Perfluoro-Tagged Benzyloxycarbonyl Protecting Group and Its Application in Fluorous Biphasic Systems

by **Dominik Schwinn** and **Willi Bannwarth***

Institut für Organische Chemie und Biochemie, Universität Freiburg, Albert-Str. 21, D-79104 Freiburg, Germany (Phone: ++49 761 203-6073; fax: ++49 761 203-8705; e-mail: willi.bannwarth@organik.chemie.uni-freiburg.de)

The synthesis of a new perfluoro-tagged benzyloxycarbonyl protecting group is reported, as well as its application in the parallel protection of amines. Isolation of the protected amines was performed by simple liquid-liquid extraction between perfluorinated and organic solvents. Deprotection was achieved by standard hydrogenolysis. The novel protecting group was also applied to cyclization protocols leading to quinazoline-2,4-diones. These products were isolated by simple extraction procedures

1. Introduction. – With the challenge to build up large libraries of compounds of pharmacological interest, the task for organic chemists is to efficiently synthesize great numbers of diverse molecules for high-throughput screening [1]. One way to achieve this goal is to perform synthesis on solid supports. This offers the advantage that the reagents can be used in excess and washed off without any loss of product [2]. Nevertheless, solid-phase synthesis also entails a number of disadvantages, most notably the lack of suitable linkers. Furthermore, it is difficult to identify the compounds attached to the solid-phase and to follow the course of reactions on the solid support. Thus, a number of alternative strategies have been developed to speed up chemical synthesis mainly by simplifying the work-up procedures after parallel synthesis [3].

One such method comprises the use of polymer-supported reagents or solid-phase-bound scavengers. The strategy combines the benefits of solution chemistry with the advantages of solid-phase synthesis. Alternative methods comprise the use of supercritical CO_2 ($scCO_2$) [4] or ionic liquids [5] as reaction media.

Recently, it was demonstrated, that 'fluorous techniques' provide new options for efficient separation and isolation steps in conducting solution chemistry. Perfluoro-tagged compounds can be easily separated from organic compounds *via* liquid-liquid extraction between a common organic and a perfluorinated solvent. Alternatively, solid-phase extraction on fluorinated reversed-phase silica gel can be performed. The approach can be used for the straightforward recycling of perfluoro-tagged catalysts and in combinatorial chemistry.

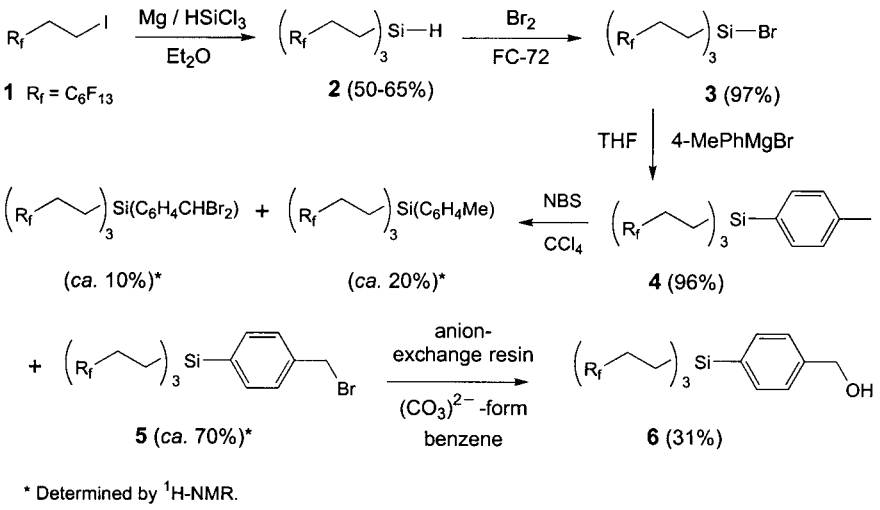
In combinatorial chemistry, the perfluoro entities are best introduced *via* protecting groups that render the parent compounds soluble in perfluorinated solvents and lead to a strong interaction with fluorinated reversed-phase silica gel. Hence, separation from non-perfluoro-tagged molecules is easily achieved. Finally, the protection group is cleaved off and can be removed from the desired compound by one of the aforementioned methods.

One of the most prominent protecting groups in organic synthesis is the benzyloxycarbonyl (Z) group, which is widely being used for the protection of amines and amino acids. It is stable under acidic and basic conditions and can be cleaved under orthogonal conditions by hydrogenolysis.

Here, we report on the synthesis of a perfluoro-tagged benzyloxycarbonyl group to be applied in fluorous-biphasic-systems (FBS) [6]. Its structure derives from a perfluoro-tagged benzyl alcohol, that carries a tris[2-(perfluorohexyl)ethyl]silyl group. We now demonstrate the utility of our protecting group for masking amines *via* carbamates and their cleavage by hydrogenolysis. Furthermore, we are going to show that certain protected amines are amenable to cyclization leading to quinazolinediones [7] and that they can be used for efficient parallel syntheses due to the simple separation of the cyclic products.

2. Results and Discussion. – The initial strategy for the synthesis of the perfluoro-tagged benzyl unit **6** is outlined in *Scheme 1*. The commercially available, fluorinated octyliodide **1** was converted into a *Grignard* reagent and reacted with Cl_3SiH to provide **2** in moderate yield. Bromination of **2** proceeded almost quantitatively to yield compound **3** [8]. The latter was reacted with the *Grignard* compound of 4-bromotoluene providing **4** in both high yield and excellent purity [9]. Bromination of **4** with *N*-bromosuccinimide (NBS) led to the desired compound **5** together with unreacted **4** and a dibrominated side-product. Compound **5** was not purified but transformed with the help of an anion-exchange resin to **6**, which was obtained after chromatographic purification in modest yield [10].

