Fluorous Synthesis: Fluorous Protocols for the Ugi and Biginelli Multicomponent Condensations

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A new protocol for multicomponent condensation reactions that uses fluorous (highly fluorinated) substrates is introduced. This method takes advantage of the ease of purification of fluorous compounds by liquid−liquid extractions between fluorous and organic solvents. The application of this method to the Ugi and Biginelli reactions is described. The condensation products of these two reactions, amino acid amides and dihydropyrimidines, are easily obtained without chromatography in high purities, even though the other reagents are used in very large excesses. This is the first demonstration of the suitability of fluorous phase methods for combinatorial synthesis of "druglike" organic molecules.

Introduction

Combinatorial chemistry has rapidly become an important method for the identification and optimization of lead compounds in drug discovery.[1] In contrast to traditional solution organic synthesis, which often requires time-consuming purification procedures, combinatorial chemistry has been conducted almost exclusively on solid polymer supports.[2] Solid phase synthesis allows very simple product isolation by filtration, but this advantage at the isolation stage can be a detraction at the synthesis stage because reaction mixtures are inhomogeneous. To overcome these drawbacks, reactions of polymers that are soluble under certain conditions and insoluble under others have been introduced.[3] It has also been shown that imaginatively designed "traditional" solution reactions of organic molecules can provide powerful tools in combinatorial synthesis.[4]

The phase behavior of any reaction mixture, combinatorial or otherwise, is a crucial feature that affects the ease of purification.[5] To avoid chromatographic purification, reactions should be planned such that the phase of the desired product is different from the phases of all the other reaction components and undesired products. The "fluorous phase" [6−10] has recently been used to advantage in traditional organic synthesis. The new techniques rely on the ability of a "fluorous" (highly fluorinated) molecule to partition into the fluorous phase in a liquid−liquid extraction between an organic solvent and a fluorous solvent.[11,12] We have introduced a number of fluorous techniques for traditional and parallel liquid phase syntheses as well,[5,8,9,13] and we describe herein the full details[13] of our work on one of these techniques: "fluorous multicomponent condensations". These reactions are a variant of fluorous synthesis, which more generally encompasses all strategies in which the products partition into the fluorous phase during the purification.[13]

Figure 1 shows the analogy between solid phase synthesis and fluorous synthesis. In fluorous synthesis, the initial organic substrate is attached to a "fluorous label", which is of sufficient structure, size, and fluorine content to render the attached organic molecule fluorous.[12] One or more reactions are then conducted, and the fluorous components of the reaction are subsequently separated from all non-fluorous (organic, inorganic, solid, volatile) components by an appropriate phase separation technique (extraction has been the focus of the early work). At the desired stage, the fluorous label is cleaved and the product is rendered organic. Unlike solid phase techniques, fluorous synthesis allows the routine use of standard reagents and reaction conditions. If solvents are well chosen, it is possible to have a homogeneous solution (that is, no phase separation) at the reaction stage, but to readily induce phase separation by changing solvents at the purification stage. Furthermore, "fluorous labels" are much more robust than most polymers and linkers in current use for solid phase synthesis.

Results and Discussion

Multicomponent condensation strategies are capable of providing in a single step durable core structures and

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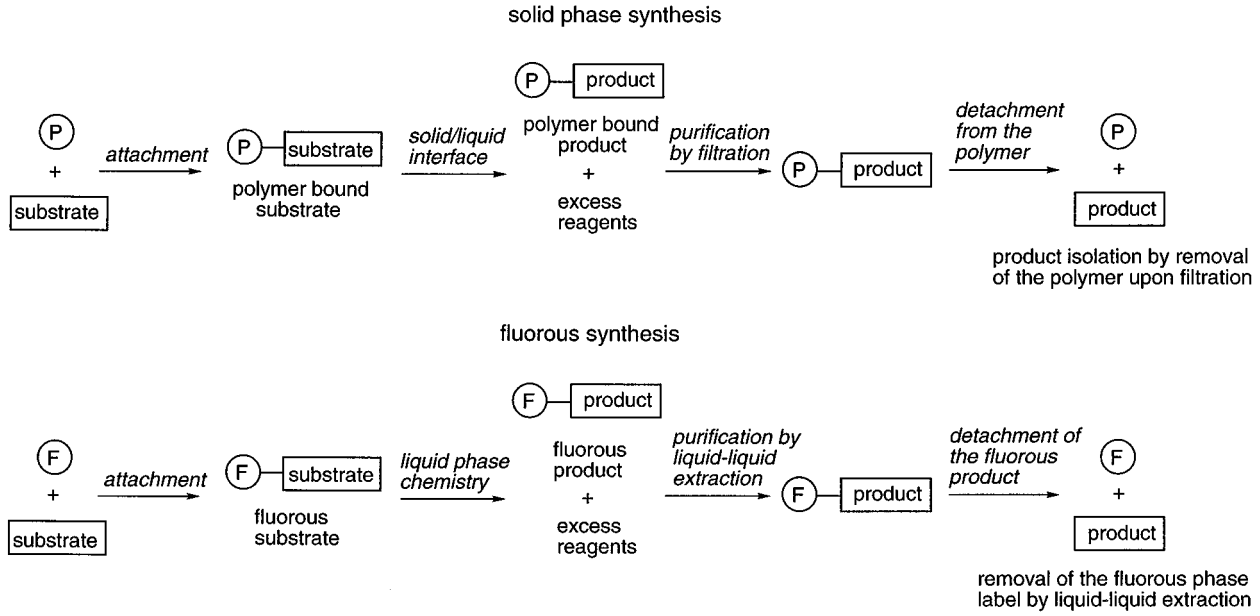
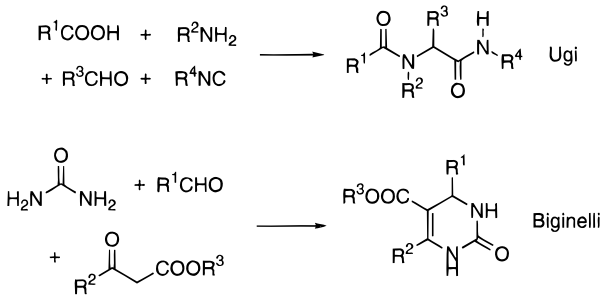


Figure 1.

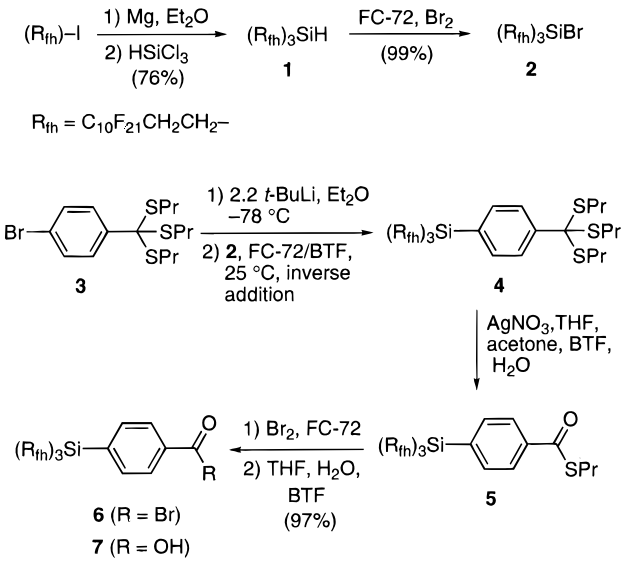
Scheme 1



highly variable side chains from simple starting materials. Therefore, these strategies are rapidly becoming a cornerstone of combinatorial syntheses of small-molecule libraries in the pharmaceutical industry.[1,16,17] The Ugi[14] and the Biginelli[15] reactions (Scheme 1) are two important classes of multicomponent condensations that have recently been adapted to solid phase techniques, and we therefore selected these reactions to test the potential of fluorous synthesis as a new strategy for multicomponent condensation.

