ChemPubSoc Europe

DOI: 10.1002/cplu.201200267

Direct Fluorination of Cyclic Carbonates and *closo*-$K_2[B_{12}H_{12}]$ in a Slug-Flow Ministructured Reactor

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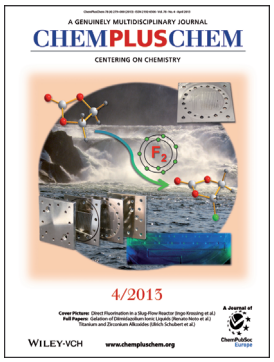
A novel minireactor for direct fluorination of organic and inorganic substances was tested. The reactor consists of nickel-coated copper blocks with mechanically machined 1 mm channels and is equipped with an active cooling system. The direct fluorination of ethylene carbonate and propylene carbonate is described. For the fluorinated propylene carbonate, the NMR data of various fluorinated isomers were determined. The Gibbs reaction energies for the direct fluorination of ethylene and propylene carbonate were calculated at the reliable G3 level of theory. The excellent decomposition stability of the cyclic carbonates against high fluorine and HF concentrations also qualifies them as good solvents for direct fluorination processes, especially for ionic substrates. In this respect, the direct fluorination of the inorganic salt *closo*-$K_2[B_{12}H_{12}]$ in cyclic carbonates is presented.

Introduction

Special applications often require the bonding of fluorine atoms in specific positions into a target molecule.[1] Fluorine, with its very high electronegativity and very stable bonds, offers a multitude of possibilities for application in chemical industrial processes. For example, fluorination is employed to vary the lipophilicity in pharmaceutical products. Today, ten of the 30 top-selling pharmaceutical products contain at least one fluorine atom.[2,3] Other examples are the enhancement of the polarity of liquid crystals for LCDs,[4] the weakly coordinating anions[5] or the fine tuning of the electrochemical stability of solvents for lithium-ion batteries such as in (fluorinated) ethylene carbonate.[6]



COVER

In order to perform fluorination of organic compounds, expensive reagents, such as DAST, Selectfluor, or the Ruppert–Prakash reagent are used.[7] Another commonly applied method is electrofluorination, which works well for perfluorination but is rather limited in terms of selectivity and the tolerance of functional groups.[8–10] After the initial work by Adcock and Lagow[11] and Rozen,[12] direct fluorination using F_2 became a real alternative and several groups successfully demonstrated its application.[13,14] Nevertheless there are two main difficulties that are commonly encountered when working with fluorine:

1) The strongly exothermic character of the reactions: for example, $CH_4 + F_2 \rightarrow CH_3F + HF$ ($\Delta_r H \approx -430\ kJ\,mol^{-1}$). A single substitution already provides enough energy to cleave a C–C bond in the molecule, which usually has a bond energy of 351–368 $kJ\,mol^{-1}$.[14] The fast rate of the direct fluorination reaction often leads to local hot spots or even explosions,[15] which is problematic with respect to selectivity and degradation reactions, not to mention operational safety. To overcome this, very fast energy transport and efficient temperature control is essential.
2) The second challenge is the toxicity of fluorine. A leak can lead to a release of highly toxic fluorine or hydrogen fluoride gases. Thus, a minimization of hazardous reagents would be desirable, given that the overall product yield is still acceptable.

One elegant possibility to handle the problems of elemental fluorine is the use of microstructured reactors. These reactors, having reaction channels less than 1 mm in diameter, were

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cplu.201200267. It contains details of the enthalpy/Gibbs free energy calculation carried out at the G3 Level; the calorimetric calculations; mass spectra of nonvolatile material after fluorination of toluene; selected NMR spectra; flow characterization results; picture of bubbles at the product outlet and graphs showing the values listed in Table 4.

used successfully for a variety of liquid organic chemical reactions since the late 1990s.[16–21] Their high surface to volume ratio provides very fast heat transfer, which is necessary to remove the high thermal energy released during the direct fluorination of a substance.[22–26] In addition, the small channels guarantee fast mixing in two-phase systems.[27] The risks of working with fluorine are minimized because of the reduced volumes.

Despite of these advantages, so far very few research groups have developed microreactors for direct fluorinations. Chambers, Sandford and co-workers developed channel and falling film reactors and used them for various selective direct fluorinations. Their reactors are based on nickel or stainless steel, and are to date the only broadly tested microreactor systems for direct fluorination. They obtained very good results for the selective direct fluorination of organic compounds such as β-ketoesters,[28] aromatic systems,[29] and ethers.[30] Jähnisch et al.[31] developed a falling film micro reactor for direct fluorination and Jensen and co-workers[32] invented a silicon-based microreactor. The channel widths were between 500–250 μm. Both groups tested their reactors with toluene in solvents like acetonitrile as their only substrate.

Herein, the direct fluorination of ethylene carbonate, propylene carbonate, and *closo*-$K_2[B_{12}H_{12}]$, using ministructured reactors is described. With channel diameters of 1 mm, this minireactor represents a proof-of-concept stepping stone toward the future goal of true microreactors.

Choice of substrates

A summary of the investigated reactions is shown in Figure 1. The main substrates are the two cyclic carbonates (reactions A and B) and *closo*-$K_2[B_{12}H_{12}]$ (reaction C). Nevertheless, we also include a short critical comment on the direct fluorination of toluene.

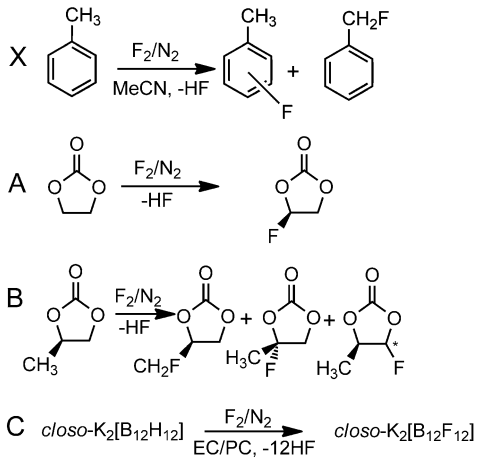


Figure 1. Summary of the investigated direct fluorination reactions with partly idealized outcome: (X) toluene; (A) ethylene carbonate; (B) propylene carbonate; (C) *closo*-$K_2[B_{12}H_{12}]$.

Toluene

In the literature the direct fluorination of toluene in acetonitrile was carried out in microreactors and is the most often described model system. Besides the main products, de Mas et al.[33] and Jähnisch et al.[31] already reported on the formation of high molecular side products.

Ethylene carbonate (EC)

The substitution of one of the four symmetry-equivalent hydrogen atoms in EC leads to a single possible product. Double fluorination only leads to three new products. Its structures are very stable against fluorine and a HF concerning fragmentation. Fluorine concentrations of 30% during direct fluorination without solvent are standard in classical batch reactions.[15,34,35] In addition, monofluorinated ethylene carbonate (F_1-EC) is used commercially as solvent additive in lithium-ion batteries and is produced on a scale of a few tons per year, which would be in the desired range for commercial production of mini- or microreactors. Because pure ethylene carbonate has a melting point of 36 °C, heating or a solvent is necessary. As solvent the product F_1-EC was used; please compare with reference [34]. Its melting point of 17 °C allowed experiments at room temperature.

