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# Organocatalysis with a Fluorous Tag: Asymmetric Reduction of Imines with Trichlorosilane Catalyzed by Amino Acid-Derived Formamides†

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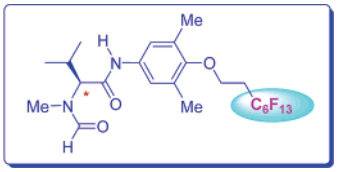
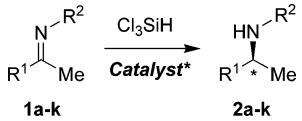



Asymmetric reduction of ketimines **1** with trichlorosilane can be catalyzed by *N*-methylvaline-derived Lewis-basic formamides **3a**−**d** with high enantioselectivity (≤95% ee) and low catalyst loading (1−5 mol %) at room temperature in toluene. Appending a fluorous tag, as in **5a**−**c**, simplifies the isolation procedure, while preserving high enantioselectivity (≤92% ee).

## Introduction

Obtaining chiral amines from ketones via imine intermediates represents an attractive strategy that opens a straightforward route to valuable building blocks for pharmaceutical and other fine chemical industries. Conversion of imines **1** into amines **2** (Scheme 1) via catalytic hydrogenation has now evolved into an established method, with a variety of metals and chiral ligands[1−4] in the portfolio. The latter methodology can be regarded as an advanced alternative to stoichiometric processes, such as hydride reduction, for which the enantioselective version[1] would be less economical.

**SCHEME 1. Asymmetric Reduction of Ketimines**[a]




[a] For $R^1$ and $R^2$ see Tables 1 and 2.

Owing to its simplicity and apparent environmental friendliness, asymmetric hydrogenation[1,2] is often regarded as the method of choice, especially in view of the fact that $H_2$ is the only stoichiometric reagent here. However, even this robust methodology is not entirely free of problems. Thus, to proceed efficiently in the case of prochiral imines, high pressure is

† Dedicated to Prof. Gilbert Stork on the occasion of his 85th birthday.

(1) For a general overview of the reduction of imines, see the following: (a) Morrison, J. D. *Asymmetric Synthesis*; Academic: New York, 1983; Vol. 2. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, 1994. (c) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; J. Wiley and Sons: New York, 2000. (d) James, B. R. *Catal. Today* **1997**, *37*, 209. (e) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (f) Cho, B. T. *Tetrahedron* **2006**, *62*, 7621.

(2) For recent reports on catalytic hydrogenation (with Ti, Ir, Rh, and Ru), see refs 1b−d and the following: (a) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425. (b) Jiang, X. B.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Andrien, J. G. O.; Boogers, J. A. F.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 1503. (c) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195. (d) Okuda, J.; Verch, S.; Stürmer, R.; Spaniol, T. S. *J. Organomet. Chem.* **2000**, *605*, 55. (e) Guiu, E.; Muñoz, B.; Castillón, S.; Claver, C. *Adv. Synth. Catal.* **2003**, *345*, 169. (f) Cobbley, C. J.; Foucher, E.; Lecouve, J.-P.; Lennon, I. C.; Ramsden, J. A.; Thominot. G. *Tetrahedron*: *Asymmetry* **2003**, *14*, 3431. (g) Chi, Y.; Zhou, Y. G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120. (h) Bozeio, A. A.; Pytkowicz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260. (i) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825. (j) Zhu, S.-F.; Xie, J.-B.; Zhang, Y.-Z.; Li, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 12886. For the Ru-catalyzed transfer hydrogenation, see: (k) Samec, J. S. M.; Bäckvall, J. E. *Chem. Eur. J.* **2002**, *8*, 2955. For Rh-catalyzed hydrogenation of enamides, see the following: (l) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2004**, *6*, 3585.

(3) For hydrosilylation, see, e.g.: (a) Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1998**, *63*, 6344. (b) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1103. (c) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713. (d) Vedejs, E.; Trapencieris, P.; Suna, E. *J. Org. Chem.* **1999**, *64*. 6724. (e) Nishikori, H.; Yoshihara, R.; Hosomi, A. *Synlett* **2003**, 561. (f) Lipshutz, B. H.; Noson, K.; Chrisman, W. *J. Am. Chem. Soc.* **2001**, *123*, 12917. (g) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2228.