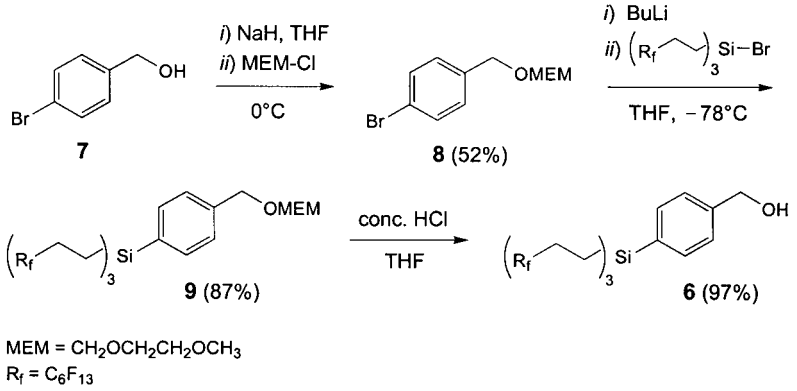
Scheme 1



Due to the rather low yields in the last two steps, we were looking for a more efficient preparation of **6**. The alternative we devised is outlined in *Scheme 2*. The synthetic pathway started with 4-bromobenzyl alcohol (**7**), which was protected with the 2-(methoxyethoxy)methyl (MEM) group according to the procedure of *Corey et al.*

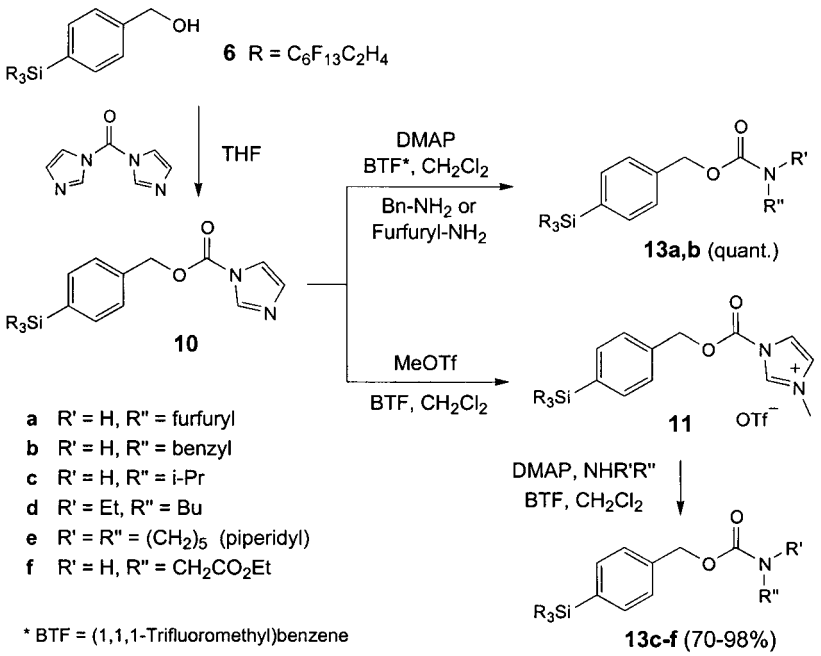
[11] thus providing compound **8**. The latter was reacted first with BuLi at $-78°$, followed by addition of **3** to yield the MEM-protected benzyl alcohol **9** in high yield. The MEM group was removed with concentrated HCl in THF to produce **6** in high yield [12]. This procedure is also amenable to the synthesis of **6** on a multi-gram scale.

Scheme 2



To demonstrate the advantage of **6** for the parallel protection of amines, it was transformed into the carbamate **10**, which readily reacted with primary amines such as furfurylamine or benzylamine after addition of catalytic amounts of 4-(dimethylamino)pyridine (DMAP) (*Scheme 3*) [13].

Scheme 3



For the protection of less nucleophilic or secondary amines, **10** had to be activated *via* *N*-methylation using methyl trifluoromethane sulfonate (MeOTf). Since CH_2Cl_2 was used as a solvent, (1,1,1-trifluoromethyl)benzene (BTF) had to be added to solubilize the fluorinated compounds [14].

The protected amines were obtained *via* extraction with perfluorohexane (FC-72) both in excellent yields and high purity (*Table*).

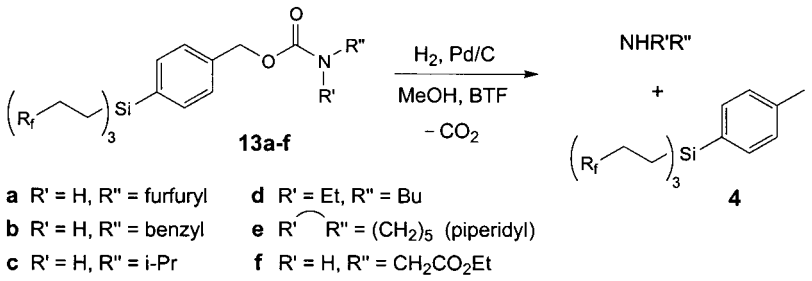
Table. *Protection and cleavage of amines*

Amines		Protection	Cleavage[a])
furfurylamine	**13a**	quant.	80%
benzylamine	**13b**	quant.	60%
isopropylamine	**13c**	70%[b])	not isolated
n-butyl-ethyl-amine	**13d**	91%[b])	80%
piperidine	**13e**	98%[b])	88%
glycine ethyl ester	**13f**	98%[b])	62%

[a]) Yields of isolated amines. [b]) Methylation with methyl trifluoromethanesulfonate.