Propylene carbonate (PC)

By having an additional methyl group compared with ethylene carbonate, the number of possible monofluorinated isomers increases to four. Thus, the regioselectivity of the direct fluorination can be determined. Propylene carbonate, like ethylene carbonate, is remarkably stable against fluorine or hydrogen fluoride, and is a liquid with a melting point of −55 °C. These factors permitted experiments without solvent and at lower temperatures. To the best of our knowledge only one group has published a direct fluorination of propylene carbonate: Nanbu et al. published a batch reaction, but did not give any details on yield or optimization.[36] However, they investigated the influence of the monofluorination on relative permittivity, density, refractive index, and dynamic viscosity. As a conclusion they expect the monofluorinated propylene carbonate to form better conducting salt solutions than nonfluorinated propylene carbonate.

closo-$K_2[B_{12}H_{12}]^{2-}$

To our knowledge, no ionic substances and no boron clusters have thus far been investigated for direct fluorination in mini/microreactors. However, Strauss and co-workers published a batch method for the direct fluorination of *closo*-$K_2[B_{12}H_{12}]$ to give $K_2[B_{12}F_{12}]$.[37] The substrate salt $K_2[B_{12}F_{12}]$ and the products are soluble in acetonitrile, which is helpful for fluorination in mini/microstructured reactors. Moreover, similar related batch reactions were reported to be susceptible to complete degradation and formation of the thermodynamic sinks BF_3 gas and $[BF_4]^-$.[37] Because the halogenated dodecaborates can be used

to stabilize for example, reactive cations or electrolyte salts in lithium-ion batteries,[38] it appeared interesting to investigate the fluorination of such an inorganic substrate in our minireactor system.

Results and Discussion

Methods and Materials

Reactor

The reactor construction and design was performed in the group of P. Woias and co-workers. Full details on the reactor design and construction were published elsewhere.[39,40]

It was constructed from four nickel-coated (10–20 μm) copper blocks. All channels and holes were conventionally machined. The meandered channels measure 1×1 mm in their profile and have 90° corners. A top view of the channels is shown in Figures 2 and 3. The reactor was designed for slug

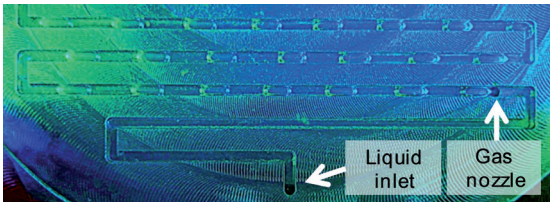


Figure 2. Picture of a nitrogen and 2-propanol slug flow for flow characterization, showing the meandered channels, the liquid inlet, and the gas nozzle.

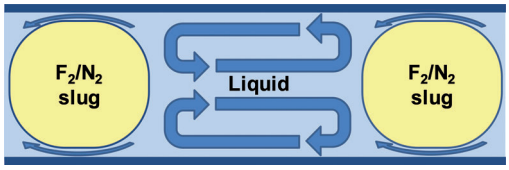


Figure 3. Scheme showing the flows within a gas liquid slug flow system.

flow. The flow parameters, like slug flow length, velocities, frequencies, and bubble surfaces were measured in experiments using nitrogen and 2-propanol.[42] A picture of the experimental setup and representative slugs are shown in Figure 2 and 4. The ranges of the slug flow regime were tested between 5 and 400 mL h^{-1} liquid and gas flow (see Figure 2 and appendix 3 in the Supporting Information). Below 25 mL h^{-1} liquid flows at a gas flow rate of 400 mL h^{-1}, and the slug flow regime changes to an annular type flow. By changes to the liquid flow the bubble length could be varied between 2 and 32 mm.

Slug flow was chosen, because we expected a higher fluorine conversion rate in comparison with annular flows. In addition, a current within the liquid slug is induced, which should improve the exchange of substrate molecules at the phase boundaries (Figure 4).[41] This current would lead to an improved heat control and a reduced probability of multiple fluorination on one molecule within a very short time. An immediate second fluorination of an already fluorinated molecule would lead to a strongly increased risk of decomposition.

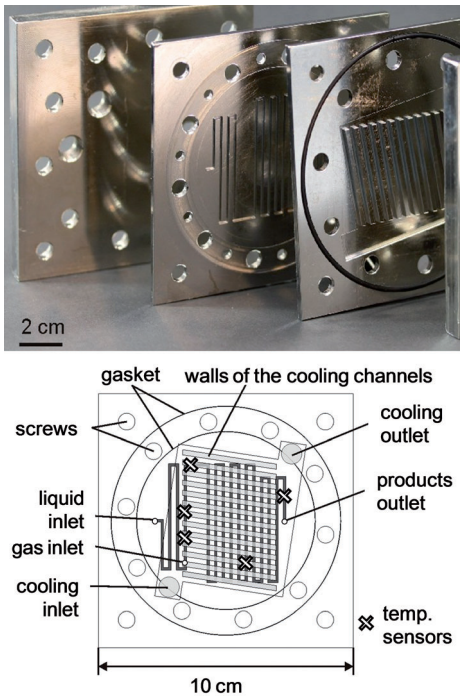


Figure 4. Above: The minireactor before being assembled. Below: Construction scheme of the minireactor.

A potent heat sink was included and optimized for a maximum cooling at the point of the gas inlet. Five T-type thermocouple sensors were placed inside the reactor block at a distance of 1 mm from the reaction channels themselves. They were placed 1, 2, 4, 29, and 53 cm behind the gas inlet. The minireactor had a reaction channel length of 53.7 cm from the junction of the gas inlet and the main reaction channel. The channel length before the gas inlet was 6.6 cm. Figure 3 shows the reactor before assembly.

Fluorine delivery system

A 5 L cylinder of fluorine (99.98%; Solvay Fluor GmbH) was used as a fluorine source. It was diluted to desired concentrations by 99.996% nitrogen. All piping was constructed from monel or perfluoroalkoxy polymer tubes. All connectors were made from monel (Swagelok). To measure the fluorine pressure, a fluorine compatible sensor (MKS Baratron) was used. The flow and the dilution of the gases were controlled by two mass flow meters (MKS M330). For mixing the nitrogen and the fluorine stream, a monel T-shaped connector was used. Before use, the system was carefully leak tested and passivated for several hours using a gradually increasing fluorine concentration, up to 100%.

Liquid delivery system

A Masterflex 7730-00 peristaltic pump with 4 mm outer diameter PFA (perfluoroalcoxy polymer) tubing and six rollers was

used to realize a cyclic system for the minireactor. The effluent was repeatedly recycled back into the reactor after separating the liquid from the remaining gaseous hydrogen fluoride and nitrogen. A self-constructed small pulsation dampener was placed between pump and the reactor inlet. For the toluene experiments a syringe pump was used. However, this noncyclic system yielded low conversions for the fluorination of toluene.