(4) For transfer hydrogenation, see, e.g., ref 2j and the following: Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472.

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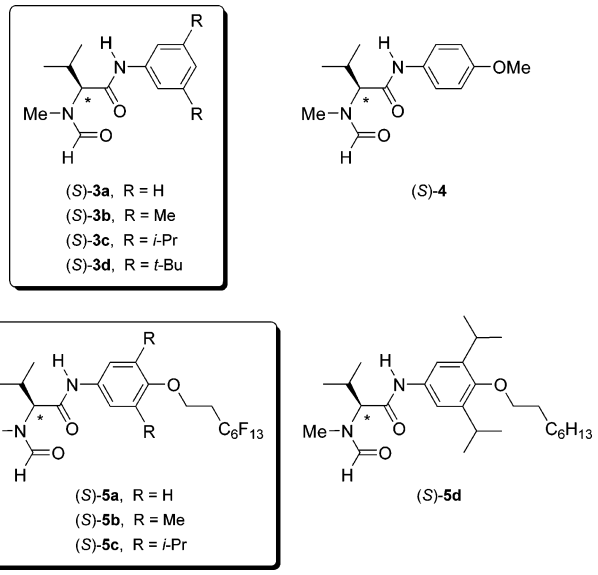
required by most metal catalysts,[2] which is associated with certain risks, especially on an industrial scale. Furthermore, metal leaching to the product must be carefully checked and reduced to the ppm level for applications in drug industry and material science.[5] Metal recovery constitutes another common problem as its cost adds to the overall bookkeeping. Finally, transition metals are generally perceived by technologists as capricious entities, since their reactivity may suddenly be reduced by unforeseen factors, such as impurities in the starting materials or solvents, which represents another obstacle hindering their widespread use in manufacturing beyond hydrogenation.

Metal-free organocatalysts[6] can be viewed as an attractive alternative to those processes, in which the metal is not vital for the key bond-forming event. The advantages are obvious: no metal leaching, much reduced toxicity, and lower cost of the catalysts and their regeneration. The prime goal here, however, is to develop new, reliable processes that could compete with their established, metal-catalyzed cousins. Aside from the astounding progress in the organocatalyzed aldol-type chemistry, witnessed since the beginning of this millennium,[6] several organocatalytic reduction processes have been developed in the past few years. Thus, following an earlier observation by Singh,[7] a highly enantioselective reduction of imines with the Hantzsch dihydropyridine (an NADH analogue), catalyzed by chiral Brønsted acids derived from BINOL, has been reported by Rueping,[8] List,[9] and MacMillan.[10]

**CHART 1**




We have recently developed a procedure for the reduction of prochiral ketimines with trichlorosilane (Scheme 1), catalyzed by Lewis basic formamides derived from *N*-methylvaline (e.g., **3a** and **3b**) and other *N*-methylamino acids (Chart 1).[11−13] Herein, we report on an improvement in the catalyst efficiency by introducing bulky groups R into 3,5-positions of the anilide moiety (as in **3b**−**d**) and on a considerable simplification of the isolation procedure by tagging the catalyst to a fluorous ponytail (as in **5a**−**c**).[14]

## Results and Discussion

In our previous work, we have introduced the valine-based *N*-methylformamide **3a** as an efficient catalyst for the reduction of imines derived from acetophenone and its congeners (**1**, $R^1$ = Ar, $R^2$ = Ar′). The optimized reaction proceeds at room temperature in toluene (or $CHCl_3$), affording the corresponding amine **2** in up to 86% ee (Table 1, entries 1 and 2).[11] The key features of our catalysts are the *N*-methylformamide moiety at the *N*-terminus of the amino acid and the anilide group at the *C*-terminus.[11] The valine scaffold was identified as optimal, exhibiting the highest enantioselectivity.[11,15] Interestingly, while this work was in progress, analogous catalysts, derived from proline,[16] picolinic, or piperazine carboxylic acid[17] scaffold, have