In order to determine the ease of deprotection, a solution of the substrates **13a**–**f** in MeOH, containing Pd/C, was exposed to H_2. The deprotected amines were recovered together with silane **4** after liquid-liquid phase extraction (*Scheme 4*). The results are summarized in the *Table.*

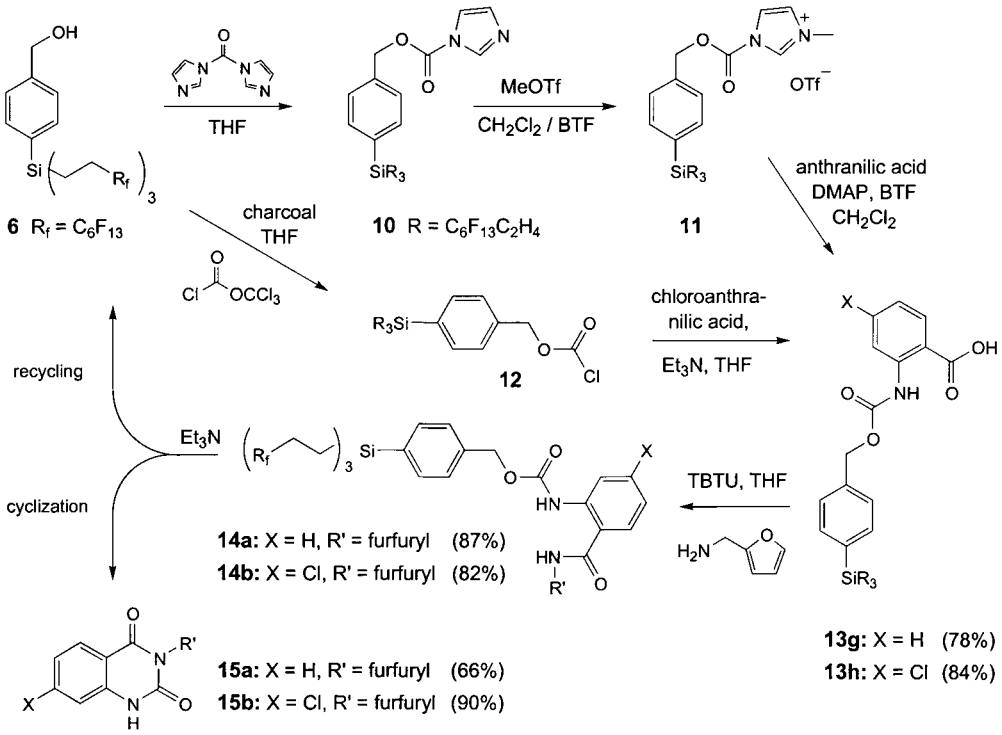
Scheme 4



Parallel synthesis on solid support represents an elegant way of accessing heterocyclic compounds [15]. Molecules that do not contain the necessary functional groups for cyclization remain bound to the resin and can be easily separated *via* filtration. In a similar way, we have used the perfluoro-tagged benzyloxycarbonyl entity to synthesize quinazoline-2,4-diones (**15**) *via* intramolecular cyclization. This class of heterocycles represents a group of attractive pharmacophores with a wide range of pharmacological activities [16]. Since the desired products lack any perfluoro-tags, they can be easily separated *via* extraction from by-products. The corresponding synthetic pathway is outlined in *Scheme 5*.

The first step comprises the coupling of anthranilic acid derivatives. This was achieved in two different ways. *N*-Methylation of the carbamate **10**, leading to **11**, and reaction with the anthranilic acid was one possibility. The preferred route however, was the activation of **10** with diphosgene [17], leading to **12**, which reacted smoothly to the

Scheme 5



desired intermediates **13g**,**h**. Next, a primary amine was coupled to the carboxylic acid function of **13g**,**h** to yield the amides **14a**,**b** [18]. The final cyclization step by means of intramolecular carbamate cleavage was initiated by Et_3N. This method allowed an easy workup (even under conditions where all the steps prior to the cyclization did not proceed quantitatively), since all the perfluoro-tag-containing products could be separated from the desired heterocycles by liquid-liquid extraction.

Conclusions. – In summary, we were able to establish a straightforward route for the (large scale) synthesis of the perfluoro-tagged benzyl alcohol **6**, which was successfully used for the parallel protection of different amines. Isolation of the products was achieved by simple liquid-liquid extraction between perfluorinated and organic solvents, thereby omitting time-consuming chromatographic steps. Deprotection could be performed by standard hydrogenolysis. The perfluoro-tagged protecting group was also applied to cyclization protocols, leading to quinazoline-2,4-diones, which could again be isolated by extraction procedures. Our strategy should therefore be generally applicable to the rapid parallel synthesis of different heterocyclic cores, a project that is currently being pursued in our group.

We would like to thank Dr. *Hunkler*, Mrs. *Schonhard*, and Mr. *Reinbold* for recording NMR spectra, Mr. *Warth* and Mr. *Wörth* for recording MS spectra, and Mr. *Hickl* for performing elemental analyses.

Experimental Part

General. All reagents were obtained from *Acros* or *Aldrich* and were of highest purity available. THF was dried over Na and freshly distilled before use. CH_2Cl_2 and 1,1,1-(trifluoromethyl)benzene (BTF) were dried over molecular sieves 4 Å. Diethyl ether (Et_2O) was dried over KOH. M.p. were measured with the electrothermal digital melting device *IA 9200* and are uncorrected. Column chromatography (CC): SiO_2 *KG 60* from *Baker*. NMR Spectra: 250 or 400 MHz (^1H), 100 MHz (^{13}C); chemical shifts δ in ppm rel. to Me_4Si (=0 ppm) for ^1H-NMR and rel. to $CHCl_3$ (=77.00 ppm) for ^{13}C-NMR, respectively. *J* in Hz. MS: *Finnigan MAT8200* (EI), *MAT312* (Cl), and *TSQ-7000* (ESI) mass spectrometer.