Fluorination of toluene

It was possible to obtain monofluorinated toluene compounds by direct fluorination of toluene in acetonitrile. With regard to selectivity, the results were similar to those published by de Mas et al. (Table 1), who used a microreactor with channel diameter of less than 500 μm.

Table 1. Relative ratios of the four possible monofluorinated toluene compounds. $T = 0\,^{\circ}C$, 12.5 vol% toluene in acetonitrile, liquid flow = 90 mL h^{-1}, gas flow = 480 mL h^{-1}, 25 vol% fluorine.[36]

	Fluorination position			
	ortho	*meta*	*para*	methyl
this study	3.4	1.0	2.0	0.9
Jensen et al.[36]	3.7	1.0	2.1	–

A deeper investigation of this system was not carried out, because of difficulties, which were occurring when toluene and acetonitrile were fluorinated. Both substances tended to form solid organic material, leading to a clogging of the reactor, after 1–3 hours of use. A mass spectrometry analysis (EI, 200 °C, 70 eV, 500 μA) of the dark organic material collected inside the reactor showed masses up to 532 *m/z* (see the Supporting Information). Evident were masses that indicated the formation of toluene di- and trimers. This is an indicative for the formation of less soluble or even solid toluene oligomers. The formation of such low-solubility materials, which led to blockages inside the reactor, makes the fluorination of toluene a difficult reaction for direct fluorination in microreactors and we recommend using other substrates for testing purposes.

Fluorination of ethylene carbonate

Some of the preliminary ethylene carbonate fluorination results were already included with the more technical article on the minireactor design by Lang et al.[39] The conversion (*C*) the yield (*Y*) and the selectivity (*S*) with respect to the formation of monofluorinated ethylene carbonate (F_1EC) are described by Equations (1)–(6).

$$C = \frac{n_{EC_0} - n_{EC_r}}{n_{EC_0}} \times 100 \quad (1)$$

$$Y = \frac{n_{F_1EC_r} - n_{F_1EC_0}}{n_{EC_0}} \times 100 \quad (2)$$

$$S = \frac{n_{F_1EC_r} - n_{F_1EC_0}}{n_{EC_0} - n_{EC_r}} \times 100 \quad (3)$$

$$\text{Space} - \text{TimeYield} = \frac{n_{F_1EC_r} - n_{F_1EC_o}}{V_{\text{reactionchannel}}} \times 100 \quad (4)$$

$$YF_2 = \frac{n_{trans F_2EC} + n_{cis F_2EC} + n_{4,4F_2EC}}{n_{F_2}} \times 100 \quad (5)$$

$$CF_2 = \frac{n_{F_1EC_r} + n_{trans F_2EC} + n_{cis F_2EC} + n_{4,4F_2EC}}{n_{F_2}} \times 100 \quad (6)$$

In Equations (1)–(6) n_{EC0} is the molar amount of ethylene carbonate before the reaction, n_{ECr} the amount after the reaction, meanwhile n_{F1EC0} is the amount of F_1EC added as solvent and n_{F1ECr} is the amount of F_1EC found in the product mixture. See Figure 5 for the structure of possible twice fluorinated ethylene carbonated isomers (F_2EC).

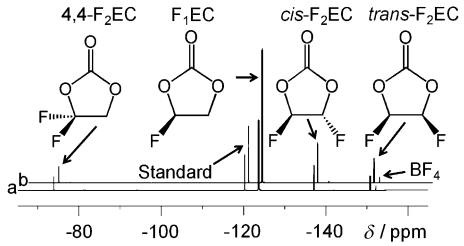


Figure 5. Two ^{19}F NMR spectra of EC after the fluorination reaction. Conditions: F_1EC (30 wt%) as solvent. Spectrum (a) 0.5 equiv F_2, $T = 22\,^{\circ}C$, liquid flow = 2.5 mL min^{-1} gas flow = 6.6 mL min^{-1}, 45 vol% F_2. Spectrum (b) 0.5 equiv F_2, $T = 22\,^{\circ}C$, liquid flow = 2.5 mL min^{-1}, gas flow = 3.4 mL min^{-1}, 88 vol% F_2, minireactor. The $[BF_4]^-$ signal is formed from residual HF.

Our aim at fluorinating ethylene carbonate (reaction A in Figure 1) was to achieve a high yield of the commercially interesting F_1EC. Therefore, a high conversion and a limited generation of difluorinated ethylene carbonates were desirable. To reach the desired high conversion, the fluorine should react completely with ethylene carbonate without causing fragmentation. As ethylene carbonate is a solid at room temperature, liquid monofluorinated ethylene carbonate was added as a solvent.[34] Adding the product as the solvent has the advantage of reducing the number of possible active reagents and allows for a straightforward separation of the products. However, the selectivity with respect to doubly fluorinated products (F_2EC) is lowered, yet all concentrations of F_1EC below 25 wt% led to crystallization of ethylene carbonate at room temperature. In our experimental setup the PFA tubing could not be heated and thus we had to tolerate this relatively high content of F_1EC and the consequent losses in selectivity. It can certainly be improved by using a heated tubing system.

In all fluorination experiments, ethylene carbonate was shown to be robust with respect to decomposition. Other than the expected difluorinated isomers, only a very small amount of side products, below 2 mol% with respect to the monofluorinated ethylene carbonate, were observed. In Figure 5 two ^{19}F spectra of direct fluorinations using 45 and 88% fluorine are shown. Even with such harsh reaction conditions, good results were obtained.

Table 2. Results of the direct fluorination of ethylene carbonate. Entry 6: laboratory batch experiment of Kobayashi et al.;[4] entry 7: patented batch reaction by Solvay Fluor;[1] entry 8: patented batch reaction by Ulsan Glas.[20]

Entry	*t* [h]	Flow of F_2 [mL min^{-1}]	Flow of N_2 [mL min^{-1}]	*T* [°C]	*C* [%]	*Y* [%]	*S* [%]	Space-time *Y*[a] [mol m^{-3} h^{-1}]	*Y* of F_2 [%]	*C* of F_2 [%]	*Y* of F_2EC [%] (*trans*/*cis*/4,4-F_1EC)	Relative ratios *trans*/*cis*/4,4-F_1EC
1	4.0	3.0	3.6	22	80	49	59	6348	52	74	20.9 (11.4:6.7:2.8)	4.0:2.4:1.0
2	1.8	3.0	3.6	22	45	32	70	10585	76	83	6.1 (3.1:2.1:0.9)	3.5:2.4:1.0
3	3.3	3.0	3.6	40	68	46	68	8174	59	77	15.5 (8.6:4.8:2.1)	4.0:2.3:1.0
4	3.1	3.0	3.6	22	69	39	58	8173	57	79	14.2 (7.5:4.6:1.9)	3.8:2.4:1.0
5	2.0	3.0	0.1	22	47	31	66	9706	80	82	5.1 (2.5:1.9:0.7)	3.5:2.6:1.0
6	41	105	245	50	–	70	–	102	39	–	75 (59:11:5)[b]	11.8:2.2:1.0[b]
7	–	–	–	35	–	64	–	–	69	–	–	–
8	5.3	6533	26133	55	–	76	93	–	57	61	–	–

[a] Calculated by using the volume of the reaction containing segment (tube volume, flask volume). [b] Separate reaction, started from pure F_1EC. *C* = conversion, *S* = selectivity, *Y* = yield.

