J. Am. Chem. Soc. **2001,** *123,* 10119−10120

Fluorous Triphasic Reactions: Transportative Deprotection of Fluorous Silyl Ethers with Concomitant Purification

Hiroyuki Nakamura,[1a] Bruno Linclau,[1b] and Dennis P. Curran*

Department of Chemistry
University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Received July 16, 2001

The use of an impure starting material in a typical organic reaction is generally a recipe for producing an impure product. Accordingly, each organic reaction is usually followed by a separation. Despite the efficiency advantage, reactions and separations are rarely coupled in any substantive way.[2] Herein, we describe the first examples of "fluorous triphasic reactions". In these processes, a liquid−liquid separation is directly coupled with a chemical reaction to provide a pure product starting from an impure precursor. The reaction and separation occur simultaneously rather than sequentially, and the reaction drives the separation.

Fluorous triphasic reactions emanate from fluorous biphasic reactions[3] and other techniques based on fluorous/organic liquid−liquid extractions.[4] They also extend so-called "fluorous synthesis" techniques in which organic molecules are reversibly tagged with fluorous tags during a part of the synthesis.[5] These techniques typically rely on solid−liquid extraction because the number of fluorines needed for liquid−liquid extractions is unduly large.[6] The transportation features of three liquid phases (usually two aqueous, one organic) are well-known[7] but are rarely used in synthesis.

The present fluorous triphasic reaction is used to remove a fluorous tag from a precursor with concomitant separation of the detagged organic product from organic impurities, as shown in Figure 1. A simple U-tube holds a lower fluorous phase (also called the "F-phase") that serves as a barrier to separate two upper organic phases. The substrate is added to one organic side (the "S-phase"), and the product is formed in the other ("the P-phase"). In the generalized reaction in Figure 1, a fluorous-tagged precursor contaminated with nontagged (organic) impurities is added to the S-phase, and a reagent to remove the fluorous tag is added to the P-phase. The reagent should have negligible solubility in the F-phase to prevent its transport to the S-phase.

Over the course of the reaction, the tagged substrate migrates from the S-phase through the F-phase to the P-phase, whereupon the tag is promptly removed by the reagent. The detagged product is now stranded in the P-phase, because it lacks the tag that rendered it soluble in the F-phase. The impurities have no tag in the first place, so they cannot migrate from the S-phase to the P-phase. The residual tag has a relatively high fluorine content and partitions back to the F-phase. The result is a kind of autopurifying process in which an impure starting material reacts to generate a pure product.

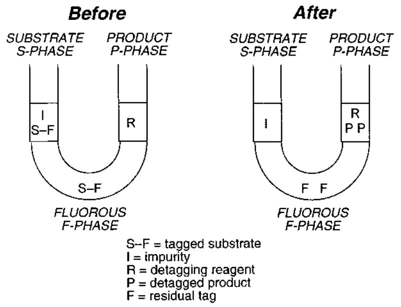
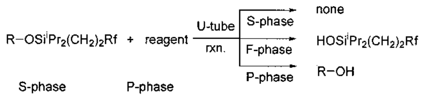


Figure 1. Cartoon of Fluorous Triphasic Transportative Detagging

We conducted a series of preliminary experiments with pure fluorous silyl ethers to identify suitable fluorous tags, reagents, and solvents for the triphasic reaction (eq 1 and Table 1). The F-phase in all cases was FC-72 (perfluorohexanes), and acetonitrile was chosen as the standard solvent for the S-phase. P-phase solvents and reagents were initially probed with silyl ether **1a** of 2-(2-naphthyl)ethanol (Rf = C_8F_{17}). This was added to the S-phase (acetonitrile), and a reagent was added to the P-phase in the indicated solvent. After completion, the reactions were worked up to determine the total yield of product from the amount isolated from the S- and P-phases. In the ideal experiment, all the product should be in the P-phase.