Tris-[2-(perfluorohexyl)ethyl]silane (**2**). A soln. of 25.0 g (52.7 mmol) of 1-iodo-1*H*,1*H*,2*H*,2*H*-perfluorooctane (**1**) in anh. Et_2O was carefully added within 1 h to a vigorously stirred suspension of 1.28 g (52.7 mmol) of Mg powder in 5 ml of anhydrous Et_2O. The suspension was refluxed for 3 h. After cooling to r.t., 6.6 ml (13 mmol) of a 2M soln. of Cl_3SiH were slowly added, and the mixture was refluxed for 70 h. The solvent was evaporated and the residue was taken up in 40 ml of CH_2Cl_2 and in 50 ml of a sat. NH_4Cl soln. The cloudy two-phase mixture was extracted with perfluorohexane (FC-72, 5 × 10 ml). The FC-72 phases were combined and evaporated. The crude silane was purified by bulb-to-bulb distillation (180°, 5 mbar) to give 9.0 g (65%) of **2**. ^1H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.15–1.27 (*m*, 3 CH_2Si); 2.28–2.43 (*m*, 3 CH_2CF_2); 4.16 (*s*, Si–H). Anal. calc. for $C_{24}H_{13}F_{39}Si$ (1070.02): C 26.93, H 1.22; found: C 26.92, H 1.27.

Bromo{tris[2-(perfluorohexyl)ethyl]}silane (**3**). Br_2 (0.24 ml, 4.7 mmol) was added dropwise to a soln. of 4.87 g (4.60 mmol) of **2** in 10 ml of FC-72. The mixture was stirred at r.t. for 18 h, and HBr was constantly removed by a stream of Ar. FC-72 (10 ml) was added. The fluorous phase was washed with anh. CH_2Cl_2 (3 × 2 ml) and concentrated *in vacuo* to yield 5.09 g (97%) of **3**. ^1H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.42–1.55 ppm (*m*, 3 CH_2Si); 2.38–2.50 (*m*, 3 CH_2CF_2). Anal. calc. for $C_{24}H_{12}BrF_{39}Si$ (1149.93): C 25.08, H 1.05; found: C 25.01, H 0.97.

[4-Methyl(phenyl)]{tris[2-(perfluorohexyl)ethyl]}silane (**4**). A soln. (5 ml), made of 0.34 g (2.0 mmol) of 4-bromotoluene in 50 ml of anh. THF, was added to 0.05 g (2.00 mmol) of Mg powder. The suspension was stirred at 35° until the reaction started. Then the remaining soln. of 4-bromotoluene was added dropwise within 0.5 h. Then, the mixture was refluxed for 3 h. A soln. of 2.00 g (1.75 mmol) of **3** in 20 ml of anh. THF was added to the *Grignard* reagent within 10 min. The resulting mixture was refluxed for 6 d. The solvent was evaporated, the residue taken up in 20 ml of MeCN and extracted with FC-72 (5 × 10 ml). The combined fluorous layers were concentrated *in vacuo* to yield 1.94 g (96%) of **4**. ^1H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.32–1.39 (*m*, 3 CH_2Si); 2.21–2.32 (*m*, 3 CH_2CF_2); 2.50 (*s*, Me); 7.40 (*d*, *J* = 8.5, 2 arom. H); 7.53 (*d*, *J* = 8.5, 2 arom. H). Anal. calc. for $C_{31}H_{19}F_{39}Si$ (1160.51): C 32.08, H 1.65; found: C 31.92, H 1.52.

[4-(Bromomethyl)phenyl]{tris[2-(perfluorohexyl)ethyl]}silane (**5**). Under Ar, 9.0 g (7.8 mmol) of **4** were taken up in 50 ml of anh. CCl_4. *N*-bromo-succinimide (NBS) (1.4 g, 7.8 mmol) and 20 mg of azo[bis(isobutyronitrile)] (AIBN) were added, and the mixture was carefully heated until the exothermic reaction started. Once the reaction had subsided, the mixture was refluxed for 4 h, then cooled to r.t., and filtered. The solvent was removed *in vacuo*. The residue was taken up in MeCN (30 ml) and extracted with FC-72 (5 × 10 ml). The combined fluorous layers were concentrated *in vacuo* to give 5.78 g of a yellowish oil, containing 70% of **5**, 20% of starting material and 10% of a dibromo derivative (see *Scheme 1*). ^1H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.38–1.45 (*m*, 3 CH_2Si); 2.21–2.38 (*m*, 3 CH_2CF_2); 4.50 (*s*, CH_2Br); 7.61 (*s*, 4 arom. H). EI-MS (230°, 70 eV): 1239 (18, $[M^+]$), 1159 (14, $[M-Br]^+$), 503 (32), 399 (58), 309 (45), 289 (29), 263 (20), 245 (54), 239 (63), 195 (30), 175 (100), 91 (32), 77 (29), 69 (29), 59 (18), 51 (29).

4-{Tris[2-(perfluorohexyl)ethyl]silyl}benzyl alcohol (**6**). A soln. of K_2CO_3 (1 l, 1M) was slowly percolated through a column filled with *Amberlite IRA 900* (Cl^--form) until a negative test for Cl^- was obtained by adding a soln. of $AgNO_3$ to the eluate. Then, the resin was washed with 200 ml of MeOH, 100 ml of Et_2O, and dried *in vacuo* for 4 h at r.t. *Amberlite 900* (CO_3^{2-}-form, 1.0 g, 3 eq.) and 0.7 g of the crude mixture, containing 0.5 g of **5** (0.4 mmol), were diluted in benzene and refluxed for 4 h. After cooling, the resin was filtered off and washed with 20 ml of Et_2O and 10 ml of FC-72. The combined filtrates were concentrated *in vacuo* to produce a yellowish oil, which was purified by CC (cyclohexane/AcOEt 9:1): 0.15 g (31%). ^1H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.34–1.42 (*m*, 3 CH_2Si); 2.21–2.38 (*m*, 3 CH_2CF_2); 4.72 (*s*, CH_2–OH); 7.53 (*d*, *J* = 8.5, 2 arom. H); 7.65 (*d*, *J* = 8.5, 2 arom. CH). CI-MS (NH_3, 220°, 240 eV): 1174 (100, $[M-2H]^+$), 867 (36). Anal. calc. for $C_{31}H_{19}F_{39}OSi$ (1176.06): C 31.65, H 1.63; found: C 31.74, H 2.07.