In Table 2, the results of our direct fluorination experiments (entries 1–5) and those from the literature (entries 6–8) are collected. Entries 1 and 2 show sets of results at different conversion levels. The selectivity for F_1EC was, as expected, reduced at higher conversion and owing to the formation of doubly fluorinated species. The yield increased up to a maximum of 49%, which is lower than already known methods, but this low value is also caused by the use of F_1EC as a solvent. The conversion with respect to the use of fluorine is very good, and values of around 74 to 80% were achieved. Entries 3 and 4 compare experiments at 22 and 40 °C, respectively: In this case the conversion remained constant, and a rise of the temperature seemed to be advantageous. Entry 5 shows an experiment using slightly diluted F_2. The results of this experiment were only slightly inferior to those obtained when using diluted fluorine. This outcome demonstrates the robustness of EC as well as the reactor system. The results of three more classical approaches by the groups of Woo,[15] Böse,[34] and Kobayashi[35] are also included with Table 2 as entries 6–8. All three are batch reactions, in which diluted fluorine was bubbled through pure EC or EC diluted with F_1EC.[15,34,35] Our resulting yields with respect to fluorine use are comparable to those of Woo and Böse, both of which were patented as optimized processes. Meanwhile Kobayashi et al. employed a relatively simple lab approach using a PFA vessel (Table 2, entry 6). Here our method is clearly superior regarding the fluorine use. The conversion of valuable fluorine with a fluorine use of up to 80%, while using a significantly higher fluorine concentration at the same time is certainly the main advantage of exploiting the ministructured reactor. On the other hand our yield with respect to the formation of F_1EC is relatively low. This value is largely influenced by use of F_1EC, which was needed as solvent.

For an overall evaluation the space-time yield was calculated. The values of our system included with Table 2 are typical for microreactors (e.g. compared to Jähnisch et al.[31]), and range from 6300 to 10500 mol m^{-3} h^{-1}, which is two orders of magnitude higher than the laboratory batch approach of Kobayashi et al.[35] However, this value was only calculated for the active reaction volume. It certainly is reduced, when the walls of the reaction volume are taken into account. Nevertheless, for better comparability this value was chosen.

The relative ratios of the doubly fluorinated ethylene carbonate isomers were constant through all of our experiments. However, they differ strongly from the results Kobayashi et al.[35] obtained when fluorinating pure F_1EC. This difference indicates a reduced kinetic influence, which could be caused either by an increased temperature (unlikely) or by a faster mixing of the biphasic gas-liquid reaction (likely).

For a better understanding of the reaction, the underlying thermochemistry of the reaction was calculated using the reliable Gaussian 3 (G3) compound method as the level of theory.[42,43] The results of these calculations are shown in Figure 6. There is no obvious trend of the $\Delta_r G^\circ$ values going from monofluorination (−468 kJ mol^{-1}) to perfluorination (−508 kJ mol^{-1}) of ethylene carbonates. Especially high values were calculated for the monofluorination and when a fluorine atom was added to a carbon center already bearing a fluorine atom. If comparing the difluorinated isomers, the 4,4-difluoroethylene carbonate (4,4-F_2EC) is the energetically most preferred isomer, which contrasts with the experimental results. This finding shows that the reaction is still kinetically con-

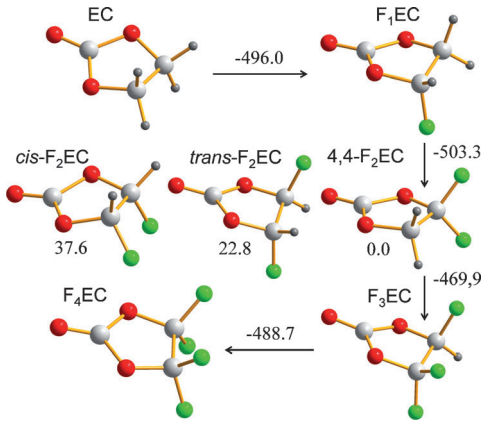


Figure 6. $\Delta_r G^\circ$ [kJ mol^{-1}] values for the direct fluorination of ethylene carbonate ($CO_3H_nF_m + F_2 \rightarrow CO_3H_{n-1}F_{n+1} + HF$). For the *cis*-$F_2$EC and the trans-$F_2$EC the relative energies are compared to the global minimum 4,4-F_2EC. Calculations were carried out with the Gaussian 3 compound method.

trolled. However, as expected for the efficient heat dissipation in our minireactor system, our results are already closer to the thermodynamic product than those in the batch experiment by Kobayashi et al., that is the amount of 4,4-F_2EC is much higher in our experiments than that in reference [35] (see Table 2).

For some of the direct fluorination experiments of ethylene carbonate, the reactor temperatures were measured by using the embedded temperature sensors. These experiments demonstrated the excellent temperature control enabled by the active cooling. No difference in temperature between the five sensors could be detected when the cooling was active. Experiments performed without active cooling and the reactor being placed in a Styrofoam box, yielded nearly adiabatic conditions and the reproducible measurement of an independent temperature at five sensor positions. Even though the sensors are placed only 1 mm vertically above the reaction channel, the thermal conductivity of the reactor copper block blurred the differences within 0.25 °C. Still, according to the temperature profile shown in Figure 7, the reaction mainly takes place within the first four centimeters of the reactor. For the temperature increase measured for the reactor block, liquid and air within the box during the reaction was equal to an uptake of 105% of the energy expected for full fluorine conversion, as calculated by using the temperature difference and the tabulated heat capacities of the reactor materials (see the Supporting Information for details). The energy release measured is thus within the uncertainty of the calculation and the experiment, thus indicating an almost complete reaction. Therefore, the system could be used in an optimized manner to experimentally determine the reaction enthalpies of direct fluorination processes.

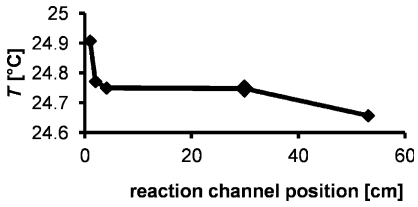


Figure 7. Temperature profile of the direct fluorination of EC in acetonitrile without active cooling, liquid flow = 0.67 mL min^{-1}, gas flow = 6 mL min^{-1}, 33 vol% F_2, minireactor.