S-phase	P-phase		
substrate	R	Rf	Product
1a	2-(2-naphthyl)ethyl	C_8F_{17}	**2**
1b	2-(2-naphthyl)ethyl	$C_{10}F_{21}$	**2**
1c	2-(2-naphthyl)ethyl	C_6F_{13}	**2**
1d	2-(2-naphthyl)ethyl	C_4F_9	**2**
1e	2-(2-naphthyl)ethyl	^{i}Pr^a	**2**
(S)-**3**	(S)-(−)-1-(2-naphthyl)ethyl	C_8F_{17}	(S)-**4**
5	$PhCH=CHCH_2$	C_8F_{17}	**6**
7	$Ph(CH_2)_6$	C_8F_{17}	**8**
9	$CH_3(CH_2)_{11}$	C_8F_{17}	**10**
11	cholestanyl	C_8F_{17}	**12**
13a	2-adamantylethyl	C_8F_{17}	**14**
13b	2-adamantylethyl	C_6F_{13}	**14**
15	mappicine	C_8F_{17}	**16**
(R)-**17**	(R)-(+)-2-phenylpropyl	C_8F_{17}	(R)-**18**

a) control (–Si(^{i}Pr)$_3$) with no fluorines

We first examined different cleavage reagents with 95% MeOH/H_2O as the P-phase solvent. In initial experiments (entries 1−6), only the F-phase was stirred. Reasonable yields and P-phase selectivities of 2-(2-naphthylethanol) **2** were obtained with AcOH and CsF (entries 1,2), but the best results were obtained by using H_2SO_4 or H_2SiF_6 in aqueous MeOH. Alcohol **2** was observed only in the P-phase in high yields (entries 3 and 4). Various solvents were examined with H_2SiF_6, and MeOH and DMF were found to be more effective than MeCN (entries 4−6). The reaction was accelerated when each phase was stirred during the reaction process (see the modified U-tube reactor in Figure 2 of the Supporting Information). The desilylation reactions were completed in 18−20 h (rather than 2−4 days) with H_2SO_4 or H_2SiF_6, and **2** was obtained only in the P-phase (entries 3 and 4 vs 7 and 8). This apparatus was adopted for all subsequent experiments.

Next, the effect of the partition coefficient (K_p) values on the reaction was examined by using silyl groups of differing fluorine content (entries 9−12). The reaction of **1b** (Rf = $C_{10}F_{21}$) with a K_p of 2.7 required 6 days to give **2** in quantitative yield (entry 9). However, the long reaction time resulted in back transport,[8] and the final product was distributed in a ratio of 84/16 in the P-

---

(1) Current addresses: (a) Department of Chemistry, Tohoku University, Graduate School of Science, Sendai 980-8578, Japan. (b) University of Southampton, Chemistry Department, Highfield, Southampton SO17 1BJ, U.K.

(2) In contrast, shifting equilibrium by simultaneous removal of small molecule byproducts such as water is common.

(3) (a) Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72. (b) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641.

(4) (a) Curran, D. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1175. (b) Curran, D. P. In *Stimulating Concepts in Chemistry*; Stoddard, F., Reinhoudt, D., Shibasaki, M., Eds.; Wiley-VCH: New York, 2000; p 25. (c) Kitazume, T. *J. Fluorine Chem.* **2000**, *105*, 265. (d) Furin, G. G. *Russ. Chem. Rev.* **2000**, *69*, 491.

(5) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S. Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823.

(6) (a) Curran, D. P. *Synlett*, **2001**, in press. (b) Curran, D. P.; Luo, Z. Y. *J. Am. Chem. Soc.* **1999**, *121*, 9069. (c) Luo, Z. Y.; Zhang, Q. S.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766.

(7) (a) Newcomb, M.; Toner, J. L.; Helgeson, R. C.; Cram, J. D. *J. Am. Chem. Soc.* **1979**, *101*, 4941. (b) For triphasic reactions with one liquid and two solid phases, see: Rebek, J. *Tetrahedron* **1979**, *35*, 723.

10.1021/ja011716c CCC: $20.00

Table 1. Deprotection of the Fluorinated Silyl Ethers Using the Triphasic Reaction System in Eq 1

