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Use of a fluorous bridge for diffusion controlled uptake of molecular chlorine in chlorine addition to alkenes[†]

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Received (in Cambridge, UK) 19th May 2003, Accepted 12th August 2003 First published as an Advance Article on the web 20th August 2003

Fluorous solvent was used for passive transport of molecular chlorine from one side of the U-tube to the other, where addition of chlorine to alkenes was quantitative and diffusion controlled.

The transport of molecules across a boundary is closely connected to their concentration gradient. This is well exploited in nature, while in chemistry membranes are mostly used for this purpose. Sometimes a bulk solvent has been utilized as a membrane and these experiments were usually performed in a U-tube apparatus with a heavier organic phase at the bottom and aqueous phases on both sides.¹ Recently, Curran et al. introduced fluorous triphasic reactions, where a fluorous solvent was used as a liquid membrane for transfer of a purified starting compound and for kinetic resolution of secondary alcohols.^{2,3} In both cases, its use was connected with fluorous synthesis, where one component of reaction is rendered fluorous by incorporating a fluoroalkyl ponytail.⁴ Furthermore, in "phase-vanishing reactions" a fluorous solvent was used for passive transport of a heavier reagent in the lower phase through the fluorous solvent to the upper organic phase and recently also through a U-tube.5,6

Fluorous solvents have a low tendency to undergo van der Waals interactions and because of that, they well solubilize a range of gases.^{7,8} Furthermore, they are chemically inert and non-flammable compounds.⁹ These properties led to their application in reactions with gases,^{4a,10} where particularly oxygen was used.^{8,11} Their use as a bulk membrane for passive transport of a gas to a reaction mixture through a U-tube would be of special interest. A particular advantage of such a system would be its application for reactions with highly reactive and corrosive gases and for exothermic reactions. This brought us to the idea of using it as a transport phase for molecular chlorine, so that this corrosive and very reactive gas would be eliminated from the reaction mixture.

The design of the apparatus enables the use of one side of the U-tube as a storage chamber (Scheme 1, storage phase) and the other side as a reaction chamber. In between would be a



† Electronic supplementary information (ESI) available: experimental. See http://www.rsc.org/suppdata/cc/b3/b305629e/ fluorous phase that would serve for passive transport of gas to the other side. Transport would be reaction driven and in this way the bulk of the chlorine would be separated from the reaction mixture.

The first condition for such a transport reaction is solubility of the reagent in the middle phase. It is well known that organic compounds are insoluble in fluorous solvents, as well as most organic solvents and water. However, there are no data for chlorine available. Therefore, we first tested the solubility of chlorine in three different fluorous solvents: perfluoro-n-octane (FC-77), perfluoro-n-hexane (FC-72) and perfluoro-2-(1-butyl)tetrahydrofuran (FC-75). We put 10 mL of solvent in a Utube; the reaction side was closed, while on the storage side chlorine was introduced under slight pressure. The fluorous phase became yellow, while its volume did not increase. The amount of chlorine in solution was determined iodometrically to be 0.066 mmol mL⁻¹ of FC-77, 0.055 mmol mL⁻¹ of FC-72 and 0.065 mmol mL⁻¹ of FC-75, respectively. Having determined that chlorine is soluble in fluorous phases we checked its solubility in a mixture of solvents. When dichloromethane was added to the yellow solution of chlorine in FC-77, all the gas was immediately transferred to the organic phase, leaving the fluorous phase colourless. The same happened with hexane, methanol and acetonitrile as organic phases. Therefore chlorine is soluble in a fluorous phase although it prefers an organic phase.