Fluorination of propylene carbonate

The direct fluorination of propylene carbonate (PC) allowed the use of a broader range of temperatures because of its much lower melting point compared with that of ethylene carbonate, without the need of a solvent. No approach for the direct fluorination of PC has been published so far. Known syntheses are the reaction of epifluorhydrin plus CO_2 or fluoropropandiol plus carbonic acid dimethyl ester. Also substitution reactions are possible. For propylene carbonate the number of isomers is larger than for ethylene carbonate. There are four

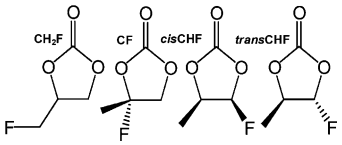


Figure 8. The four possible monofluorinated propylene carbonate products. CFH_2 = 4-fluoromethyl-1,3-dioxolan-2-one, CF = 4-fluoro-4-methyl-1,3-dioxolan-2-one, *trans*CHF = 4-*trans*-fluoro-5-methyl-1,3-dioxolan-2-one, *cis*CHF = 4-*cis*-fluoro-5-methyl-1,3-dioxolan-2-one.

monofluorinated isomers (F_1PC, Figure 8) and a large amount of polyfluorinated compounds. To decrease the amount of polyfluorinated products, only 0.44 equivalents of fluorine was used in most experiments.

Eight experiments were investigated in a simple 2^3 factorial design of experiment (DOE) approach, using temperatures of −10 and +40 °C and nitrogen and fluorine flows of 2 and 4 mL min^{-1}. The results are shown in Tables 3 and 4, and the formulas for conversion, yield, and selectivity are given in the Equations (7)–(9). Where n_{PC0} is the initial PC amount and n_{PCr} the amount after the reaction.

$$C = \frac{n_{PC_0} + n_{PC_r}}{n_{PC_0}} \times 100 \quad (7)$$

$$Y = \frac{n_{CH_2FFPC} + n_{CHFF_1PC} + n_{cisCHFF_1PC} + n_{transCHFF_1PC}}{n_{PC_0}} \times 100 \quad (8)$$

$$S = \frac{n_{F_1PC}}{n_{PC_0} - n_{PC_r}} \times 100 \quad (9)$$

Unexpectedly the conversion and the yield did not show any significant changes when the fluorine concentration was varied between 33 and 66% and the total gas flow between 4 and 8 mL min^{-1}. This stability of the system with respect to the fluorine concentration was unexpected. To see how far this can be pushed, a reaction using 100% fluorine was performed (Table 3, entry 9). In this case the lowest yield of all experiments was obtained. This indicates at least a small relation between the fluorine concentration and the yield. When the reaction was run with 100% fluorine and the nitrogen gas flow switched off, some small gas bubbles were still observed in the product stream (see the Supporting Information). This might be a sign for some decomposition of the propylene carbonate. In contrast with the fluorine concentration and the total gas flow, lowering the temperature showed a small effect: the yield and conversion both were slightly improved.

Isomer distribution

In all experiments, at a conversion of around 30% (Table 4), the relative abundance of the four possible isomers did not change. The distribution of the fluorinated isomers showed the methyl group to be mainly fluorinated, next favored was fluorination at the tertiary carbon atom, even though it has just one hydrogen atom and it is sterically shielded by the methyl group. The secondary carbon's hydrogen atoms are the least favored. Here the *cis* isomer was fluorinated slightly more

Table 3. Results of an eight experiments matrix of the direct fluorination of propylene carbonate. The N_2 flow and the F_2 flow were set to 2 and 4 mL min^{-1} and the temperature to −10 and 40 °C. PC (3.75 g, 36.7 mmol) and F_2 (0.44 equiv) were added in each experiment. The reaction time was 180 minutes for a F_2 flow of 2.0 and 90 minutes for a flow 4.0 mL min^{-1}.

Entry	T [°C]	Flow of F_2 [mL min^{-1}]	Flow of N_2 [mL min^{-1}]	C [%]	Y [%]	S [%]	CH_2F/*cis*CHF/*trans*CHF/CH [%][a]
1	−10	4.0	2.0	32	23	72	32:21:19:27
2	40	2.0	2.0	26	19	72	31:22:20:27
3	−10	2.0	4.0	33	26	77	32:21:19:27
4	40	4.0	4.0	26	21	80	31:21:20:27
5	40	4.0	2.0	26	20	79	31:21:21:27
6	−10	2.0	2.0	30	22	73	32:21:19:28
7	−10	4.0	4.0	29	22	75	32:21:19:28
8	40	2.0	4.0	29	20	68	31:22:20:28
9[b]	−10	4.0	0.0	24	17	71	32:21:19:27

[a] Relative abundance, normalized by the number of hydrogen atoms at the position of propylene carbonate and to a total sum of 100%. [b] Experiment with undiluted fluorine. Not part of the eight DOE experiments.

Table 4. Influence of the temperature and the gas flows of F_2 and N_2 on conversion yield and selectivity based on the experiments shown in Table 4. Each value is the average result of the four experiments with the same +/— parameter for each to the three variables.

	+/−[a]	T −10/+40 °C	F_2 flow 2/4 mL min^{-1}	N_2 flow 2/4 mL min^{-1}
C [%]	−	31	29	29
C [%]	+	27	29	29
Y [%]	−	23	21	21
Y [%]	+	20	22	22
S [%]	−	74	73	74
S [%]	+	75	76	75

[a] − = minimum value, + = maximum value.

often. Figure 9 shows the NMR distributions of the F_1PC isomers in the mixture after quenching the HF. They are plotted against different equivalents of fluorine used in the fluorination reaction. The increase in F_1PC concentration lowers with increasing amount of fluorine used because of the formation of doubly fluorinated propylene carbonates. The amounts of CF-F_1PC as well as the two CHF-F_1PC isomers were found to reach around 7% concentration at most. For those isomers a more conventional synthesis should be developed. The concentration for CH_2F-F_1PC was found to reach around 24% at best; it seems to be the most easily accessible isomer by direct fluorination.

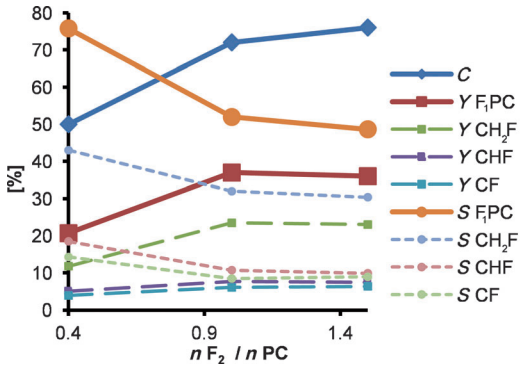


Figure 9. Conversion plus yield and selectivity of the F_1PC isomers (sum and individual) plotted against equivalents fluorine used. Values after quenching the HF. T = −20 °C, 240 mL h^{-1} F_2, 240 mL h^{-1} N_2, 150 mL h^{-1} PC. C = conversion, Y = yield, S = selectivity.

Quantum chemical calculations using the Gaussian 3 method (Figure 10) revealed CF-F_1PC to be the thermodynamically preferred monofluorinated propylene carbonate isomer.