(5) (a) Committee for Proprietary Medicinal Products (CPMP) (December 17, 2002). Note for Guidance on Specification Limits for Residues of Metal Catalysts. http://www.emea.eu.int/pdfs/human/swp/444600en.pdf (accessed October 2006). (b) Note for Guidance on Specification Limits for Residues of Metal Catalysts, The European Agency for the Evaluation of Medicinal Products, Evaluation of Medicines for Human Use; London, December 17, 2002; http://www.emea.eu.in.

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(9) (a) Hoffman, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. See also: (b) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074.

(10) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.

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(12) For chiral pyridyloxazoline as chiral catalysts in the reduction of both imines and ketones, see: Malkov, A. V.; Stewart Liddon, A. J. P.; Bendová, L.; Haigh, D. Z.; Kočovský, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432.

(13) For leading reviews on activation of silicon reagents by Lewis bases, see the following: (a) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (b) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (d) Kočovský, P.; Malkov, A. V. *Izv. Akad. Nauk, Ser. Khim.* ***2004****, 1733. Russ. Chem. Bull., Int. Ed.* **2004**, *59*, 1806. (e) Orito, Y.; Nakajima. M. *Synthesis* **2006**, 1391. (f) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29. For recent, selected examples, see, e.g.: (g) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4*, 1047. (h) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674. (i) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 9659. (j) Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219.

(14) For an overview and philosophy of fluorous tags, see, e.g., the following: (a) Gladysz, J. A.; Curran, D. P.; Horvath, I. T. *Handbook of Fluorous Chemistry*; Wiley: New York, 2004. (b) Nakamura, Y.; Takeuchi. S.; Ohgo, Y.; Curran, D. P. *Tetrahedron* **2000**, *41*, 57. (c) Nakamura, Y.; Takeuchi. S.; Ohgo, Y.; Curran, D. P. *Tetrahedron* **2000**, *56*, 351. (d) Nakamura, Y.; Takeuchi, S.; Okumura, K.; Ohgo, Y.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3963. (e) Simonelli, B.; Orlandi, S.; Benaglia, M.; Pozzi, G. *Eur. J. Org. Chem.* **2004**, 2669.

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(16) (a) Iwasaki, F.; Omonura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525. (b) Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett*. **2006**, *47*, 3751. For a related reduction of ketones, see: (c) Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, *40*, 7507. (d) Matsumura, Y.; Ogura, K.; Kouchi, Y.; Iwasaki, F.; Onomura, O. *Org. Lett.* **2006**, *8*, 3789.

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**TABLE 1. Reduction of Ketimines 1a−k with Trichlorosilane, Catalyzed by the Valine-Derived *N*-Methyl Formamides (*S*)-3a−d, (*S*)-4, and (*S*)-5a−d[a]**