We designed a fluorous tag based on silane chemistry because silanes are among the most useful substituents and protecting groups in modern organic synthesis.[18] Silane **1** is a new compound that was prepared by following the literature procedure for a lower analog.[19] The Grignard reagent derived from the commercially

Scheme 2



available 1-iodo-1*H*,1*H*,2*H*,2*H*-perfluorododecane was reacted with trichlorosilane in Et_2O (76%, Scheme 2). Brominolysis of **1** in FC-72[20] afforded bromosilane **2** in quantitative yield. This bromosilane is a generally useful fluorous labeling reagent. For the applications at hand, we selected acid **7** as a suitable common precursor.

Bromine−lithium exchange of orthothiobenzoate **3**[21] in Et_2O at −78 °C afforded the corresponding aryllithium compound, which was then transferred to a solution of **2** in FC-72/benzotrifluoride (BTF, $C_6H_5CF_3$) to provide the silylated orthothioester **4**. The fluorous orthothioester **4** was isolated by aqueous workup followed by partitioning of the crude product between benzene and FC-72.

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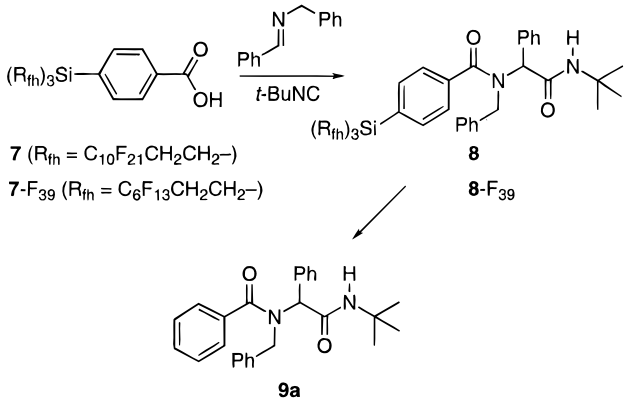
(20) FC-72 is a commercially available (3M) fluorocarbon liquid consisting mostly of isomers of C_6F_{14} (bp 56 °C; price $389/1 gal).
(21) **3** was prepared according to Breslow, R.; Pandey, P. S. *J. Org. Chem.* **1980**, *45*, 740.
(22) In the ^1H NMR spectrum of orthothioester **4** we could always observe some fluorous impurities. Attempts to purify **4** were not successful.

Scheme 3



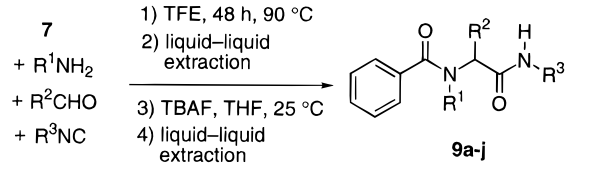
Evaporation of the FC-72 phase provided **4**, which was used for the subsequent reaction without further purification.[22] Treatment of **4** with $AgNO_3$ in a mixture of BTF, THF, acetone, and water yielded after column chromatography thioester **5** in 40−60% overall yield.[23] Oxidative cleavage of the thioester sulfur−carbon bond with bromine in FC-72 afforded the corresponding acyl bromide **6** (not characterized), which was hydrolyzed in aqueous THF to provide the highly fluorinated acid **7** as a white solid in 97% yield.

The Fluorous Ugi (or Flugi) Reaction. In the Ugi four-component reaction, an acid, an aldehyde, an amine, and an isonitrile are condensed to form the corresponding amino acid amide, as shown in Scheme 1.[14] Fluorous acid **7** can directly be used as the "labeled" component in the Ugi reaction.[24] To optimize the reaction conditions for the multiple component condensation, the reactions of acid **7** with a preformed imine (benzylbenzylideneamine) and *tert*-butyl isocyanide in different solvents were studied (Scheme 3). These trial reactions were run in sealed tubes with large excesses (up to 17 equiv each) of the imine and the isonitrile. After removal of the solvents, the crude reaction mixture was diluted with benzene and extracted three times with FC-72. Evaporation of the fluorous phase yielded the desired fluorous Ugi product **8** together with unreacted acid **7**. No resonances from these fluorous products could be identified in the ^{1}H NMR spectrum of the residue from the benzene layer, thereby proving the high efficiency of the extraction process. With CH_2Cl_2 as the organic phase for the extraction, more than 10% of the fluorous Ugi product remained in the organic layer even after multiple extractions with FC-72.

Three-component condensation reaction of **7**, benzylbenzylideneamine, and *tert*-butyl isocyanide in BTF/THF (1:1) at 90 °C for 38 h resulted in 30% conversion as determined by ^{1}H NMR analysis. In MeOH, the solvent normally used in non-fluorous Ugi reactions, 60% conversion was obtained after 48 h. Trifluoroethanol (CF_3CH_2OH, TFE) was found to be the solvent of choice. Like BTF,[8] TFE serves as a "hybrid organic/fluorous" solvent with the ability to dissolve both organic and fluorous compounds. High conversion (>90%) in the Ugi test reaction was obtained in 48 h by using TFE.

Acid **7** contains 63 fluorine atoms. We have also synthesized a "lower homolog" of acid **7** containing 39 fluorine atoms (4-tris((2-(perfluorohexyl)ethyl)silyl)benzoic acid, **7**-F_{39}). However, the corresponding Ugi product **8**-F_{39} obtained by three-component condensation with benzylbenzylideneamine and *tert*-butyl isocyanide could not efficiently be extracted from different organic solvents into FC-72. After three extractions with FC-72, only 11% (benzene), 9% (MeOH), and 8% (CH_2Cl_2) of **8**-F_{39} could be isolated from the fluorous phase. In simple terms, **8**-F_{39} is an organic compound rather than a fluorous compound.

Table 1. Examples of Fluorous Ugi Condensations



entry	R^1	R^2	R^3	**9**	yield (%)	purity (%)[a]
1	Bn	Ph	*t*-Bu	**a**	83	85
2	Bn	4-MeO-Ph	*t*-Bu	**b**	81	87
3	Bn	*c*-Hex	*t*-Bu	**c**	32	89
4	Pr	*c*-Hex	*c*-Hex	**d**	99	>95
5	Bn	Ph	*c*-Hex	**e**	92	80
6	Pr	*i*-Pr	*c*-Hex	**f**	71	>95
7	Bn	*i*-Pr	*c*-Hex	**g**	61	>95
8	Bn	*c*-Hex	*c*-Hex	**h**	84	>95
9	Bn	Et	*t*-Bu	**i**	75	93
10	Pr	*i*-Pr	*t*-Bu	**j**	78	81

[a] Determined by GC analysis.

The last step in the synthesis is desilylation, which corresponds to the cleavage of the product from the polymer in solid phase synthesis (see Figure 1). The silyl group was surprisingly stable toward many common desilylation procedures. No reaction occurred under basic conditions with LiOH in a mixture of THF and water. Exposure to HF·pyridine in THF and CsF in THF/MeOH also did not cleave the aryl−silicon bond, nor did trifluoroacetic acid in CH_2Cl_2.[25] However, with tetrabutylammonium fluoride (TBAF, 1.5 equiv) in THF, cleavage was accomplished within 30 min at room temperature. After evaporation of the solvent, the crude product was purified by two-phase extraction using benzene and FC-72. The fluorous phase containing the fluorosilane was discarded. The organic layer was additionally washed with 0.1 N HCl, aqueous Na_2CO_3, and brine to remove benzoic acid derived from unreacted acid **7**, excess TBAF, and any compounds derived from TBAF. The desired benzoylated amino acid amide **9a** was obtained in 83% yield.