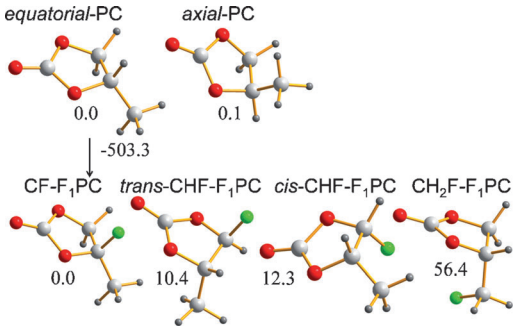


Figure 10. $\Delta_r G°$ [kJ mol^{-1}] values for the direct monofluorination of propylene carbonate ($CO_3H_6 + F_2 \rightarrow CO_3H_5F + HF$). The energy difference for the axial and equatorial propylene carbonate are also shown, as well as the relative energies of the F_1PC isomers with respect to the minimum isomer CF-F_1PC. Calculations were carried out with the Gaussian 3 compound method.

This thermodynamic stability of the CF-F_1PC isomer can be an explanation of why this position was preferred over fluorination at the CH_2 position, even though this position is sterically shielded by the methyl group. On the other hand, the fluorination of the kinetically most accessible methyl group was computed to be thermodynamically the least favored, less stable by 56 kJ mol^{-1} if compared with CH-F1PC. Nevertheless it was the major product isomer found experimentally and clearly shows that the reaction carried out in the minireactor is also controlled by kinetics and not by thermodynamics.

Fluorination of *closo*-$K_2[B_{12}H_{12}]$

After showing good fluorination stability of the cyclic carbonates (EC and PC), their performance to act as highly polar solvents with $\varepsilon_r = 98$ (EC)[44] and 64 (PC)[45] for direct fluorination of ionic substrates was tested with the salt *closo*-$K_2[B_{12}H_{12}]$. To date few results on the direct fluorination of inorganic substances in mini/microreactors has been published. As a test, the salt *closo*-$K_2[B_{12}H_{12}]$ was almost completely dissolved to a formal concentration of 2.5 wt% in a mixture of EC/PC (4:1; a light clouding of the liquid remained). The finely suspended nondissolved salt went into solution within the first 30 minutes of the reaction. In Figure 11 the ^{19}F NMR spectrum of the reaction mixture after quenching the hydrogen fluoride is shown.

The yield of the perfluorinated material was determined by NMR analysis and found to be 58%, with only 12% of polyfluorinated material remaining. The main side reactions that occurred were the formation of $[BF_4]^-$ and BF_3. Strauss and co-

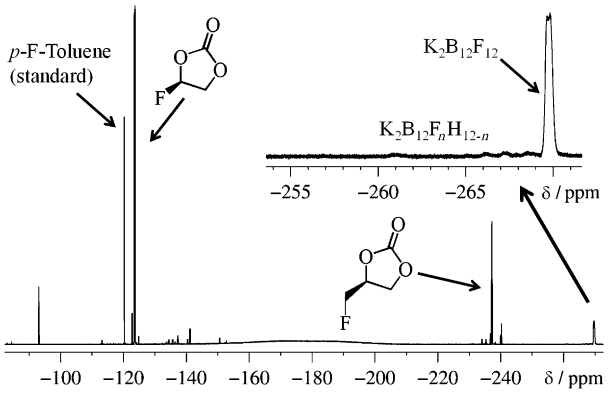


Figure 11. ^{19}F NMR spectrum of the $K_2[B_{12}H_{12}]$ after the reaction. Conditions: 2.5 wt% in a mixture of EC/PC (3.3:1), $T = 20\,^{\circ}C$, liquid flow 5 mL min^{-1}, gas flow 6.6 mL min^{-1}, 30% F_2.

workers reported an yield of 74%[37] for the isolated product by using a classical batch approach with acetonitrile as solvent. In their approach, the HF formed was constantly removed by addition of sodium fluoride and a work-up in the middle of the reaction was necessary. The fluorination carried out using the minireactor and our EC/PC solvent combination already shows promise, although the yield is still lower than others reported in the literature. However, our experiment was carried out only on a 100 mg scale and was not optimized in terms of temperature and gas/liquid flow rates. Preliminary tests indicate that the use of pure PC as a solvent is also possible, but more fluorine would be required. Thus, the cyclic carbonates were shown to be suitable solvents for direct fluorination of *closo*-$K_2[B_{12}H_{12}]$. Acetonitrile has also been tested as a possible alternative solvent that also leads to the fluorinated product, but tended to cause undesirable clogging of the reactor. Similar to the experiments with toluene, it forms solid organic material within the reactor.

Conclusion

The direct fluorination of ethylene carbonate was successfully carried out in our minireactor (channel diameter of 1 mm) and the results were comparable to optimized large-scale batch processes. Propylene carbonate was directly fluorinated for the first time. The isomer distribution was investigated and CH_2F-PC was found to be the major monofluorinated isomer. The distribution of the isomers was very stable under different reaction conditions. Direct fluorinations without solvent and using highly concentrated fluorine of up to 100% were shown to be possible with only small losses in yield and conversion. Thermodynamic calculations for ethylene and propylene carbonate were presented. They showed the reaction to be kinetically controlled.

Toluene was found to be a difficult substrate for direct fluorination in microreactors because of the formation of solids of high molecular mass as side products.

Direct temperature measurements inside the reactors reveal opportunities for experimental observation and determination of thermodynamic and kinetic parameters. Those data will help to design reactors, which are precisely optimized to the conditions required for direct fluorination.

In this study we also noted the high stability of polar cyclic carbonates EC and PC against decomposition even with high fluorine concentrations and in the presence of hydrogen fluoride. This compatibility makes them an interesting solvent alternative for fluorinations of ionic or other substrates in comparison to the volatile polar solvents currently employed for such fluorinations (acetonitrile or methanol). In support of this notion, our experiments on the fluorinations of toluene or *closo*-$[B_{12}H_{12}]^{2-}$ with the commonly used solvent acetonitrile tended to cause a clogging of the reactor, and which was avoided in carbonate solvents. Moreover, the favorable fluorination of *closo*-$[B_{12}H_{12}]^{2-}$ in the EC/PC solvent system is the first example of an inorganic ionic substance being fluorinated within a mini/microreactor.

Finally it should to be mentioned that our minireactor has been hitherto used for an active operation time of more than 300 hours and still shows no signs of degradation. This underlines the robustness of the system and how well the reactor can withstand the corrosive conditions of direct fluorination reactions.