1-Bromo-4-[[(2-methoxyethoxy)methoxy]methyl]benzene (**8**). To a stirred soln. of 1.0 g (5.4 mmol) of benzyl alcohol **7** in 20 ml of anh. THF, 0.22 g (5.50 mmol) of NaH (60% in oil) were added under Ar at 0°. The

resulting suspension was stirred for 15 min, then 0.8 g (6.4 mmol) of MEM-Cl were added dropwise, and the mixture was stirred for 0.5 h at 0°. The solvent was removed *in vacuo*, and the residue was taken up in 20 ml of Et_2O. The organic phase was washed with H_2O (2 × 50 ml), dried over Na_2SO_4, and concentrated *in vacuo*. The yellowish oil was purified by CC (cyclohexane/AcOEt 8:2) to yield 0.77 g (52%) of **8**. ^{1}H-NMR (250 MHz, $CDCl_3$): 3.33 (*s*, MeO); 3.52 (*t*, *J* = 4, C*H*$_2$OMe); 3.67 (*t*, *J* = 4, MeOCH$_2$C*H*$_2$); 4.50 (*s*, PhC*H*); 4.72 (*s*, OCH_2O); 7.15 (*d*, *J* = 7.5, 2 arom. H); 7.40 (*d*, *J* = 7.5, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 59.1 (OMe); 67.1 (CH_2); 68.6 (CH_2); 71.8 (Ph*C*H$_2$); 94.9 (OCH_2O); 121.6, 129.5, 131.6, 137.0 (4 arom. C). Anal. calc. for $C_{11}H_{15}BrO_3$ (260.00): C 48.02, H 5.49; found: C 48.08, H 5.30.

(4-{[(2-Methoxyethoxy)methoxy]methyl}phenyl){tris[2-(perfluorohexyl)ethyl]}silane (**9**). To a stirred soln. of 100 mg (0.36 mmol) of **8** in 40 ml of anh. THF at −78°, 0.18 ml (0.45 mmol) of BuLi (2.5M in toluene) were added dropwise. The soln. was stirred at −78° for 0.5 h. Then 300 mg (0.26 mmol) of **3** were added and the mixture was allowed to warm up to r.t. within 1.5 h. A sat. soln of aq. NH_4Cl was added, and the org. solvent was removed *in vacuo*. After addition of 20 ml of CH_2Cl_2, the cloudy biphasic mixture was extracted with FC-72 (5 × 10 ml). The combined fluorous layers were concentrated *in vacuo* to give 0.29 g (87%) of **9**. ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.35–1.42 (*m*, 3 CH_2Si); 2.21–2.37 (*m*, 3 CH_2CF_2); 3.46 (*s*, OMe); 3.63 (*t*, *J* = 4, CH_2); 3.82 (*t*, *J* = 4, CH_2); 4.79 (*s*, OCH_2O); 4.89 (*s*, PhC*H*$_2$); 7.63 (*s*, 4 arom. H). EI-MS: (230°, 70 eV): 1231 (3), 1176 (10), 1175 (24), 1159 (17), 437 (16), 309 (22), 239 (31), 89 (100).

Synthesis of **6** from **9**. To a mixture of 100 mg (0.08 mmol) of **9** in 20 ml of THF, 5 ml of conc. HCl were added. The emulsion was refluxed for 3 h. After cooling, the soln. was concentrated *in vacuo*, and to the remaining aq. layer was added 20 ml of CH_2Cl_2. The binary mixture was extracted with FC-72 (5 × 10 ml), and the combined fluorous layers were dried over Na_2SO_4. FC-72 was removed *in vacuo* to give 91 mg (97%) of **6**, which was identical to a sample prepared by the previous route. This procedure is amenable to the synthesis of **6** on multigram scale.

*(4-{Tris[2-(perfluorohexyl)ethyl]silyl}benzyl) 1*H*-Imidazole-1-carboxylate* (**10**). To a stirred soln. of 55 mg (0.34 mmol) of CDI[1]) in 5 ml of anh. THF, a soln. of 200 mg (0.17 mmol) of **6** in 5 ml of anh. THF was added at 0°. The mixture was stirred at 0° for 1 h and for another at r.t. The solvent was removed *in vacuo*, and the residue was taken up in 20 ml of FC-72. The fluorous layer was washed with a diluted soln. of aq. NH_4Cl (2 × 10 ml) and concentrated by bulb-to-bulb condensation *in vacuo* to yield 210 mg (97%) of **10**. ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.40–1.45 (*m*, 3 $SiCH_2$); 2.25–2.37 (*m*, 3 CH_2CF_2); 5.50 (*s*, PhC*H*$_2$); 7.05 (*s*, 1 H, imid.); 7.41 (*s*, 1 H, imid.); 7.67 (*d*, *J* = 7.0, 2 arom. H); 7.73 (*d*, *J* = 7.0, 2 arom. H); 8.04 (*s*, N^+H). ESI-MS (MeOH, 100 µl/min, 70 eV): 1271 (100, $[M+H]^+$), 1227 (26, $[M-C_2H_5N]^+$).