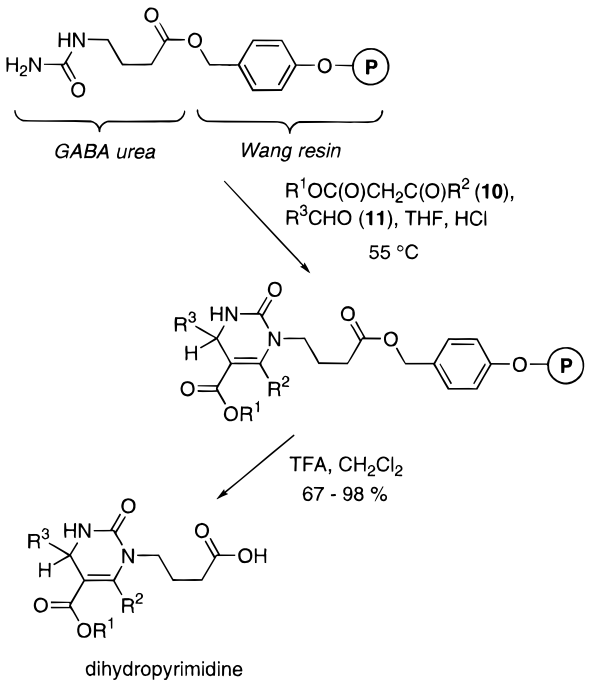
We applied these optimized conditions to the preparation of a small library of amino acids, and the results of these experiments are summarized in Table 1. Reactions were run on a 15 μmol scale to provide 2−5 mg of the final benzoylated amino acids **9b**−**j**. In two examples (entries 1 and 5), preformed imine was used. For the phenylglycine derivative **9a**, the corresponding four-component condensation reaction with benzaldehyde and benzylamine gave similar results to those described in entry 1. The yields of the overall process were modest to high (32−99%). For comparison, authentic samples of the products were synthesized by using the standard Ugi protocol (see Experimental Section). Purities were determined by GC analysis. The average purity of about

(23) Reactions were usually run on 0.5−0.7 mmol scale. If the reaction sequence was performed on a larger scale, a decrease in the yield was observed.

(24) For Ugi reactions on solid polymer supports, see ref 17.

(25) NMR spectra of acid **7** were recorded in neat deuterated trifluoroacetic acid.

Scheme 4



90% is in line with current standards for combinatorial synthesis. The purity seems to depend mainly on the aldehyde component: alkyl aldehydes give higher purities than aryl ones. The yields and purities are impressive considering that the Ugi products **9** are only minor components of the reaction due to the large excesses of reactants and the high molecular weight of the fluorous tag. These products consist of only 4 of the 52 molar equiv of reactants that are mixed in the Ugi reaction, and they have less than 6% of the total mass after desilylation.

The Fluorous Biginelli (or Fluginelli) Reaction. In the Biginelli dihydropyrimidine synthesis,[15] the one-pot cyclocondensation of β-keto esters, aldehydes, and ureas provides heterocycles of well-established pharmacological potential. We have recently reported[26] the first solid phase version of the Biginelli reaction and demonstrated its suitability for combinatorial chemistry.[27]

The solid phase Biginelli protocol uses a polymer bound urea which is reacted with different β-keto esters **10** and aldehydes **11** as shown in Scheme 4. This offers a superior alternative to the standard solution-based experimental variations of this reaction. Yields are generally higher by a margin of 10−20%, and no crystallization or chromatographic purification is necessary. We were able to obtain dihydropyrimidines of >90% purity (^{1}H NMR) and 80−95% yield after cleavage from the resin and filtration. However, this protocol has limitations imposed by the nature of the linkage group to the resin and the acidic conditions required in the cleavage reaction.

We have now developed a new protocol for the Biginelli reaction that takes advantage of the extraction of the product heterocycles into the fluorous phase. The major advantages of the solid phase protocol[26] such as the use of an excess of two or more reaction components and product separation without chromatography are preserved. The use of fluorous labels in the separation process allows for a greater flexibility in the choice of anchoring functions and cleavage conditions.

In a typical reaction, the urea **13** ($R_{fh} = C_{10}F_{21}CH_2CH_2$), obtained in 89% yield by the acylation of urea alcohol **12** with acyl bromide **6**, was stirred for 3 d at 50 °C with 10 equiv each of β-keto ester **10** and aldehyde **11** in the presence of catalytic HCl (Scheme 5). As with the Ugi reaction, the large excess of reactants was used both to drive the reaction to completion and to deliberately generate the separation of large amounts of organic reaction products. Optimal solubility of all the reaction components and a homogenous solution were achieved in a 2:1 mixture of THF/BTF. The crude reaction mixture was extracted with FC-72, and desilylation with TBAF in THF/BTF provided dihydropyrimidines **14** in 47−71% yield and >90% purity by ^{1}H NMR. Table 2 presents a range of examples of this method.

For comparison, the yields of standard Biginelli reactions with urea **15** according to Scheme 5 are listed side-by-side with the fluorous yields. In the absence of the fluorous or solid phase linkages, the excess of aldehyde and β-keto ester components had to be limited to 2 equiv to reduce the number of tedious chromatographic separations. We noted, however, a slight decrease in the reaction rate of the fluorous compared to the standard Biginelli reactions that might require a more extensive reaction optimization. In some fluorous Biginelli reactions (entries 7−10), we obtained a mixture of products. Our hypothesis is that in the case of a longer side chain ($R_2 = CH_2Bn$) or a less reactive aldehyde (R_3 = 4-MeO-Ph), the Biginelli reaction proceeds only slowly, giving rise to side products. This is reflected by a low product yield under the corresponding standard reaction conditions. The fluorous Biginelli heterocycles and the side products, sharing the same phase, were not separated in the liquid−liquid extraction step.

Attachment of one of the reactants in the Biginelli reaction to a fluorous tag allows a straightforward separation of the heterocyclic product by liquid−liquid extraction. The dihydropyrimidine can be obtained in an analytically pure form by cleavage of the fluorinated silyl group with TBAF and renewed liquid−liquid extraction. Compared to the standard protocol,[15] this method allows the rapid preparation of Biginelli products in comparable yields without any chromatographic separations. Compared to the solid phase procedure,[26] the fluorous Biginelli condensation results in slightly lower reaction yields but offers a greater flexibility in the selection of side-chain functionalities.

Conclusions

This work shows that a highly fluorinated silyl group containing 63 fluorine atoms can be used as a "fluorous phase marker" to replace the solid polymer support in combinatorial synthesis. "Organic" molecules with molecular weights of up to almost 500 were rendered "fluorous" upon attachment to this fluorous tag. The fluorous Ugi and Biginelli products have molecular weights of about 2000, of which roughly $^3/_5$ is fluorine, $^1/_5$ is other atoms of the tag (C, H, Si), and $^1/_5$ is the tagged organic moiety itself.

In contrast to most solid phase syntheses, reactions can be run in homogeneous phase and can be followed by TLC or other standard techniques. The products are single

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(27) For a related solid-phase modification of the Biginelli reaction, see: Robinett, L. D.; Yager, K. M.; Phelan, J. C. 211th National Meeting of the American Chemical Society, New Orleans, 1996; American Chemical Society: Washington, DC, 1996; ORGN 122.

Scheme 5

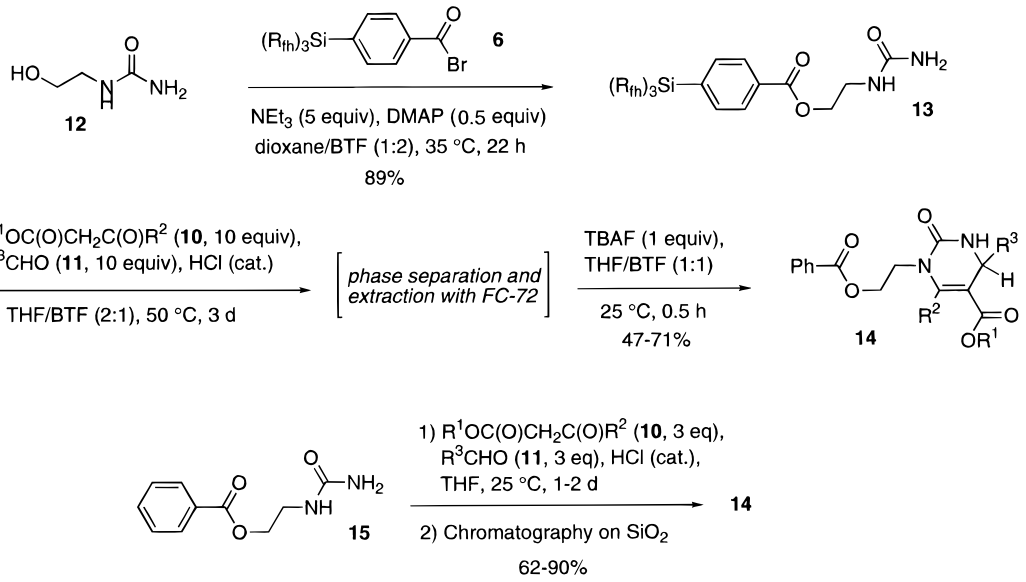

Table 2. Yields of Fluorous and Standard Biginelli Reactions according to Scheme 5