Experimental Section

Materials and equipment

The 99.98% fluorine was donated by Solvay Fluor GmbH, Germany. Commercially available ethylene carbonate (99%) from Alfa Aesar, acetonitrile (HPLC grade) form VWR, and sodium fluoride (pure) from Merck. 4-fluoro-ethylencarbonate was donated by the Solvay Fluor, Germany. The $K_2[B_{12}H_{12}]$ was prepared according to the method report by Knapp and co-workers.[46] For the NMR analysis of the experiments an Advance II + 400 NMR (Bruker, Germany) with a 5 mm broadband fluorine observation head was used. To enable a precise integration of the NMR signals (ethylene and propylene carbonate reactions), the spectra were recorded using the following optimized settings: For acquisition of the ^{19}F NMR spectra at 377 MHz were set to a spectral width of 41667 Hz, an acquisition time of 3.15 seconds and a relaxation D1 delay of 30 seconds. The spectrum comprised 262144 data points. For acquisition of the ^{1}H NMR spectrum at 400 MHz, a spectral width of 6410 Hz, an acquisition time of 5.11 seconds, and a D1 delay of 30 seconds was used. The spectrum comprised 65536 data points. For both nuclei, spectra with 32 scans were recorded. An exponential function with a value of 0.5 Hz was applied to the spectra before processing. The phase and baseline corrections were checked for reproducibility. By using this procedure, the error bars of the measurements were found to be around ±1%.

Fluorination procedure for toluene

First, the nitrogen flow was started to fill the gas inlet line and the reaction channel. The liquid solution (reagent dissolved in acetonitrile) was loaded into a glass syringe, which was equipped with a Luer-lock valve. The syringe was placed into the syringe pump and the pump was started at the desired flow level, resulting in simultaneous flow of nitrogen and liquid solution within the reaction channel. When the liquid started to exit the reactor, the fluorine flow was started and turned off when the syringe had another

two minutes before being empty. During the reaction, the toluene solution tended to show a light brown color after the reaction. The liquid flow was switched off when the syringe was empty. After a further 20 minutes of purging the PFA vessel and the reactor, the nitrogen flow was switched off. The product was transferred to a different vessel, equipped with excess sodium to scrub the hydrogen fluoride. The mixture was then washed three times with water to remove acetonitrile. Remaining sodium fluoride and difluoride were removed by filtration. Because of the low maximal conversion, caused by the syringe pump, yields were not determined.

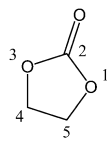
Fluorination of ethylene carbonate and propylene carbonate

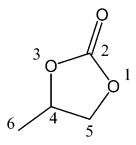
Before fluorination, ethylene carbonate was dissolved in F_1EC at 40 °C prior to the experiment. First the nitrogen flow was started and the liquid was filled into the separator vessel. The circulation pump was started with a low flow of 0.5 mL min^{-1}. When stable gas slugs were observed at the outlet, the liquid flow was carefully increased to the desired level of between 0.5 mL min^{-1} and 2.5 mL min^{-1}. Once the system was running in a stable manner, the fluorine flow was started and turned off after the desired reaction time was complete. The liquid flow was switched off 5 minutes after the fluorine flow was turned off. After a further 20 minutes of purging the PFA vessel and the reactor, the nitrogen flow was switched off. Two different work-up methods were used: For low amounts of HF the mixture was transferred to a different vessel, equipped with excess sodium fluoride (3 g per 3 g of substrate) and acetonitrile (4 mL per 3 g of substrate) to scrub the hydrogen fluoride. The mixture was stirred for two minutes, and then the solution was filtered. For high amounts of HF the mixture was transferred into a PFA beaker containing an excess of silica gel and acetonitrile. After stirring for 3 hours, the mixture was filtered and washed with acetonitrile. *p*-Fluorotoluene was used as an internal standard for NMR analysis (typically 0.3–0.7 g per 3 g of substrate).

NMR data for several mono- and difluorinated propylene carbonates

All data are based on various 2D NMR experiments of isomer mixtures. The NMR data is also given for 4,4-difluoro-1,3-dioxolan-2-one. These data have been previously published by Kobayashi[34] and Ishii,[47] but both groups misinterpreted the signals in the ^{1}H and ^{19}F NMR spectra. The signal formed by the CF_2CH_2 group is, though it appears to be a triplet with a coupling constant of 12.0 Hz, of higher order. It is an AA′XX′ system in which a dominating ^{19}F–^{19}F coupling is responsible for the formation of a pseudo triplet.

Structures show relevant atom numbering





4,4-F_2EC

4,4-Difluoro-1,3-dioxolan-2-one: ^{1}H NMR (400 MHz, CD_3CN): δ = 4.79–4.85 ppm (2H, m, 2×H5); ^{13}C NMR (100.6 MHz, CD_3CN): δ = 71 (C5), 125 (C4), 148 ppm (C2; ^{19}F NMR (376.5 MHz, CD_3CN): δ = −74.10–−74.16 ppm (1H, m, F4 + F4),

Monofluorinated isomers of propylene carbonate

4-Fluoromethyl-1,3-dioxolan-2-one: ^{1}H NMR (400 MHz, CD_3CN): δ = 4.35 (dd, 1H, $^2J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.1 Hz, H5), 4.58 (ddd, 1H, $^2J_{HF}$ = 64.9 Hz, $^2J_{HH}$ = 11 Hz, $^2J_{HF}$ = 3.7 Hz, H6), 4.58 (ddd, $^2J_{HF}$ = 8.8, $^2J_{HF}$ = 8.8, $^4J_{HF}$ = 1.4, H5), 4.71 (ddd, 1H, $^2J_{HF}$ = 64.9, $^2J_{HH}$ = 11.3 Hz, $^3J_{HF}$ = 2.0 Hz, H6), 4.91–5.02 ppm (m, 1H, H4); ^{13}C NMR (100.6 MHz, CD_3CN): δ = 65.0 (C5), 75.2 (C4) 82.2 ($^1J_{CF}$ = 155 Hz, C6), 154.9 ppm (C2); ^{19}F NMR (376.5 MHz, CD_3CN): δ = −236.4–237.6 ppm (t, 1F, $^2J_{FH}$ = 46.9 Hz, $^3J_{FH}$ = 25.3 Hz, $^2J_{FH}$ = 1.4 HZ, F6)

trans-4-Fluoro-5-methyl-1,3-dioxolan-2-one: ^{1}H NMR (400 MHz, CD_3CN): δ = 1.45 (dd, 3H, $^3J_{HH}$ = 6.8 Hz, $^4J_{HF}$ = 0.7 Hz, H6), 4.86 (dqd, 1H, $^3J_{HF}$ = 19.6 Hz, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 0.9 Hz, 5), 6.07 ppm (1H, dd, $^2J_{HF}$ = 63.4 Hz, $^3J_{HH}$ = 0.9 Hz, H4); ^{13}C NMR (100.6 MHz, CD_3CN): δ = 15.7 (C6), 79.9 (C4), 109.2 (5), 152.4 ppm (C2); ^{19}F NMR (376.5 MHz, CD_3CN): δ = −122.4 ppm (ddq, 1F, $^3J_{FH}$ = 19.6 Hz, $^2J_{FH}$ = 63.4 Hz, $^4J_{HF}$ = 0.7 Hz, F5)

cis-4-Fluoro-5-methyl-1,3-dioxolan-2-one: ^{1}H NMR (400 MHz, CD_3CN): δ = 1.46 (dd, 3H, $^3J_{HH}$ = 6.6 Hz, $^4J_{HF}$ = 2.4 Hz, H6), 4.95 (dqd, 1H, $^3J_{HF}$ = 25.6 Hz, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 4.0 Hz, H4), 6.25 ppm (dd, 1H, $^2J_{HF}$ = 64.2 Hz, $^3J_{HH}$ = 4.0 Hz, H5), ^{13}C NMR (100.6 MHz, CD_3CN): δ = 11.3(C6), 77.8 (C4) 106.1(C5) 152.4 ppm (C2); ^{19}F NMR (376.5 MHz, CD_3CN): δ = −141.2 ppm (ddq, 1F, $^3J_{FH}$ = 64.2 Hz, $^2J_{FH}$ = 25.6 Hz, $^4J_{HF}$ = 2.4 Hz, F5)