| entry | catalyst (mol %) | R | imine | $R^1$ | $R^2$ | solvent | yield, %[b] | **2**[c] % ee[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | **3a** (10) | H | **1a** | Ph | Ph | $CHCl_3$ | 79 | 86[e] |
| 2 | **3a** (10) | H | **1b** | Ph | 4-$MeOC_6H_4$ | $CHCl_3$ | 96 | 85[e] |
| 3 | **3b** (10) | Me | **1a** | Ph | Ph | toluene | 81 | 92[e] |
| 4 | **3b** (10) | Me | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 85 | 91[e] |
| 5 | **3c** (10) | *i*-Pr | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 99 | 94 |
| 6 | **3c** (5) | *i*-Pr | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 95 | 93 |
| 7 | **3c** (5) | *i*-Pr | **1c** | 4-$CF_3C_6H_4$ | 4-$MeOC_6H_4$ | toluene | 82 | 92 |
| 8 | **3c** (5) | *i*-Pr | **1d** | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | toluene | 87 | 91 |
| 9 | **3c** (5) | *i*-Pr | **1e** | 2-Naphth | 4-$MeOC_6H_4$ | toluene | 83 | 92 |
| 10 | **3d** (5) | *t*-Bu | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 95 | 94 |
| 11 | **3d** (2.5) | *t*-Bu | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 92 | 94 |
| 12 | **3d** (1) | *t*-Bu | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 92 | 93 |
| 13 | **3d** (5) | *t*-Bu | **1f** | Ph | 3-$MeC_6H_4$ | toluene | 93 | 95 |
| 14 | **3d** (5) | *t*-Bu | **1g** | Ph | 3,5-$Me_2C_6H_3$ | toluene | 89 | 92 |
| 15 | **3d** (5) | *t*-Bu | **1h** | Ph | 3,5-*t*-$Bu_2C_6H_3$ | toluene | 90 | 70 |
| 16 | **3d** (5) | *t*-Bu | **1c** | 4-$CF_3C_6H_4$ | 4-$MeOC_6H_4$ | toluene | 92 | 92 |
| 17 | **3d** (5) | *t*-Bu | **1d** | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | toluene | 91 | 91 |
| 18 | **3d** (5) | *t*-Bu | **1e** | 2-Naphth | 4-$MeOC_6H_4$ | toluene | 93 | 92 |
| 19 | **3d** (5) | *t*-Bu | **1i** | *c*-$C_6H_{11}$ | 4-$MeOC_6H_4$ | toluene | 86 | 85 |
| 20 | **3d** (5) | *t*-Bu | **1j** | *i*-Pr | 4-$MeOC_6H_4$ | toluene | 83 | 62 |
| 21 | **3d** (5) | *t*-Bu | **1k** | (*E*)-PhCH=CH | 4-$MeOC_6H_4$ | toluene | 94 | 81 |
| 22 | **4** (10) | H | **1a** | Ph | Ph | $CHCl_3$ | 62 | 85[e] |
| 23 | **5a** (10) | H | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 80 | 84 |
| 24 | **5a** (5) | H | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 73 | 82 |
| 25 | **5a** (3) | H | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 62 | 74 |
| 26 | **5b** (10) | Me | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 90 | 91 |
| 27 | **5b** (10) | Me | **1c** | 4-$CF_3C_6H_4$ | 4-$MeOC_6H_4$ | toluene | 67 | 88 |
| 28 | **5b** (5) | Me | **1c** | 4-$CF_3C_6H_4$ | 4-$MeOC_6H_4$ | toluene | 72 | 92[f] |
| 29 | **5b** (5) | Me | **1d** | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | toluene | 84 | 84 |
| 30 | **5b** (10) | Me | **1e** | 2-Naphth | 4-$MeOC_6H_4$ | toluene | 65 | 86 |
| 31 | **5b** (5) | Me | **1e** | 2-Naphth | 4-$MeOC_6H_4$ | toluene | 68 | 92[f] |
| 32 | **5c** (10) | *i*-Pr | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 98 | 89 |
| 33 | **5d** (10) | *i*-Pr | **1b** | Ph | 4-$MeOC_6H_4$ | toluene | 98 | 90 |

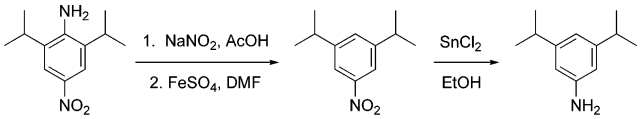
[a] The reaction was carried out at 0.2 mmol scale with 2.0 equiv of $Cl_3SiH$ at 18 °C for 16 h unless stated otherwise. [b] Isolated yield. [c] The absolute configuration was established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Experimental Section) and/or by HPLC via comparison with authentic samples. Amines **2a**−**e** were (*S*)-configured; the configuration of **2f**−**k** is assumed to be (*S*) in analogy with the rest of the series. [d] Determined by chiral HPLC. [e] Reference 11. [f] The reaction was carried out at 10 °C.

been reported by Matsumura and by Sun to induce the formation of the opposite enantiomers of the amines. Furthermore, gradual lowering of the ee up to the reversal was identified by us for phenylalanine- and alanine-based catalysts, which demonstrates the role of conformational effects associated with the nature of the individual backbones.[11]