	β-keto ester **10**		aldehyde **11**	yields of dihydropyrimidine **14**		
entry	R^1	R^2	R^3	fluorous[a]	standard[b] [%]	compd
1	Et	Me	Ph	71	74	**a**
2	Et	Me	2-naphthyl	55	62	**b**
3	Et	Me	(4-MeO)Ph	69	78	**c**
4	Me	Me	2-naphthyl	70	90	**d**
5	Et	Et	2-naphthyl	60	66	**e**
6	Et	Et	Ph	47	73	**f**
7	Et	Et	(4-MeO)Ph	mixture	38	**g**
8	Me	Ch_2Bn	Ph	mixture	56	**h**
9	Me	Ch_2Bn	2-naphthyl	mixture	33	**l**
10	Me	Ch_2Bn	(4-MeO)Ph	mixture	18	**k**

[a] With urea **13**. [b] With urea **15**.

entities that can be characterized by standard spectroscopic methods as well. Purities can be assessed at any stage. Detachment and extractive purification provide the corresponding organic products in reasonable yields and acceptable purities without using conventional separation methods even when an unduly large excess of reactants is added. Considering the simple experimental techniques used in this fluorous chemistry, automation should be feasible, thus allowing the preparation of libraries of small molecules.

Experimental Section

General. Anhydrous solvents were freshly distilled from sodium benzophenone ketyl, P_2O_5, or CaH_2. FC-72 and FC-84 were obtained from 3M. FC-84 consists mostly of isomers of C_7F_{16} (bp 80 °C) and can be used instead of FC-72.

Tris(2-(perfluorodecyl)ethyl)silane (1). Magnesium powder (0.45 g, 18.5 mmol) was suspended in dry Et_2O (20 mL), and 1-iodo-1*H*,1*H*,2*H*,2*H*-perfluorododecane (0.50 g, 0.77 mmol) was added. The resulting suspension was sonicated for 30 min. A solution of 1-iodo-1*H*,1*H*,2*H*,2*H*-perfluorododecane (9.50 g, 14.7 mmol) in Et_2O (70 mL) was slowly added. The mixture was heated at reflux for 2 h. Trichlorosilane (0.40 mL, 3.87 mmol) was slowly added, and the reaction mixture was stirred under reflux for 16 h. After the mixture was cooled to 25 °C, saturated aqueous NH_4Cl and CH_2Cl_2 were added. The cloudy biphase was extracted five times with FC-72. Evaporation of the combined fluorous extracts yielded the crude product as a white solid. Removal of the impurity (dimer, Wurtz coupling product) by bulb-to-bulb distillation (0.5 Torr, 210 °C) yielded tris(2-(perfluorodecyl)ethyl)silane as a white solid (4.7 g, 76%): mp 76−78 °C; IR (FC-72) 2977, 2950, 2914, 2873, 2136, 1444, 1426 cm^{-1}; ^1H NMR (300 MHz, FC-72 with benzene as internal lock) δ 1.15−1.22 (m, 6 H), 2.24−2.41 (m, 6 H), 4.14 (s, 1 H).

Bromotris(2-(perfluorodecyl)ethyl)silane (2). Tris(2-(perfluorodecyl)ethyl)silane (**1**) (0.56 g, 0.34 mmol) was dissolved under argon in FC-72 (10 mL). Bromine (0.03 mL, 0.50 mmol) was added, and the mixture was stirred at 25 °C for 12 h. FC-72 (40 mL) was added, and the fluorous phase was washed with CH_2Cl_2. Evaporation of the fluorous layer yielded bromotris(2-(perfluorodecyl)ethyl)silane as a white solid (586 mg, 99%): mp 80−81 °C; IR (FC-72) 2980, 2953, 2907, 2847, 1444, 1423 cm^{-1}; ^1H NMR (300 MHz, FC-72 with benzene as internal lock) δ 1.41−1.55 (m, 6 H), 2.33−2.44 (m, 6 H).

Tripropyl 4-Bromoorthothiobenzoate (3). 4-Bromobenzoic acid (2.00 g, 9.95 mmol) was suspended in thionyl chloride (3 mL, 41.2 mmol) and heated at reflux for 60 min. Removal of the excess thionyl chloride and vacuum drying provided 4-bromobenzoyl chloride as a colorless solid. Propanethiol (10 mL, 109 mmol) was slowly added to a mixture of 4-bromobenzoyl chloride and anhydrous $AlCl_3$ (5.30 g, 39.7 mmol). The mixture was heated at 60 °C for 48 h, cooled, and poured slowly with stirring into ice-cooled 4 N aqueous NaOH (75 mL). Extraction with ether and washing of the organic phase with brine afforded after drying ($MgSO_4$) the crude product as a red oil. Purification by flash column chromatography (SiO_2, hexanes containing 1% of NEt_3) provided the orthothiobenzoate **3** as a colorless oil (1.78 g, 45%): IR (neat) 2962, 2929, 2871, 1582, 1483, 1456, 1391, 1378, 1337, 1291, 1237, 1076, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 9 H), 1.48−1.55 (m, 6 H), 2.54 (t, J = 7.3 Hz, 6 H), 7.43 (d, J = 8.7 Hz, 2 H), 7.73 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.80, 21.80, 33.82, 72.87, 121.53, 129.68, 130.94, 141.33. MS (EI) m/z 351 (M^+ − propyl), 349, 319 (M^+ − $S(CH_2)_2CH_3$), 317, 201, 109; HRMS calcd for $C_{13}H_{18}S_2{}^{81}Br$ (M^+ − $S(CH_2)_2CH_3$) m/z 319.0013, found 319.0000.

4-Tris((2-(perfluorodecyl)ethyl)silyl)thiobenzoic Acid *S*-Propyl Ester (5). Tripropyl 4-bromoorthothiobenzoate (**3**) (250 mg, 0.66 mmol) was dissolved in Et_2O (7.5 mL) and cooled to −78 °C under argon. *t*-BuLi (1.7 molar in pentane, 0.82 mL, 1.39 mmol) was slowly added, and the resulting yellow solution was stirred at that temperature for 45 min. The yellow aryllithium solution was then transferred via canula to a 25 °C mixture of bromo tris(2-(perfluorodecyl)ethyl)silane (**2**) (500 mg, 0.29 mmol) in BTF (15 mL) and FC-72 (2.5 mL). The reaction mixture was stirred at 25 °C for 30 min. After addition of H_2O, the reaction mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated to afford an oil which was taken up into FC-72 and washed with benzene. The benzene layer was

additionally extracted twice with FC-72. The combined fluorous layers were evaporated to yield the crude orthothioester **4** which was dissolved in BTF (7.5 mL), THF (7.5 mL), acetone (5 mL), and H_2O (0.5 mL) at 25 °C. $AgNO_3$ (135 mg, 0.80 mmol) was added, and the resulting suspension was stirred at 25 °C for 12 h. After filtration and evaporation of the filtrate, the crude product was purified by flash column chromatography (SiO_2, Et_2O/hexanes; 1/40) to afford **5** as a colorless solid (319 mg, 60%): mp 69−71 °C; IR ($CHCl_3$) 2970, 2935, 1668, 1246, 1193, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 3 H), 1.15−1.21 (m, 6 H), 1.68−1.75 (m, 2 H), 1.94−2.06 (m, 6 H), 3.08 (t, J = 7.1 Hz, 2 H), 7.54 (d, J = 8.0 Hz, 2 H), 8.03 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C) δ 1.60, 13.43, 23.00, 25.60 (t, J = 23.0 Hz), 31.19, 108.45−118.40 (m, CF_2, CF_3), 127.23, 133.99, 137.79, 139.27, 191.85.