4-Fluoro-4-methyl-1,3-dioxolan-2-one: ^{1}H NMR (400 MHz, CD_3CN): δ = 1.82 (d, 3H, $^3J_{HF}$ = 18.0 Hz, H6), 4.46 (1H, $^3J_{HF}$ = 32.4 Hz, $^2J_{HH}$ = 10.6 Hz, H5), 4.60 ppm (dd, 1H, $^3J_{HF}$ = 17.6 Hz, $^2J_{HH}$ = 10.6 Hz, H); ^{13}C NMR (100.6 MHz, CD_3CN): δ = 19.9 ($^2J_{CF}$ = 34 Hz, C6), 74.9 (C5), 115.2 (C4), 152.7 ppm (C2); ^{19}F NMR (376.5 MHz, CD_3CN): δ = −92.1–−93.8 ppm (m,1F, F4)

Difluorinated isomers of propylene carbonate

4-Difluoromethyl-1,3-dioxolan-2-one: ^{1}H NMR (400 MHz, CD_3CN): δ = 4.51 (dd, 1H, $^2J_{HH}$ = 9.36 Hz, $^3J_{HH}$ = 5.08 Hz, H5), 4.60–4.62 (m, 1H, H5), 4.95–5.00 (m, 1H, H4), 6.05 ppm (td, 1H, $^2J_{HF}$ = 26.9 Hz, $^2J_{HH}$ = 2.6 Hz, H6); ^{13}C NMR (100.6 MHz, CD_3CN): δ = 64 (C5), 73 (C4), 113 (C6), 155 ppm (C2); ^{19}F NMR (376.5 MHz, CD_3CN): δ = −134.0–−136.2 ppm (m, 2F, F6)

cis-4-Fluoromethyl-5-fluoro-1,3-dioxlan-2-one: ^{1}H NMR (400 MHz, CD_3CN): δ = 4.77 (ddd, 1H, $^2J_{HF}$ = 47.3 Hz, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 6.6 Hz, H5), 4.87 (ddd, 1H, $^2J_{HF}$ = 45.3 Hz, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 3.6 Hz, H5) 5.02–5.18 (m, 1H, H4), 6.43 ppm (dd, 1H, $^2J_{HF}$ = 63.8 Hz, $^3J_{HH}$ = 4.5 Hz, H5); ^{13}C NMR (100.6 MHz, CD_3CN): δ = 79 (C4) 79 (C6), 105 (C5), 152 ppm (C2); ^{19}F NMR (376.5 MHz, CD_3CN): δ = −140.8–−140.6 (m, 1F, F5), −234.1 ppm (dddd, 1F, $^2J_{HF}$ = 47.3 Hz, $^2J_{HF}$ = 45.3 Hz, $^3J_{HF}$ = 17.7 Hz, $^4J_{FF}$ = 4.56 Hz, F6)

trans-4-Fluoromethyl-5-fluoro-1,3-dioxlan-2-one: ^{1}H NMR (400 MHz, CD_3CN): δ = 4.83 (ddd, 1H, $^2J_{HF}$ = 45.4 Hz, $^2J_{HH}$ = 12 Hz, $^3J_{HH}$ = 2.4 Hz, H6), 4.77 (ddd, 1H, $^2J_{HF}$ = 47.2 Hz, $^2J_{HH}$ = 12 Hz, $^3J_{HF}$ = 4.6 Hz, H6), 4.92–5.07 (m, 1H, H4), 6.39 ppm (dd,1H, $^2J_{HF}$ = 62.5 Hz, $^3J_{HH}$ = 1.0 Hz, H5); ^{13}C NMR (100.6 MHz, CD_3CN): δ = 81 (C6), 81 (C4), 106 (C5), 152 ppm (C2); ^{19}F NMR (376.5 MHz, CD_3CN): δ = −125.0 (ddd, 1F, $^2J_{HF}$ = 62.5 Hz, $^2J_{HF}$ = 20.1 Hz, F5), −240.2 ppm (ddd, 1F, $^2J_{HF}$ = 47.2 Hz, $^2J_{HF}$ = 45.4 Hz, $^3J_{HF}$ = 29.0 Hz, F6)

4-Fluoromethyl-4-fluoro-1,3-dioxolan-2-one: ^{1}H NMR (400 MHz, CD_3CN): δ = 4.78 (ddd, 2H, $^2J_{HF}$ = 45 Hz, $^3J_{HF}$ = 10 Hz, $^4J_{HH}$ = 2.5 Hz, H6), 4.63–4.72 ppm (m, 2H, H5), ^{13}C NMR (100.6 MHz, CD_3CN): δ = 70.5 (C5), 79.5 (C6), 112.2 (C4), 151.7 ppm (C2); ^{19}F NMR

(376.5 MHz, CD_3CN): $\delta = -112.79 - -113.00$ (m, 1F, F4), −236.36–236.66 ppm (m, 1F, F6)

Fluorination of *closo*-$K_2[B_{12}H_{12}]$

Well dried *closo*-$K_2[B_{12}H_{12}]$ (0.0907 g, 0.44 mmol) was dissolved in EC (3.0 g) and PC (0.9 g). First the nitrogen flow of 400 mL h^{-1} was started and the mixture was transferred into a separator vessel. The circulation pump was started at a low flow of 30 mL h^{-1}. When stable gas slugs were observed at the outlet, the liquid flow was slowly increased to 300 mL h^{-1}. The reaction gas flow was set to a total gas flow of 400 mL h^{-1}. During the reaction, the fluorine concentration was increased from 22% to 45%. The average fluorine concentration was 33%. After 5.6 hours the fluorine was switched of and the reactor purged with nitrogen. After quenching the HF with calcium carbonate the standard was added and a NMR sample prepared.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft DFG for funding support of this project, and Solvay Fluor GmbH for donating fluorine and 4-fluoro-ethylene carbonate. This study was also supported by the Freiburg Materials Research Center FMF and the Freiburg Institute of Advanced Studies FRIAS. We also thank Franz Richardt in the Laboratory for Design of Microsystems Machine Shop for helpful discussions and manufacture of the reactors.

Keywords: *closo*-dodecaborates · cyclic carbonates · direct fluorination · flow reactors · microreactors

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Received: October 10, 2012
Revised: January 16, 2013
Published online on February 19, 2013