General Procedure for the Protection of Amines With **10**. The imidazole-1-carboxylate **10** (0.13 g, 0.10 mmol) was taken up in 20 ml of anh. CH_2Cl_2, and 3 ml of BTF[2]), 0.13 mmol of amine, and 5 mg of DMAP[3]) were added. The mixture was stirred at r.t. for 10 h. The solvent was removed *in vacuo*, and the residue was extracted with FC-72 (4 × 5 ml). The combined fluorous layers were washed with 10 ml of aq. solns. of citric acid (10%), dried over Na_2SO_4, and concentrated *in vacuo* to give both the carbamates **13a** and **13b** in quantitative yield.

(4-{Tris[2-(perfluorohexyl)ethyl]silyl}benzyl) Furfurylcarbamate (**13a**): ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.35–1.42 (*m*, 6 H, CH_2Si); 2.22–2.36 (*m*, 3 CH_2CF_2); 4.35 (*d*, *J* = 3.5, NCH_2); 5.16 (*s*, PhCH_2); 5.67 (*t*, *J* = 3.5, NH); 6.25 (*s*, 1 H, furan); 6.33 (*s*, 1 H, furan); 7.34 (*s*, 1 H, furan); 7.50 (*d*, *J* = 7.5, 2 arom. H); 7.60 (*d*, *J* = 7.5, 2 arom. H). EI-MS (230°, 70 eV): 1176 (16), 1175 (41), 1159 (68), 399 (100), 96 (14), 91 (86).

(4-{Tris[2-(perfluorohexyl)ethyl]silyl}benzyl) Benzylcarbamate (**13b**): ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.30–1.41 (*m*, 3 CH_2Si); 2.20–2.35 (*m*, 3 CH_2CF_2); 4.38 (*d*, *J* = 5.0, NCH_2); 5.19 (*s*, OCH_2); 5.43 (*s*, NH); 7.28–7.37 (*m*, 5 arom. H); 7.49 (*d*, *J* = 7.0, 2 arom. H); 7.57 (*d*, *J* = 7.0, 2 arom. H). EI-MS (230°, 70 eV): 1205 (12, $[M-C_7H_7]^+$), 1159 (100, $[M-C_6H_5CH_2NHCO_2]^+$), 437 (58), 239 (41), 175 (95).

General Procedure for the Protection of Amines with in situ *Generated* **11**. Compound **10** (0.16 mmol) was treated with 5 ml of anh. CH_2Cl_2 and 1 ml of BTF. MeOTf[4]) (1.6 mmol) was slowly added and the soln. was stirred at r.t. for 1 h. The excess reagent and the solvent were removed *in vacuo* by bulb-to-bulb condensation. Then, 10 ml of anh. CH_2Cl_2, 2 ml of BTF, 0.48 mmol of amine, and 5 mg of DMAP[3]) were added to the residue. The mixture was stirred at r.t. for 16 h. The solvent was removed *in vacuo*, and the residue was extracted with

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[1]) 1-[(1*H*-Imidazol-1-yl)carbonyl]-1*H*-imidazole ('carbonyldiimidazole').

[2]) 1,1,1-(Trifluoromethyl)benzene.

[3]) 4-(*N*,*N*-Dimethylamino)pyridine.

[4]) Methyl trifluoromethylsulfonate.

FC-72 (4 × 5 ml). The combined fluorous layers were washed with solns. of aq. citric acid (10%) (2 × 10 ml), dried over Na_2SO_4, and concentrated *in vacuo* to yield the carbamates **13c**–**f**. All compounds described below were synthezised in parallel. The yields are outlined in the *Table*.

(4-{Tris[2-(perfluorohexyl)ethyl]silyl}benzyl) Isopropylcarbamate (**13c**). ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.28 (*d*, *J* = 6.0, 2 Me); 1.38–1.44 (*m*, 3 CH_2Si); 2.22–2.37 (*m*, 3 CH_2CF_2); 4.00 (*m*, Me_2CH); 4.56 (*m*, NH); 5.21 (*s*, $PhCH_2$); 7.56 (*d*, *J* = 7.5, 2 arom. H); 7.62 (*d*, *J* = 7.5, 2 arom. H). EI-MS (200°, 70 eV): 1261 (2, M^+), 1176 (18), 811 (5), 399 (19), 239 (20), 175 (55), 107 (100).

(4-{Tris[2-(perfluorohexyl)ethyl]silyl}benzyl) (Butyl)(ethyl)carbamate (**13d**). ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.13 (*t*, *J* = 7.0, Me); 1.28 (*t*, *J* = 7.0, Me); 1.35–1.42 (*m*, 3 CH_2Si); 1.49 (*m*, CH_2); 1.70 (*m*, CH_2); 2.22–2.38 (*m*, 3 CH_2CF_2); 3.43–3.51 (*m*, 2 CH_2); 5.27 (*s*, $PhCH_2$); 7.54 (*d*, *J* = 8.0, 2 arom. H); 7.63 (*d*, *J* = 8.0, 2 arom. H). EI-MS (200°, 70 eV): 1303 (100, M^+), 994 (79), 850 (6), 144 (8).

(4-{Tris[2-(perfluorohexyl)ethyl]silyl}benzyl) Piperidine-1-carboxylate (**13e**). ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.35–1.42 (*m*, 3 CH_2Si); 1.65–1.71 (*m*, 4 H, pip.); 1.76–1.82 (*m*, 2 H, pip.); 2.22–2.36 (*m*, 3 CH_2CF_2); 3.60–3.66 (*m*, 4 H, pip.); 5.28 (*s*, $PhCH_2$); 7.50 (*d*, *J* = 7.5, 2 arom. H); 7.58 (*d*, *J* = 7.5, 2 arom. H). EI-MS (230°, 70 eV): 1287 (100, M^+), 978 (91), 128 (5).