4-Tris((2-(perfluorodecyl)ethyl)silyl)benzoic Acid (7). 4-Tris((2-(perfluorodecyl)ethyl)silyl)thiobenzoic acid *S*-propyl ester (**5**) (210 mg, 0.11 mmol) was dissolved in FC-72 (15 mL). Bromine (0.05 mL, 0.83 mmol) was added at 25 °C, and the mixture was stirred for 3 h. After addition of FC-72 (15 mL) and washing with CH_2Cl_2, the fluorous layer was evaporated to afford 4-tris((2-(perfluorodecyl)ethyl)silyl)benzoic acid bromide (**6**) as a colorless solid. The acid bromide **6** was dissolved in THF (12 mL) and BTF (3 mL). H_2O (1.5 mL) was added, and the solution was stirred at 25 °C for 12 h. Evaporation of the solvents afforded **7** as a colorless solid (196 mg, 97%): mp 134−136 °C; ^1H NMR (300 MHz, TFA-*d*) δ 1.35−1.39 (m, 6 H), 2.10−2.35 (m, 6 H), 7.78 (d, J = 8.1 Hz, 2 H), 8.27 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (75 MHz, TFA-d) δ 2.95, 27.42, 105−120 (m, CF_2, CF_3), 131.78, 132.05, 136.15, 142.95, 175.38; MS (EI) m/z 1243 ($M^+ - CH_2CH_2(CF_2)_9CF_3$), 706, 601, 474, 423, 378, 175.

4-Tris((2-(perfluorohexyl)ethyl)silyl)benzoic acid (7-F_{39}) was prepared according to the procedure for the preparation of acid **7**: mp 64−65 °C; IR ($CHCl_3$) 3500−2500 br, 1694, 1441, 1422, 1361, 1318, 1291, 1237, 1211 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17−1.23 (m, 6 H), 2.01−2.07 (m, 6 H), 7.59 (d, J = 8.0 Hz, 2 H), 8.18 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$ and two drops of CD_3OD) δ 1.18, 25.28 (t, J = 24 Hz), 104.61−122.89 (m, CF_2, CF_3), 129.78, 132.41, 133.66, 137.50, 168.82; MS (EI) m/z 1173 ($M^+ - OH$), 843 ($M^+ - CH_2CH_2(CF_2)_5CF_3$), 517, 414, 309, 239, 187.

***N*-(4-Tris([2-perfluorohexylethyl]silyl)benzoyl)-*N*-benzylphenylglycine *tert*-Butylamide (8-F_{39}).** 4-Tris((2-(perfluorohexyl)ethyl)silyl)benzoic acid (**7**-F_{39}) (0.070 g, 0.059 mmol), benzylbenzylideneamine (0.032 g, 0.164 mmol), and *tert*-butyl isocyanide (16 μL, 0.l4 mmol) were dissolved in MeOH (1 mL). The solution was heated at reflux for 46 h. Removal of the solvent and purification by flash column chromatography (SiO_2, 1/5 gradient ether/hexanes to 1/3 ether/hexanes) afforded the silylated amino acid amide as a foam (82 mg, 86%): IR ($CHCl_3$) 3424, 3067, 3031, 2969, 2934, 2245, 1682, 1636, 1515, 1498, 1451, 1364, 1350, 1315, 1294, 1238, 1210, 1145, 1121, 921, 900 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12−1.15 (m, 6 H), 1.33 (s, 9 H), 1.90−2.25 (m, 6 H), 4.44 (d br, J = 16.4 Hz, 1 H), 4.72 (d, J = 16.7 Hz, 1 H), 5.57 (s br, 1 H), 5.66 (s br, 2 H), 6.91 (s br, 2 H), 7.10 (s br, 4 H), 7.19−7.49 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.35, 25.32 (t, J = 24 Hz), 28.53, 51.73, 105.47−121.24 (m, CF_2, CF_3), 126.91, 128.24, 128.74, 128.93, 129.75, 133.66, 135.10, 137.48, 138.75, 168.25, 172.49; MS (FAB) m/z 1491 $(M + Na)^+$, 1469 $(M + H)^+$, 1173 $((R_f)_3SiC_6H_4CO)^+$. In extraction experiments, purified **8**-F_{39} was dissolved in the organic solvent and extracted three times with FC-72.

General Procedure for the Ugi Four-Component Condensation (General Procedure 1). 4-Tris((2-(perfluorodecyl)ethyl)silyl)benzoic acid (**7**) (26.2 mg, 0.015 mmol), the amine (0.25 mmol), the aldehyde (0.25 mmol), and the isonitrile (0.25 mmol) were added to a sealed tube with CF_3CH_2OH (0.3 mL). (For some examples, the preformed imine was used.) The suspension was heated under argon to 90 °C for 48 h. After removal of the solvent, the residue was diluted with FC-72 (15 mL) and washed with benzene (15 mL). The benzene layer was additionally extracted twice with FC-72 (15 mL). The combined fluorous phases were evaporated to yield the perfluorosilylated amino acid amide. For desilylation, the amino acid amide was dissolved at 25 °C in THF (2 mL); TBAF (1 M in THF, 0.022 mL, 0.022 mmol) was added, and the resulting solution was stirred at 25 °C for 30 min. After removal of the solvent, the residue was diluted with benzene (30 mL) and washed twice with FC-72 (15 mL). Et_2O (30 mL) was added to the organic layer which was washed with 0.1 N HCl, saturated aqueous Na_2CO_3, and brine (15 mL each). The organic phase was dried ($MgSO_4$) and evaporated to yield the benzoylated amino acid amide **9**. The purity was checked by GC analysis.

***N*-Benzoyl-*N*-benzylphenylglycine *tert*-butylamide (9a)** was prepared according to general procedure 1 with the acid **7** (26.2 mg, 0.015 mmol), benzylbenzylideneamine (51 mg, 0.25 mmol), and *tert*-butyl isocyanide (30 μL, 0.25 mmol) to afford the silylated amino acid **8**: IR ($CHCl_3$) 1684, 1631, 1518, 1240, 1218, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1,14 (s br, 6 H), 1.34 (s, 9 H), 1.90−2.20 (br, 6 H), 4.35−4.50 (br, 1 H), 4.71 (d, J = 17.6, 1 H), 5.52 (s, 1 H), 5.63 (s, 1 H), 6.91 (s br, 2 H), 7.26 (s br, 4 H), 7.30−7.49 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.50, 25.54, 28.75, 51.93, 105−125 (m, CF_2, CF_3), 127.08, 127.15, 127.24, 128.45, 128.95, 129.15, 129.25, 129.98, 137.63, 138.89, 168.42, 172.70. Desilylation as described in general procedure 1 in THF (2 mL) with TBAF (0.022 mL, 0.022 mmol) afforded **9a** (5.0 mg, 83%) with 85% purity: IR ($CHCl_3$) 3424, 3066, 3032, 2969, 2934, 2907, 2246, 1681, 1635, 1514, 1496, 1453, 1430, 1409 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9 H), 4.47 (s br, 1 H), 4.73 (d, J = 16.4 Hz, 1 H), 5.46 (s, 1 H), 5.40−5.75 (s br, 1 H), 7.03 (s br, 2 H), 7.13−7.16 (m, 4 H), 7.26−7.49 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.67, 51.74, 126.79, 127.02, 128.41, 128.66, 128.92, 129.73, 129.90, 135.33, 136.46, 168.53, 173.38; MS (EI) m/z 328 ($M^+ - NHC(CH_3)_3$), 300 ($M^+ - CONHC(CH_3)_3$), 210, 191, 105, 91, 77; HRMS calcd for $C_{21}H_{18}NO$ ($M^+ - CONHC(CH_3)_3$) m/z 300.1388, found 300.1389.