	substrate	*K*p[a]	reagent[b]	solvent (R-phase)	time	product	yield (%)	product ratio (P-/S-phase)
1	**1a**	0.92	AcOH	MeOH−H_2O[c]	6 d[h]	2	54[d]	96/4
2	**1a**		CsF	MeOH−H_2O[c]	4 d[h]	2	80[e]	>99/1
3	**1a**		H_2SO_4	MeOH−H_2O[c]	4 d[h]	2	92	>99/1
4	**1a**		H_2SiF_6	MeOH	2 d[h]	2	96	>99/1
5	**1a**		H_2SiF_6	DMF	1 d[i]	2	89	>99/1
6	**1a**		H_2SiF_6	MeCN	1 d[i]	2	99	91/9
7	**1a**		H_2SO_4	MeOH−H_2O[c]	18 h[i]	2	97	>99/1
8	**1a**		H_2SiF_6	MeOH	20 h[i]	2	92	>99/1
9	**1b**	2.7	H_2SiF_6	MeOH	6 d[i]	2	>99	84/16
10	**1c**	0.39	H_2SiF_6	MeOH	1.5 d[i]	2	90	86/14
11	**1d**	0.12	H_2SiF_6	MeOH	3 d[i]	2	96	67/33
12	**1e**	0.015	H_2SiF_6	MeOH	7 d[i]	2	97	59/41
13	**(S)-3**	1.5	H_2SiF_6	MeOH	2 d[i]	(S)-4	87	98/2
14	**5**	1.3	H_2SiF_6	MeOH	1.5 d[i]	6	90	>99/1
15	**7**	0.72	H_2SiF_6	MeOH	3 d[i]	8	95	95/5
16	**9**	8.2	H_2SiF_6	MeOH	7 d[i]	10	91	84/16
17	**11**	5.0	H_2SiF_6	MeOH	7 d[i]	12	38[f]	74/26
18	**13a**	5.7	H_2SiF_6	MeOH	7 d[i]	14	>99	91/9
19	**13b**	1.9	H_2SiF_6	MeOH	1.5 d[i]	14	93	96/4
20	**15**	0.11	H_2SO_4	MeOH−H_2O[c]	7 d[i]	16	65[g]	>99/1

[a] The K_P values of substrates were measured between FC-72 and MeOH. [b] The amount of reagents used is as follows: HCl (2 equiv) in entry 1, AcOH (35 equiv) in entry 2, CsF (3 equiv) in entry 3, H_2SO_4 (1 equiv) in entries 4 and 8, H_2SiF_6 (2 equiv) in entries 5−7 and 9−20. [c] The ratio of MeOH/H_2O is 20/1. [d] Compound **1a** was recovered in 36% and 8% yields from the S- and F-phases, respectively. [e] Compound **1a** was recovered in ~10% yield from the F-phase. [f] The reaction was not complete in 7 days, and **11** was recovered in 55% yield from the F-phase. [g] The reaction was carried out at 40 °C. The reaction was not complete in 7 days, and **15** was recovered in 35% yield from the S-phase. [h] Stirring of F-phase only. [i] All three phases stirred; see apparatus in Supporting Information.

Table 2. Purificative Deprotection from the Mixture of Fluorinated and Nonfluorinated Compounds Using the Triphasic Reaction System in Eq 2

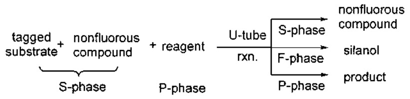
	tagged substrate	nonfluorinated contaminant (equiv)[a]	time	yield (%)	ratio of product (P-/S-phases)
1	**1a**	1-(2-naphthyl)ethanol (0.2)	1 d	**2**, 87	99/1
2	**1a**	1-(2-naphthyl)ethanol (0.4)	1.5 d	**2**, 96	96/4
3	**1a**	1-(2-naphthyl)ethanol (0.6)	3 d	**2**, 97	95/5
4	**1a**	1-(2-naphthyl)ethanol (1.0)	2.5 d	**2**, 96	94/6
5	(S)-**3**	(R)-(+)-1-(2-naphthyl)-ethanol (1.0)	2 d	**4**, 83[b]	41/59 (>97%ee/90%ee)[c]
6	(R)-**17**	(S)-(−)-2-phenylpropanol (1.0)	2 d	**18**, 76[b,d]	39/61 (89%ee/87%ee)[c,d]

[a] The equivalents were based on the tagged substrates. [b] The yields were based on the total amount of both enantiomers in the reaction. [c] The enantiomeric purity of the corresponding alcohols obtained in each phase is shown in parentheses. The ee values were determined by optical rotation. [d] The yields and ee values were determined after conversion of 2-phenylpropanol into the corresponding benzoate.

and S-phases. Reactions of **1c**,**d**, which contain fewer fluorines (C_6F_{13}, C_4F_9) with lower K_p values (0.39, 0.12), also required longer reaction times; this caused an increase in the back transport of product **2** (entries 10,11). The control substrate **1e** bearing no fluorines ($^iC_3H_7$) gave especially poor results (entry 12). These results suggested that the optimal K_p for triphasic deprotection reactions of small organic molecules in U-tubes is roughly 1.

