluorous Technologies, Inc.
- (2). (a) Gladysz, JA.; Emnet, C. *The Handbook of Fluorous Chemistry*. Gladysz, JA.; Curran, DP.; Horvath, IT., editors. Wiley-VCH; Weinheim: 2004. p. 11-23. (b) Ryu, I.; Matsubara, H.; Emnet, C.; Gladysz, JA.; Takeuchi, S.; Nakamura, Y.; Curran, DP. *Green Reaction Media in Organic Synthesis*. Blackwell; Ames IO: 2005. p. 59-124. (c) Iskra J. *Lett. Org. Chem* 2006;3:170–175. (d) Ryu I, Matsubara H, Nakamura H, Curran DP. *Chem. Rec* 2008;351. [PubMed: 19107865]
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- (4). Luo ZY, Swaleh SM, Theil F, Curran DP. *Org. Lett* 2002;4:2585. [PubMed: 12123382]

- (5). The controls were conducted similarly to the transport experiments. Aldehydes were vortexed with 1 equiv of amine or hydrazine for 1 h in MeCN. Formation of the imine or hydrazone was quantitative as assayed by GC. These samples then served as standards for the transport experiments.
- (6). Gladysz, JA.; Emnet, C.; Rábai, J. *The Handbook of Fluorous Chemistry*. Gladysz, JA.; Curran, DP.; Horvath, IT., editors. Wiley-VCH; Weinheim: 2004. p. 56-100.
- (7). The K_p ($[\text{FC-72}]/[\text{CH}_3\text{CN}]$) of **3** and **5** were measured by direct partitioning as 2.3 and 0.8, respectively.
- (8). About 5-10% of the volume of the FC-72 phase was lost in each cycle, presumably due to evaporation. This was made up by adding additional FC-72 at the beginning of each new cycle to return the volume to 7 mL.
- (9). We also considered that transport of the aldehyde might occur by accidental transfer of some of the organic source phase to the receiving phase during the cycles. But we did not observe back transfer of the hydrazine or hydrazone, so

Figure 1.
Transportative detagging of a ester-alcohol mixture generated by enzymatic kinetic resolution

Figure 2. Simplified illustration of the iterative reaction and extraction cycle with infinite partition coefficients. In reality, the organic components have high partition coefficients, but the fluorous components **3** and **5** distribute between both phases

Figure 3.
Plot of transport of 4 to from 7 as a function of cycle

Figure 4. Active transport with amine **3** (10%) and 4-fluorobenzaldehyde (top line) plotted with control for passive transport (bottom line)

source phase-reaction

5, transported forward

receiving-phase reaction

7 **3, transported back**

Scheme 1.

Reactions involved in the catalytic transport with fluoros amine carrier 3