Facile fluorous phase transfer of chlorine (gas/liquid, liquid/ liquid) serves as a good basis for further studies on the use of a fluorous phase for passive transport of gas. In the first experiment, a U-tube was charged with perfluorooctane (FC-77), on the reaction side of the tube 1 mL of a 2 M solution of cyclooctene in hexane was added and the tube closed. On the storage side, a chlorine line was connected through a normal glass joint. The pressure of chlorine was controlled by opening of the line and by the level of the two phases. A slight pressure of chlorine was applied and within a few minutes the fluorous phase started to turn yellow. The fluorous phase was stirred at the bottom with a magnetic stirbar in order to facilitate transport of gas through the transport phase, while care had to be taken not to mix the liquid phases. After 2 h reaction, the starting compound was completely consumed and the organic phase started to turn yellow. Chlorine gas was present in the reaction mixture only after the end of the reaction, as could be seen from its colour. The organic phase was then taken out, washed with a diluted solution of NaHSO₃, a saturated solution of NaHCO₃ and dried. NMR analysis of the reaction mixture revealed that only trans-1,2-dichlorocyclooctane was formed. After flash chromatography on silica gel with hexane, dichlorocyclooctane was isolated in 90% yield (Table 1).

As the fluorous phase is immiscible with the majority of organic solvents, we tested this chlorination method in various solvents. As may be seen from Table 1, different non-polar and polar organic solvents were successfully used and dichloro product **2a** was isolated in very good yields. A special case was the nucleophilic solvent methanol, where besides **2a** (58%) different products were formed, that could not be isolated. On the other hand, in a mixture of "light" fluorous solvents— 2,2,2-trifluoroethanol and benzotrifluoride—chlorination was

DOI: 10.1039/b305629e

not selective. For liquid alkenes there is no need to have a solvent present in the reaction mixture. By this method, chlorination could be solventless, yet the dichloro adduct is still selectively formed.

The reactions were performed in chloroform as the phases were better separated (Table 2). With all tested alkenes chlorination was quantitative and only dichloro adducts were detected and isolated by flash chromatography on silica gel. Cyclooctene and cyclohexene gave *trans*-1,2-dichloro derivatives. Styrene was also completely converted to the dichlorinated product, while traces of an eliminated compound were detected after isolation on column chromatography. Similar results were observed in reaction with β -methylstyrene and 1,2-dihydronaphthalene. Chlorination also works well with

Table 1 Chlorination of cyclooctene in a U-tube

 Solvent	React. time ^a /h	Yield ^b (%)	
Hexane	2	90	
CHCl ₃	2	91	
CH ₃ CN	2	89	
DMF	1	84	
TFE/BTF (2:1)	3	50^{c}	
MeOH	2	58^d	
none	2	88	

^{*a*} U-tube charged with 6 mL FC-77, a solution of 2 mmol of **1a** in 1 mL of solvent was added and stirred gently at room temperature. ^{*b*} Isolated yield after flash chromatography. ^{*c*} A complex reaction mixture was obtained with 50% of product **2a** as determined from NMR spectra. ^{*d*} The rest was a mixture of products.

Table 2 Chlorine addition to alkenes with a fluorous bridge system

	Alkene	Time ^a / h	Product	Yield ^b (%)
1		2	CI CI	90
2	\bigcirc	2	CI	82
3	$\bigcirc \neg$	1		98 ^c
4	\bigcirc	2		94 (1/1) ^d
5	$\bigcirc\bigcirc\bigcirc$	1.5	CI CI	93 (3 : 1) ^d
6		1.5		97
7	$\checkmark \sim \sim \sim$	1		88
8	Ph COOEt	2		74 (1/1) ^d

^{*a*} U-tube charged with 6 mL FC-77, a solution of 2 mmol of alkene in 1 mL of CHCl₃ was added and stirred gently at room temperature. ^{*b*} Isolated yield after flash chromatography. ^{*c*} Product contained 15% of 1,2,2-trichloro-1-phenylethane. ^{*d*} syn/anti ratio determined by NMR spectroscopy and compared to literature values.

aliphatic olefins (*trans*-4-octene), as well as with terminal ones (1-octene). Even a deactivated alkene like the ethyl ester of cinnamic acid was quantitatively chlorinated.

In conclusion, fluorous transportive chlorination in a U-tube could offer many advantages in direct chlorination reactions with molecular chlorine, namely: the reaction phase is separated from the bulk of the reagent, which is of special interest with reactive, dangerous and highly corrosive compounds like molecular chlorine; transport of chlorine through the fluorous phase is slow and this slow uptake of reagent is very important with reactive reagents and exothermic reactions; in terms of "green" chemistry¹² a solventless reaction phase is possible and the fluorous solvent is completely recovered and reused.

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