***N*-Benzoyl-*N*-benzyl-4-methoxyphenylglycine *tert*-butylamide (9b)** was prepared according to general procedure 1 with the acid **7** (26.1 mg, 0.015 mmol), benzylamine (27 μL, 0.25 mmol), anisaldehyde (30 μL, 0.25 mmol), and *tert*-butyl isocyanide (30 μL, 0.25 mmol) to afford after desilylation **9b** (5.1 mg, 81%) with 87% purity: IR ($CHCl_3$) 3423, 3066, 3031, 2968, 2937, 2911, 2246, 1681, 1633, 1581, 1512, 1455, 1412, 1395, 1366, 1339, 1306, 1252, 1224, 1179, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9 H), 3.77 (s, 3 H), 4.43 (s br, 1 H), 4.72 (d, J = 16.4 Hz, 1 H), 5.43 (s, 1 H), 5.40−5.70 (s br, 1 H), 6.79 (d, J = 8.3 Hz, 2 H), 7.02−7.47 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.70, 51.67, 55.42, 114.24, 126.77, 126.92, 127.25, 128.35, 128.58, 129.79, 131.18, 136.60, 159.76, 168.84, 173.28; MS (EI) m/z 430 (M^+), 358 ($M^+ - NHC(CH_3)_3$), 330 ($M^+ - CONHC(CH_3)_3$), 240, 224, 105, 91, 77; HRMS calcd for $C_{22}H_{20}NO_2$ ($M^+ - CONHC(CH_3)_3$) m/z 330.1494, found 330.1498.

***N*-Benzoyl-*N*-benzylcyclohexylglycine *tert*-butylamide (9c)** was prepared according to general procedure 1 with the acid **7** (24.0 mg, 0.013 mmol), benzylamine (27 μL, 0.25 mmol), cyclohexanecarboxaldehyde (30 μL, 0.25 mmol), and *tert*-butyl isocyanide (30 μL, 0.25 mmol) to afford after desilylation **9c** (1.7 mg, 32%) with 89% purity: mp 140−141 °C; IR ($CHCl_3$) 2964, 2935, 2858, 2249, 1674, 1618, 1510, 1452, 1363 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90−2.00 (m, 10 H), 1.31 (s, 9 H), 2.38 (m, 1 H), 4.14 (d, J = 10.5 Hz, 1 H), 4.44 (d, J = 16.1 Hz, 1 H), 4.70 (d, J = 16.1 Hz, 1 H), 5.30 (s br, 1 H), 6.90−7.50 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.06, 25.88, 26.49, 28.80, 29.77, 30.32, 36.50, 51.19, 52.65, 126.72, 127.25, 127.64, 128.31, 128.53, 129.74, 136.99, 137.41, 169.42, 173.99; MS (EI) m/z 406 (M^+), 306 ($M^+ - CONHC(CH_3)_3$), 216, 197, 105, 91, 77; HRMS calcd for $C_{26}H_{34}N_2O_2$ m/z 406.2620, found 406.2635.

***N*-Benzoyl-*N*-propylcyclohexylglycine cyclohexylamide (9d)** was prepared according to general procedure 1 with the acid **7** (26.4 mg, 0.015 mmol), propylamine (21 μL, 0.25 mmol), cyclohexanecarboxaldehyde (30 μL, 0.25 mmol), and cyclohexyl isocyanide (31 μL, 0.25 mmol) to afford after desilylation **9d** (5.7 mg, 99%) with >95% purity: mp 110−112 °C; IR ($CHCl_3$) 2934, 2856, 2244, 1660, 1613, 1578, 1529, 1450, 1419, 1352 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.61 (t, J = 7.3 Hz, 3 H), 0.85−1.84 (m, 22 H), 2.39 (m, 1 H), 3.20 (m,

2 H), 3.75−3.78 (m, 1 H), 4.00 (s br, 1 H), 7.34−7.43 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.21, 22.59, 24.71, 25.79, 26.50, 29.69, 30.47, 32.79, 32.97, 35.53, 47.75, 126.64, 128.61, 129.76, 136.96, 170.27, 173.70; MS (EI) *m*/*z* 384 (M^+), 258 (M^+ − $CONHC_6H_{11}$), 223, 105, 77; HRMS calcd for $C_{24}H_{36}N_2O_2$ *m*/*z* 384.2777, found 384.2781.

***N*-Benzoyl-*N*-benzylphenylglycine cyclohexylamide (9e)** was prepared according to general procedure 1 with the acid **7** (27.1 mg, 0.015 mmol), benzylbenzylideneamine (51 mg, 0.25 mmol), and cyclohexyl isocyanide (31 μL, 0.25 mmol) to afford after desilylation **9e** (5.2 mg, 92%) with 80% purity: IR ($CHCl_3$) 3422, 3066, 3031, 2935, 2857, 2246, 1673, 1634, 1603, 1515, 1497, 1452, 1431, 1411, 1349, 1313, 1253 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07−2.20 (m, 10 H), 3.83 (m br, 1 H), 4.47 (s br, 1 H), 4.70 (s br, 1 H), 5.47 (s, 1 H), 5.67 (s br, 1 H), 7.12−7.49 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.91, 25.60, 32.84, 48.71, 126.83, 127.15, 128.51, 128.73, 128.99, 129.73, 129.96, 135.24, 136.34, 168.39, 173.36; MS (EI) *m*/*z* 321 (M^+ − PhCO), 300 (M^+ − $CONHC_6H_{11}$), 217, 210, 105, 91, 77; HRMS calcd for $C_{21}H_{18}NO$ (M^+ − $CONHC_6H_{11}$) 300.1388, found 300.1398.

***N*-Benzoyl-*N*-propylvaline cyclohexylamide (9f)** was prepared according to general procedure 1 with the acid **7** (25.8 mg, 0.014 mmol), propylamine (21 μL, 0.25 mmol), isobutyraldehyde (23 μL, 0.25 mmol), and cyclohexyl isocyanide (31 μL, 0.25 mmol) to afford after desilylation **9f** (3.5 mg, 71%) with >95% purity. The physical data are in agreement with those reported in literature.

***N*-Benzoyl-*N*-benzylvaline cyclohexylamide (9g)** was prepared according to general procedure 1 with the acid **7** (26.1 mg, 0.015 mmol), benzylamine (27 μL, 0.25 mmol), isobutyraldehyde (23 μL, 0.25 mmol), and cyclohexyl isocyanide (31 μL, 0.25 mmol) to afford after desilylation **9g** (3.5 mg, 61%) with >95% purity: mp 131−133 °C; IR ($CHCl_3$) 3423, 3303, 3064, 3029, 2970, 2931, 2860, 2242, 1665, 1617, 1518, 1450, 1340, 1309 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78−1.37 (m, 11 H), 1.51−1.79 (m, 5 H), 2.69 (m br, 1 H), 3.63 (m br, 1 H), 4.16 (d, J = 10.6 Hz, 1 H), 4.44 (d, J = 15.8 Hz, 1 H), 4.67 (d, J = 15.9 Hz, 1 H), 6.93 (s br, 2 H), 7.11−7.26 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.39, 19.91, 24.63, 25.53, 27.24, 32.58, 32.87, 47.76, 52.54, 68.17, 126.57, 127.20, 127.49, 128.17, 128.42, 129.64, 136.79, 137.08, 169.27, 173.92; MS (EI) *m*/*z* 287 (M^+ − PhCO), 266 (M^+ − $CONHC_6H_{11}$), 211, 183, 105, 91, 77; HRMS calcd for $C_{18}H_{27}N_2O$ (M^+ − PhCO) *m*/*z* 287.2123, found 287.2128.