To assay generality, fluorinated silyl ethers derived from various alcohols were examined. The aromatic silyl ethers (S)-**3**, **5**, **7**, and **13b** underwent the triphasic deprotection very smoothly to give (S)-**4**, **6**, **8**, and **14** in 87−95% yields with high P-phase selectivities (entries 13−15,19). The K_p values of (S)-**3**, **5**, **7**, and **13b** were 0.72−1.9. However, the reactions of the aliphatic silyl ethers **9**, **11**, and **13a**, whose K_p values were 5.0−8.2, needed longer reaction times (7 days or more), which resulted in decreased selectivities (entries 16−18).[9] The fluorous silyl ether **15** of the natural product mappicine[6c] underwent desilylation at 40 °C to give free mappicine **16** in 65% yield, although the reaction did not go to completion in 7 days because of the low K_p (0.11) of **15** (entry 20). Mappicine (**16**) is highly insoluble in FC-72, so back transport was not observed.

To show that triphasic reactions can be used to purify products derived from impure reactants, we examined the purificative deprotection of silyl ethers doped with impurities (eq 2). Fluorinated compound **1a** was mixed with various amounts of (rac)-1-(2-naphthyl)ethanol, (rac)-**4**. This mixture was added to the S-phase and subjected to the usual triphasic reaction conditions. The corresponding alcohol **2** was obtained free of 1-(2-naphthyl)ethanol, (rac)-**4** (entries 1−4, in Table 2).



(2)

Purificative deprotections of the chiral silyl ethers ((S)-**3** and (R)-**17**) were examined in the presence of the enantiomerically pure mirror image alcohols using the triphasic reaction system. The deprotection reaction of (S)-**3** (1.0 equiv) proceeded in the presence of (R)-(+)-1-(2-naphthyl)ethanol, (R)-**4** (1.0 equiv), and 1-(2-naphthyl)ethanol, **4**, was obtained in 83% total yield in a ratio with 41/59 in the P-/S-phases (entry 5). The ee values of 1-(2-naphthyl)ethanol obtained were >97% (S) and 90% (R) in the P- and S-phases, respectively. The chiral silyl ether (R)-**17** (1.0 equiv) also underwent the purificative deprotection in the presence of (S)-(−)-2-phenylpropanol (1.0 equiv), (S)-**18**, and 2-phenylpropyl benzoate was obtained in 76% total yield in a 39/61 ratio in P-/S-phases after protection of 2-phenylpropanol with benzoyl chloride. The ee values of 2-phenylpropyl benzoate were 89% (R) and 87% (S) in the P- and S-phases, respectively.

These triphasic reactions use the fluorous tag to allow transportation of the impure tagged substrate from the S-phase through the F-phase to the P-phase where it is detagged to provide the final pure product. The detagging reaction drives the non-equilibrium transport of the product to the P-phase in this intimate coupling of reaction and separation. This class of fluorous triphasic reactions is ideal for use in final detagging of a fluorous substrate in a fluorous synthesis exercise.[5] In addition, enantioselective fluorous tagging of racemic mixtures[10] followed by triphasic detagging provides a new option for resolution of racemates. Many other applications of triphasic reactions can be envisioned. For example, the use of a fluorous reagent or catalyst in the F-phase will allow the transportative coupling of two organic reactants. Finally, the ability to couple triphasic reactions in sequence may ultimately allow for real-time, multistep synthesis/separation processes.

Acknowledgment. We thank the National Institutes of Health for funding this work. We are grateful for the experimental contributions of Dr. Shigeru Wada, who initially developed the fluorous silyl groups.

Supporting Information Available: Detailed experimental procedures for all the data in the Tables along with transport rates, partition coefficients, and a photograph of the apparatus (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA011716C

---

(8) See Supporting Information for control experiments measuring transport rates of nonfluorous compounds.

(9) The reaction of **11** was not completed even after 2 days under the ordinary monophasic conditions, whereas the reaction of **1** was completed in 30 min under the same conditions.

(10) Hungerhoff, B.; Sonnenschein, H.; Theil, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 2492.