We have also shown that introducing two methyl groups into 3,5-positions of the anilide moiety of the catalyst (**3b**) had a beneficial effect, increasing the enantioselectivity up to 92% (entries 3 and 4).[11] Therefore, it was of interest to synthesize catalysts with even bulkier groups in the 3,5-positions, namely the diisopropyl and di-*tert*-butyl derivatives **3c** and **3d**. Furthermore, the corresponding 4-methoxy derivative **4** exhibited similar levels of enantioselectivity as did the unsubstituted catalyst **3a**, albeit at lower temperature (compare entries 1 and 2 with 22),[11] which suggests that an ether link could be employed as the point of entry for appending a fluorous tag (**5a**), with an additional option of increasing the steric bulk by substituents in 3,5-positions (**5b**,**c**). For comparison, derivative **5d** with a non-fluorous side chain of the same length as the fluorous ponytail in **5a**−**c** was also synthesized.

**Catalyst Synthesis.** Construction of the *N*-methylformamido moiety of the catalyst relies on the *N*-methylation of the BOC-protected valine, followed by BOC deprotection and formylation, as described in our previous work (vide infra).[11,18,19] The anilide counterpart was then introduced via amidation of the carboxyl group by substituted anilines.[11] The same strategy has now been employed in the synthesis of **3c**,**d** and **5a**−**d**. However, while 3,5-(*t*-Bu)$_2$C$_6$H$_3$NH$_2$, required for the synthesis of **3d**, is commercially available, its lower homologue 3,5-(*i*-Pr)$_2$C$_6$H$_3$-NH$_2$ (**8**) was essentially unknown.[20] We have now synthesized **8** (Scheme 2) via reduction of the corresponding nitro derivative **7** ($SnCl_2$, 99%), which in turn was prepared from 2,6-diisopropyl-4-nitroaniline (**6**)[21] in two steps, using diazotation ($NaNO_2$, AcOH), followed by reduction ($FeSO_4$, DMF; 63%).[22]

**SCHEME 2. Synthesis of 8**




(18) To obtain the BOC-protected *N*-mehtylvaline (**14**) in high yield, it is crucial to add NaH (in small portions) to a mixture of BOC-valine and MeI. If the deprotonation of BOC-valine is carried out prior to the addition of MeI, the methylation becomes inefficient.[11]

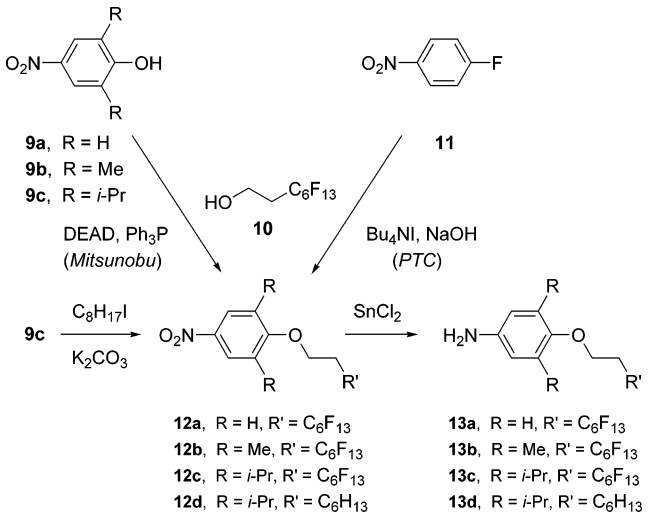
(19) (a) Andrus, M. B.; Li, W.; Keyes, R. F. *J. Org. Chem.* **1997**, *62*, 5542. (b) Cheung, S. T.; Benoiton, N. L. *Can. J. Chem.* **1977**, *55*, 906.

(20) The formation of **8** in 8% yield has been reported in the amination reaction of 1,3-diisopropylbenzene with trichloroamine-aluminum chloride but a preparative protocol has never been developed: Kovacic, P.; Field, K. W.; Roskos, P. D.; Scalzi, F. V. *J. Org. Chem.* **1967**, *32*, 585.