Ethyl 2-({[(4-{Tris[2-(perfluorohexyl)ethyl]silyl}benzyl)oxy]carbonyl}amino)acetate (**13f**). ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.31 (*t*, *J* = 8.5, Me); 1.35–1.42 (*m*, 3 CH_2Si); 2.22–2.36 (*m*, 3 CH_2CF_2); 3.99 (*d*, *J* = 3.0, $NHCH_2$); 4.32 (*q*, *J* = 8.5, $MeCH_2O$); 5.21 (*s*, $PhCH_2$); 5.49 (*t*, *J* = 3.0, NH); 7.57 (*d*, *J* = 7.5, 2 arom. H); 7.63 (*d*, *J* = 7.5, 2 arom. H). EI-MS (200°, 70 eV): 1305 (7, M^+), 1159 (23), 811 (15), 483 (36), 239 (32), 175 (100).

General Procedure for the Hydrogenolytic Cleavage of the Carbamates **13a**–**f**. To a soln. of 0.09 mmol amine in 10 ml of MeOH and 2 ml of BTF, 10 mg Pd on charcoal (10%) were added under Ar. The atmosphere was saturated with H_2 and shaken at r.t. for 16 h. The catalyst was filtered off, and the solvent was evaporated. The residue was taken up in FC-72 (4 × 5 ml), and the fluorous phase was extracted with 5 ml of MeCN. The two phases were concentrated separately *in vacuo* to yield **4** and the parent amine. The latter were identified by ^{1}H-NMR. The yields are outlined in the *Table*.

2-({[(4-{Tris[2-(perfluorohexyl)ethyl]silyl}benzyl)oxy]carbonyl}amino)benzoic Acid (**13g**). Compound **10** (0.20 g, 0.16 mmol) was taken up in 10 ml of anh. CH_2Cl_2 and 2 ml of BTF. Methyl trifluoromethane sulfonate (MeOTf) (0.18 ml, 1.6 mmol) was slowly added and the soln. was stirred at r.t. for 1 h. The excess of MeOTf and the solvent were removed *in vacuo* by bulb-to-bulb condensation. Then, 10 ml of anh. CH_2Cl_2, 2 ml of BTF, 0.48 mmol of amine, and 5 mg of DMAP[3]) were added to the residue. The mixture was stirred at r.t. for 16 h. The solvent was removed *in vacuo*, and the residue was extracted with FC-72 (4 × 5 ml). The combined fluorous layers were washed with solns. of aq. citric acid (10%) (2 × 10 ml), dried over Na_2SO_4, and concentrated *in vacuo* to yield 167 mg (78%) of **13g**. ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.25–1.34 (*m*, 3 CH_2Si); 2.18–2.36 (*m*, 3 CH_2CF_2); 5.12 (*s*, $PhCH_2$); 6.92 (*t*, *J* = 5.0, 1 arom. H); 7.40–7.49 (*m*, 3 arom. H); 7.60 (*m*, 2 arom. H); 7.91 (*d*, *J* = 5.0, 1 arom. H); 8.48 (*d*, *J* = 6.5, 1 arom. H); 10.59 (*s*, NH). EI-MS (230°, 70 eV): 1339 (7, M^+), 1295 (13), 1159 (13), 399 (89), 239 (71), 175 (100).

4-Chloro-2-({[(4-{tris[2-(perfluorohexyl)ethyl]silyl}benzyl)oxy]carbonyl}amino)benzoic Acid (**13h**). A suspension of 63 mg (0.32 mmol) of trichloromethyl chloroformate and 5 mg of activated charcoal in 25 ml of anh. THF were stirred under Ar for 10 min. A soln. of 0.5 g (0.43 mmol) of **6** in 10 ml of anh. THF was added dropwise within 1 h. After stirring at r.t. for 15 h, the mixture was filtered over 2 g of SiO_2. The filtrate was concentrated *in vacuo* to give 52 mg (0.42 mmol, 98%) of **12**. (In the ^{1}H-NMR spectrum of **12**, the peak for the benzylic methylene group was shifted from 4.72 to 5.88 ppm. The MS spectrum showed fragments of the molecule, but not the mass peak itself. The product was directly converted to **13h**, because of its sensitivity to moisture.) The chloroformate **12** (0.49 g, 0.40 mmol), 86 mg (0.50 mmol) of 4-chloroanthranilic acid, and 0.2 ml (1.6 mmol) of *Hünig*'s base ($NEt(i\text{-}Pr)_2$) were taken up in 10 ml of anh. THF. The soln. was stirred at r.t. for 16 h. The solvent was removed *in vacuo* and the residue was taken up in 30 ml of FC-72. The fluorous phase was washed with 0.1M HCl soln. (3 × 10 ml), dried over Na_2SO_4, and concentrated *in vacuo* to yield 451 mg (84%) of **13h**. ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.25–1.34 ppm (*m*, 3 CH_2Si); 2.18–2.36 (*m*, 3 CH_2CF_2); 5.25 (*s*, $PhCH_2$); 6.92 (*m*, 1 arom. H); 7.40–7.70 (*m*, 4 arom. H); 7.95 (*s*, 1 arom. H); 8.51 (*s*, 1 arom. H); 10.90 (*s*, NH). EI-MS (230°, 70 eV): 1373 (8, M^+), 1329 (36), 1159 (80), 399 (57), 239 (52), 175 (87), 91 (100).

General Procedure for the Preparation of **14a**,**b**. The carbamates **13g**,**h** (0.15 mmol), 15 µl (0.17 mmol) of furfurylamine, 22 mg (0.17 mmol) of *Hünig*'s base, and 55 mg (0.17 mmol) of TBTU[5]) were taken up in 20 ml of

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[5]) *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate.

anh. THF under Ar. The soln. was stirred at r.t. for 16 h. The solvent was removed *in vacuo*, and the residue was taken up in 20 ml of FC-72. The fluorous phase was washed with aq. citric acid solns. (10%) (2×5 ml), dried over Na_2SO_4, and concentrated *in vacuo*.