***N*-Benzoyl-*N*-benzylcyclohexylglycine cyclohexylamide (9h)** was prepared according to general procedure 1 with the acid **7** (26.2 mg, 0.015 mmol), benzylamine (27 μL, 0.25 mmol), cyclohexanecarboxaldehyde (30 μL, 0.25 mmol), and cyclohexyl isocyanide (31 μL, 0.25 mmol) to afford after desilylation **9h** (5.3 mg, 84%) with >95% purity: mp 181−182 °C; IR ($CHCl_3$) 2933, 2856, 2246, 1671, 1620, 1515, 1451, 1415, 1351, 1329 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85−1.84 (m, 20 H), 2.41 (m, 1 H), 3.65−3.71 (m, 1 H), 4.15 (d, J = 11.0 Hz, 1 H), 4.45 (d, J = 15.8 Hz, 1 H), 4.67 (d, J = 15.9 Hz, 1 H), 4.92 (s br, 1H), 6.96 (s br, 2 H), 7.15−7.43 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.72, 25.62, 25.77, 26.41, 29.73, 30.32, 32.69, 32.99, 36.31, 47.85, 126.67, 127.25, 127.50, 128.25, 128.47, 129.70, 136.89, 137.24, 169.26, 174.01; MS (EI) *m*/*z* 432 (M^+), 327 (M^+ − PhCO), 306 (M^+ − $CONHC_6H_{11}$), 223, 105, 91, 77; HRMS calcd for $C_{28}H_{36}N_2O_2$ (M^+) *m*/*z* 432.2793, found 432.2778.

***N*-Benzoyl-*N*-benzylethylglycine *tert*-butylamide (9i)** was prepared according to general procedure 1 with the acid **7** (26.3 mg, 0.015 mmol), benzylamine (27 μL, 0.25 mmol), propanal (18 μL, 0.25 mmol), and *tert*-butyl isocyanide (30 μL, 0.25 mmol) to afford after desilylation **9i** (3.9 mg, 75%) with 93% purity: IR ($CHCl_3$) 3417, 2974, 2937, 2879, 2249, 1675, 1512, 1458, 1367 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80−1.10 (m br, 3 H), 1.32 (s, 9 H), 1.70−2.10 (m, 2 H), 4.58 (s br, 2 H), 4.70−4.80 (br, 1H), 6.90−7.60 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.08, 21.52, 28.68, 51.25, 51.51, 126.67, 127.74, 128.41, 128.64, 129.98, 136.50, 168.68, 173.98; MS (EI) *m*/*z* 352 (M^+), 300, 280 (M^+ − $NHC(CH_3)_3$), 252 (M^+ − $CONHC(CH_3)_3$), 210, 105, 91, 77; HRMS calcd for $C_{22}H_{28}N_2O_2$ (M^+) *m*/*z* 352.2151, found 352.2165.

***N*-Benzoyl-*N*-propylvaline *tert*-butylamide (9j)** was prepared according to general procedure 1 with the acid **7** (23.1 mg, 0.013 mmol), propylamine (21 μL, 0.25 mmol), isobutyraldehyde (23 μL, 0.25 mmol), and *tert*-butyl isocyanide (30 μL, 0.25 mmol) to afford after desilylation **9j** (3.2 mg, 78%) with 81% purity: IR ($CHCl_3$) 2967, 2935, 2875, 2245, 1679, 1668, 1613, 1578, 1550, 1535, 1496, 1458, 1419, 1340, 1225 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.56 (t, J = 7.1 Hz, 3 H), 0.75−1.60 (m, 8 H), 1.31 (s, 9 H), 2.60 (m, 1 H), 3.17 (t, J = 7.3 Hz, 2 H), 3.90 (s br, 1 H), 7.26−7.36 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.27, 19.35, 20.08, 22.57, 26.54, 28.74, 50.93, 126.61, 128.62, 129.73, 136.95, 170.38, 173.67; MS (EI) *m*/*z* 318 (M^+), 246 (M^+ − $NHC(CH_3)_3$), 218 (M^+ − $CONHC(CH_3)_3$), 105, 91, 77; HRMS calcd for $C_{19}H_{30}N_2O_2$ (M^+) *m*/*z* 318.2307, found 318.2322.

General Procedure for Conventional Ugi Reactions. Benzoic acid (122 mg, 1.00 mmol), the aldehyde (1 mmol), the amine (1 mmol), and the isonitrile (1 mmol) were dissolved in MeOH (2 mL) and stirred at room temperature (16−24 h). After evaporation of the solvent, the residue was diluted with Et_2O and washed with 0.1 N HCl, saturated aqueous Na_2CO_3, and brine. The organic phase was dried ($MgSO_4$) and evaporated to yield the crude product. Purification by flash column chromatography (SiO_2, Et_2O/hexanes; 1/1) afforded the amino acid amide **9**.

(2-((4-(Tris(2-(perfluorodecyl)ethyl)silyl)benzoyl)-oxy)ethyl)urea (13). A solution of thioester **5** (88 mg, 47.6 μmol) in FC-72 (6 mL) was treated at 25 °C with bromine (30 μL, 0.58 mmol). After 0.5 h, the mixture was extracted with dichloromethane (10 mL). The dichloromethane phase was extracted with FC-72 (3 × 10 mL). The combined fluorous phases were filtered and evaporated. The resulting acid bromide **6** (88 mg) was diluted with BTF (1.0 mL) and added to a suspension of (hydroxyethyl)urea **12** (27 mg, 0.26 mmol), triethylamine (36 μL, 0.26 mmol), and 4-(dimethylamino)pyridine (3 mg, 25 μmol) in dry dioxane (0.50 mL) at 35 °C. After the mixture was stirred for 22 h at 35 °C, the volatiles were removed in vacuo and FC-72 (20 mL), water (10 mL), and toluene (5 mL) were added. The combined water/toluene phases were washed with FC-72 (5 × 10 mL). The combined fluorous phases were filtered and concentrated to give **13** as a white solid (79 mg, 89%): mp 101−103 °C; IR (neat) 3500−3100, 1718, 1662, 1558, 1207, 1149, 896, 739, 665, 532 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 8.10 (d, J = 8.1 Hz, 2 H), 7.86 (d, J = 8.1 Hz, 2 H), 5.96 (bs, 1 H), 5.13 (bs, 2 H), 4.35 (t, J = 5.5 Hz, 2 H), 3.53 (q, J = 5.5 Hz, 2 H), 2.45−2.20 (m, 6 H), 1.50−1.40 (m, 6 H); ^{13}C NMR (acetone-d_6) δ 166.6, 159.3, 139.7, 135.2, 132.8, 129.8, 119.5−109.5 (m, CF_2, CF_3), 65.6, 39.6, 26.0 (t, J = 23.9 Hz), 1.7; MS (El) *m*/*z* (relative intensity) 1329 ([M^+ − $CH_2CH_2C_{10}F_{21}$], 4), 1268 (25), 1243 (8), 1225 (9), 740 (46), 615 (29), 509 (93), 439 (100).

General Procedure for Fluorous Biginelli Reactions (General Procedure 2). A solution of **13** (18 mg, 9.6 μmol) in THF/BTF (2/1, 0.75 mL) was treated at 25 °C with 10 equiv of β-keto ester **10**, 10 equiv of aldehyde **11**, and concentrated HCl (1 μL). After 3 days at 50 °C, volatiles were removed in vacuo and FC-84 and toluene (10 mL each) were added. The toluene phase was extracted with FC-84 (5 × 5 mL). The combined fluorous phases were filtered and concentrated. The resulting white solid was diluted with THF/BTF (1:1, 0.50 mL) and treated dropwise with a 1 M tributylammonium fluoride (TBAF) solution in THF (10 μL, 10 μmol). After the mixture was stirred for 0.5 h at 25 °C, volatiles were removed in vacuo and FC-84 and toluene were added (10 mL each). The fluorous phase was extracted with toluene (3 × 5 mL). The combined toluene phases were extracted with saturated aqueous $NaHCO_3$ solution (3 × 10 mL) and brine (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting dihydropyrimidines **14** were spectroscopically (^{1}H NMR) identical to those prepared by the conventional procedure.