(21) Carver, F. J.; Hunter, C. A.; Livingstone, D. J.; McCabe, J. F.; Seward, E. M. *Chem. Eur. J.* **2002**, *8*, 2847.

(22) For the metod, see: Wassmundt, F. W.; Kiesman, W. F. *J. Org. Chem.* **1995**, *60*, 1713.

**SCHEME 3. Synthesis of Flurorous Anilines**

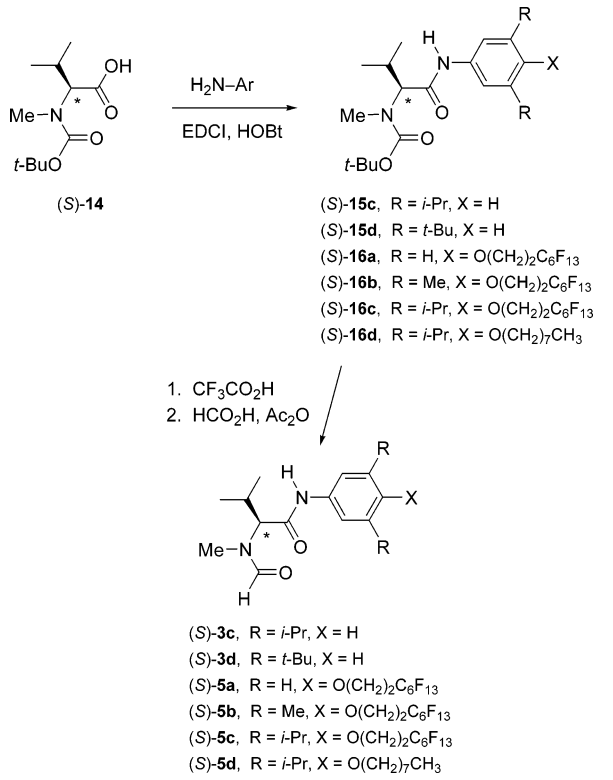



We envisaged that appending a fluorous tag to the catalyst (as in **5a**-**c**) would be best attained via an ether link (vide supra), which could be constructed either by alkylation of a suitable aminophenol with an appropriate fluorous alkylating agent, or conversely, from an aryl halide and a complementary fluorous alcohol via aromatic nucleophilic substitution (Scheme 3). While the former approach would require a selective protection of the amine functionality, the latter reaction would be facilitated by activation of the aromatic system by an electron-withdrawing group. The nitro group was chosen for both approaches as a suitable precursor of the amino group, playing the role of protection in the former alternative and that of activation in the latter.

Initial attempts at alkylation of *p*-nitrophenol (**9a**) with a triflate derived from the commercially available fluorous alcohol **10** (Scheme 3) or with the corresponding iodide proved fruitless under various conditions (using, e.g., $K_2CO_3$, KF, or KH as a base). Therefore, aromatic nucleophilic substitution was explored next: the alkoxide, generated from the fluorous alcohol **10** and NaH, was treated with *p*-nitrofluorobenzene (**11**) at 60 °C for 18 h, which indeed gave rise to the desired ether **12a** though in a rather low yield (17%). On the other hand, heating of a mixture of **10**, **11**, and $Bu_4NI$ in a 28% aqueous solution of NaOH at 45 °C for 48 h under the phase-transfer conditions afforded, after optimization, the desired ether **12a** in 80% yield.[23]

The more hindered ethers **12b**,**c** were constructed via the Mitsunobu reaction of phenols **9b**,**c**[24] with the fluorous alcohol **10**: standard conditions, using $Ph_3P$ and DEAD (25 °C, 18 h),[25] proved efficient for 2,6-dimethyl-4-nitrophenol (**9b**) and the desired ether **12b** was obtained in 41% yield. Rather surprisingly, the Mitsunobu reaction was successful even with the more hindered diisopropyl analogue **9c**, which was converted into ether **12c** in 33% yield, demonstrating the power of this methodology. Octyl ether **12d** was prepared by alkylation of **9c** with octyl iodide in the presence of $K_2CO_3$ in acetone (94%).