(4-{Tris[2-(perfluorohexyl)ethyl]silyl}benzyl) 2-{[(Furfuryl)amino]carbonyl}phenylcarbamate (**14a**): 160 mg (87%). ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.28–1.42 (*m*, 3 CH_2Si); 2.21–2.39 (*m*, 3 CH_2CF_2); 4.55 (*s*, NCH_2); 5.21 (*s*, PhCH_2); 6.29 (*d*, *J* = 1.5, 1 arom. H (furan)); 6.31 (*d*, *J* = 1.5, 1 arom. H (furan)); 6.79 (*t*, *J* = 5.0, NH); 7.25 (*t*, *J* = 5.0, 1 arom. H); 7.32 (*s*, 1 arom. H (furan)); 7.40 (*d*, *J* = 7.0, 1 arom. H); 7.51 (*d*, *J* = 7.5, 2 arom. H); 7.60 (*d*, *J* = 7.5, 2 arom. H); 7.72 (*m*, 1 arom. H); 8.34 (*d*, *J* = 6.5, 1 arom. H); 10.88 (*s*, NH). CI-MS (220°, 50 eV): 1419 (13, M^+), 1158 (53), 399 (7), 243 (100), 147 (14).

(4-{Tris[2-(perfluorohexyl)ethyl]silyl}benzyl) 4-Chloro-2-{[(furfuryl)amino]carbonyl}phenylcarbamate (**14b**): 175 mg (82%). ^{1}H-NMR (400 MHz, FC-72/C_6D_6-capillary): 1.31–1.40 (*m*, 3 CH_2Si); 2.21–2.41 (*m*, 3 CH_2CF_2); 4.60 (*s*, NCH_2); 5.25 (*s*, PhCH_2); 6.34 (*d*, *J* = 1.5, 2 arom. H (furan)); 6.82 (*d*, *J* = 4.5, NH); 7.35 (*m*, 2 arom. H); 7.55 (*d*, *J* = 7.5, 2 arom. H); 7.64 (*d*, *J* = 7.5, 2 arom. H); 7.80 (*m*, 1 arom. H); 8.38 (*s*, 1 arom. H); 10.95 (*s*, NH). EI-MS (230°, 70 eV): 1452 (4, M^+), 1175 (10), 1159 (34), 399 (41), 175 (51), 96 (100).

General Procedure for the Cyclization of the Amides **14a**,**b** to the Quinazoline-2,4-diones **15a**,**b**. To a soln. of 0.1 mmol of **14a**,**b** in 10 ml of DMF, 0.2 ml (0.14 mg, 1.0 mmol) of Et_3N were added. The cloudy mixture was heated in a vial with a screw cap to 110° for 16 h. After cooling to r.t., the vial was carefully opened, and the contents were poured into 50 ml of H_2O. The aq. phase was extracted with FC-72 (2×10 ml) and with AcOEt (2×10 ml). The org. phase[6]) was washed with 0.5M solns. of aq. HCl (2×5 ml), dried over Na_2SO_4, and concentrated *in vacuo* to yield the quinazoline-2,4-diones as colorless crystalline powders.

3-Furfurylquinazoline-2,4-dione (**15a**): 16 mg (66%). M.p. 245°. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 5.06 (*s*, PhCH_2); 6.29 (*d*, *J* = 2.6, 1 arom. H (furan)); 6.38 (*t*, *J* = 2.5, 1 arom. H (furan)); 7.20 (*m*, 2 arom. H); 7.52 (*s*, 1 arom. H (furan)); 7.65 (*t*, *J* = 7.8, 1 arom. H); 7.93 (*d*, *J* = 8.0, 1 arom. H); 11.00 (*s*, NH). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): 36.1 (NCH_2); 108.1 (arom. C); 109.8 (arom. C); 113.6 (arom. C); 114.9–134.3 (4 arom. C); 139.0 (arom. C); 141.2 (arom. C); 149.9 (arom. C); 150.0 (C=O); 161.7 (C=O). EI-MS (230°, 70 eV): 242 (100, M^+), 213 (16), 146 (22), 81 (45). Anal. calc. for $C_{13}H_{10}N_2O_3$ (242.07): C 64.46, H 4.16, N 11.56; found: C 64.33, H 4.10, N 11.52.

7-Chloro-3-furfurylquinazoline-2,4-dione (**15b**): 24 mg (90%). M.p. 256°. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 5.06 (*s*, PhCH_2); 6.30 (*d*, *J* = 2.6, 1 arom. H (furan)); 6.37 (*t*, *J* = 2.5, 1 arom. H (furan)); 7.20 (*s*, 1 arom. H); 7.25 (*d*, *J* = 7.8, 1 arom. H); 7.54 (*s*, 1 arom. H (furan)); 7.93 (*d*, *J* = 8.0, 1 arom. H); 11.60 (*s*, NH). ^{13}C-NMR (100 MHz, $(CD_{3)_2}SO$): 36.6 (NCH_2); 108.0 (arom. C); 110.5 (arom. C); 112.6 (arom. C); 114.6–139.5 (4 arom. C); 140.5 (arom. C); 142.1 (arom. C); 149.6 (arom. C); 150.1 (C=O); 160.8 (C=O). EI-MS (230°, 70 eV): 276 (100, M^+), 247 (13), 180 (36), 129 (76), 81 (91). Anal. calc. for $C_{13}H_9ClN_2O_3$ (276.03): C 56.43, H 3.28, N 10.13; found: C 55.98, H 3.02, N 9.83. FC-72 phase: 105 mg.

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6) The fluorous phase contained no cyclic products but some unreacted **14a** (*ca.* 25%) or **14b** (traces) together with compound **6**.

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