1-(2-(Benzoyloxy)ethyl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (14a) was prepared according to general procedure 2 to afford **14a** (2.8 mg, 6.9 μmol, 71%): mp 129 °C; IR ($CHCl_3$) 3425, 3016, 1711, 1684, 1623, 1450, 1392, 1270, 1178 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 7.8 Hz, 2H), 7.60−7.10 (m, 8 H), 5.39

(bs, 2 H), 4.50−4.40 (m, 3 H), 4.15−3.90 (m, 3 H), 2.60 (s, 3 H), 1.18 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.3, 165.9, 153.4, 148.0, 143.0, 133.1, 129.6, 128.6, 128.4, 127.7, 126.0, 105.3, 63.4, 60.2, 54.0, 40.9, 16.4, 14.1; MS (El) m/z (relative intensity) 408 (M^+, 4), 393 (16), 331 (16), 303 (8), 286 (6), 259 (20), 209 (10), 149 (100), 105 (99), 77 (54); HRMS calcd for $C_{23}H_{24}N_2O_5$ 408.1672, found 408.1685.

1-(2-(Benzoyloxy)ethyl)-6-methyl-2-oxo-4-(2-naphthyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (14b) was prepared according to general procedure 2 to afford **14b** (2.4 mg, 5.2 μmol, 55%): IR (neat) 3342, 2977, 1714, 1679, 1621, 1450, 1390, 1269, 1219, 1182, 1108, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.95−7.25 (m, 12 H), 5.58 (d, J = 2.8 Hz, 1 H), 5.49 (d, J = 2.8 Hz, 1 H), 4.60−4.35 (m, 3 H), 4.15−4.00 (m, 3 H), 2.63 (s, 3 H), 1.18 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.4, 166.2, 153.7, 148.4, 140.5, 133.2, 132.9, 129.7, 128.8, 128.5, 128.0, 127.6, 126.3, 126.0, 125.0, 124.4, 105.3, 63.6, 60.4, 54.3, 41.2, 16.6, 14.3; MS (El) m/z (relative intensity) 458 (M^+, 26), 443 (22), 412 (9), 385 (11), 353 (11), 331 (24), 309 (30), 263 (6), 209 (12), 149 (100), 105 (87), 77 (36); HRMS calcd for $C_{27}H_{26}N_2O_5$ 458.1842, found 458.1842.

1-(2-(Benzoyloxy)ethyl)-6-methyl-2-oxo-4-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (14c) was prepared according to general procedure 2 to afford **14c** (2.9 mg, 6.6 μmol, 69%): mp 75 °C; IR ($CHCl_3$) 3425, 3025, 1704, 1677, 1621, 1514, 1454, 1392, 1270, 1174, 1114, 1069 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 7.1 Hz, 2 H), 7.56 (t, J = 7.6 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 2 H), 7.14 (d, J = 8.7 Hz, 2 H), 6.62 (d, J = 8.7 Hz, 2 H), 5.34 (bs, 2 H), 4.50−4.40 (m, 3 H), 4.15−3.95 (m, 3 H), 3.66 (s, 3H), 2.60 (s, 3 H), 1.19 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.4, 166.2, 159.0, 153.9, 147.9, 135.5, 133.2, 129.7, 128.5, 127.4, 113.9, 105.8, 63.6, 60.3, 55.1, 53.3, 40.9, 16.5, 14.3; MS (El) m/z (relative intensity) 438 (M^+, 5), 423 (27), 365 (13), 331 (7), 316 (6), 289 (30), 243 (6), 209 (5), 149 (92), 105 (100), 77 (50); HRMS calcd for $C_{24}H_{26}N_2O_6$ 438.1787, found 438.1791.

1-(2-(Benzoyloxy)ethyl)-6-methyl-2-oxo-4-(2-naphthyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (14d) was prepared according to general procedure 2 to afford **14d** (3.0 mg, 6.8 μmol, 70%): mp 116 °C; IR ($CHCl_3$) 3425, 3012, 1708, 1683, 1623, 1454, 1392, 1275, 1188, 1115, 1076 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 2 H), 7.70−7.30 (m, 10 H), 5.57 (d, J = 2.6 Hz, 1 H), 5.52 (bs, 1 H), 4.55−4.45 (m, 3 H), 4.10−3.95 (m, 1 H), 3.66 (s, 3 H), 2.63 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.5, 166.3, 153.9, 148.7, 140.3, 133.1, 132.8, 129.5, 128.7, 128.3, 128.0, 127.5, 126.1, 125.9, 124.7, 124.2, 104.9, 63.5, 53.8, 51.5, 41.0, 16.5; MS (El) m/z (relative intensity) 444 (M^+, 10), 429 (10), 339 (6), 317 (12), 295 (15), 149 (81), 105 (100), 77 (35); HRMS calcd for $C_{26}H_{24}N_2O_5$ 444.1686, found 444.1685.

1-(2-(Benzoyloxy)ethyl)-6-ethyl-2-oxo-4-(2-naphthyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (14e) was prepared according to general procedure 2 to afford **14e** (2.7 mg, 5.7 μmol, 60%): IR (neat) 3340, 2981, 1704, 1681, 1614, 1454, 1382, 1269, 1182, 1108, 1067 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 7.1 Hz, 2H), 7.70−7.25 (m, 10 H), 5.55 (d, J = 3.3 Hz, 1 H), 5.52 (bs, 1 H), 4.55−4.45 (m, 3 H), 4.20−4.05 (m, 2 H), 4.05−3.85 (m, 1 H), 3.55−3.35 (m, 1 H), 2.90−2.75 (m, 1 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.4, 165.7, 154.4, 154.1, 140.4, 133.2, 133.0, 129.7, 129.5, 128.9, 128.4, 128.1, 127.7, 126.3, 126.1, 125.0, 124.3, 104.5, 63.7, 60.5, 53.9, 40.8, 22.1, 14.3, 13.1; MS (El) m/z (relative intensity) 472 (M^+, 14), 443 (25), 350 (11), 323 (14), 277 (7), 223 (13), 149 (100), 105 (95), 77 (41); HRMS calcd for $C_{28}H_{28}N_2O_5$ 472.1980, found 472.1998.

1-(2-(Benzoyloxy)ethyl)-6-ethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (14f) was prepared according to general procedure 2 to afford **14f** (1.9 mg, 4.5 μmol, 47%): mp 111 °C; IR (neat) 3340, 2981, 1714, 1687, 1616, 1450, 1383, 1269, 1209, 1172, 1108, 1074 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 7.2 Hz, 2 H), 7.55−7.05 (m, 8 H), 5.41 (bs, 1 H), 5.36 (d, J = 3.2 Hz, 1 H), 4.55−4.40 (m, 3 H), 4.20−4.00 (m, 2 H), 4.00−3.85 (m, 1 H), 3.50−3.30 (m, 1 H), 2.90−2.70 (m, 1 H), 1.23 (t, J = 7.3 Hz, 3 H), 1.19 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.4, 165.7, 154.2, 154.1, 143.2, 133.2, 129.7, 128.7, 128.5, 127.8, 126.2, 104.6, 63.7, 60.4, 53.7, 40.7, 22.0, 14.2, 13.0; MS (El) m/z (relative intensity) 422 (M^+, 5), 393 (95), 377 (10), 345 (31), 317 (14), 273 (35), 243 (8), 223 (36), 195 (11), 149 (100), 105 (92), 77 (52); HRMS calcd for $C_{24}H_{26}N_2O_5$ 422.1827, found 422.1842.

General Procedure for Conventional Biginelli Reactions. A solution of ((benzoyloxy)ethyl)urea (**15**) (174 mg, 0.84 mmol) in THF (5 mL) was treated with β-keto ester **10** (2.52 mmol), aldehyde **11** (2.52 mmol), and concentrated HCl (25 μL). The solution was stirred at room temperature. The reaction was followed by TLC, and after completion (1−2 d), the reaction mixture was concentrated in vacuo and the residue purified by chromatography on SiO_2 (ethyl acetate/hexanes 1:1) to provide the dihydropyrimidine **14**.

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Supporting Information Available: ^{1}H NMR spectra of the precursors and products of the Ugi and Biginelli condensations (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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