**SCHEME 4. Synthesis of the Formamide Catalysts**




The nitro ethers **12a**−**d** were then reduced to the respective amines **13a**−**d** and, after some experimentation, we settled for tin(II) chloride in refluxing EtOH (10−12 h),[26] which gave respectable yields (83%, 76%, 79%, and 74%, respectively).[27]

Coupling of the respective aniline derivatives Ar-$NH_2$ with the BOC-protected *N*-methylvaline[11,18,19] (*S*)-**14** (Scheme 4), using the standard carbodiimide methodology (EDCI, HOBt, $Et_3N$, rt, 24 h), afforded anilides **15c** (71%), **15d** (95%), **16a**, (68%), **16b**, (58%), **16c** (80%), and **16d** (83%). The end game, comprising a BOC-deprotection with $CF_3CO_2H$ (0 °C or rt, 1 h), followed by *N*-formylation ($HCO_2H$, $Ac_2O$, rt, 18 h), produced the desired catalyst candidates **3c** (99%), **3d** (99%), **5a** (73%), **5b** (82%), **5c** (78%), and **5d** (60%).

**Asymmetric Reduction of Ketimines with $Cl_3SiH$ Catalyzed by Chiral Formamides 3a−d.** Reduction of imines **1a**−**k** (Scheme 1) catalyzed by formamides **3a**,**b** has been reported previously by us[11] and the key results are shown in Table 1 (entries 1−4) for comparison with the present study. As expected, increasing the steric bulk in the anilide moiety by introducing the *i*-Pr (**3c**) and *t*-Bu (**3d**) groups resulted in an enhancement of the enantioselectivity (entries 5−21), with **3d** (Sigamide)[28] emerging as the champion catalyst, with up to 95% ee. In particular, a major improvement of enantioselectivity was attained in the reduction of aliphatic imines **1i**−**j** (entries 19 and 20) and the α,*β*-unsaturated imine **1k** (entry 21). Furthermore, with **3d**, the catalyst loading could be reduced to 1 mol % without loss of reactivity or enantioselectivity (compare entries 10−12). Increasing the steric bulk of the imine *N*-aryl part, as in **1f**,**g**, was well tolerated by the bulky catalyst **3d**

(23) Ether **12a** was actually prepared before in a similar way by another group but the conditions were not fully described and the product was only characterized by $^1$H NMR: Beaune, O.; Bessière, J. M.; Boutevin, B.; Robin, J. J. *J. Fluorine Chem.* **1994**, *67*, 159.

(24) For the synthesis of **9c**, see: Helfenbein, J.; Lartigue, C.; Noirault, E.; Azim, E.; Legailliard, J.; Galmier, M. J.; Madelmont, J. C. *J. Med. Chem.* **2002**, *45*, 5806.

(25) For the method, see: Ragnoli, M.; Pucci, E.; Bertolucci, M.; Gallot, B.; Galli, G. *J. Fluorine Chem.* **2004**, *125*, 283.

(26) For the method, see: Thiele, T.; Prescher, D.; Ruhmann, R.; Wolff, D. *J. Fluorine Chem.* **1997**, *85*, 155.

(27) Amine **13a** was also prepared by catalytic hydrogenation of Pd/C catalyst at 30 bar and 120 °C.[23]

(28) **Sig**itas (the first name of one of the authors) + form**amide**.

**TABLE 2. Reduction of Ketimine 1b with Trichlorosilane, Catalyzed by the Recycled Formamides (*S*)-5a−c[a]**

| entry | catalyst (run) | yield, %[b] | **2b**[c] % ee[d] | catalyst recovery, % |
|---|---|---|---|---|
| 1 | **5a** (1) | 80 | 84 | 99 |
| 2 | **5a** (2) | 82 | 84 | 92 |
| 3 | **5a** (3) | 78 | 76 | 83 |
| 4 | **5a** (4) | 70 | 74 | 70 |
| 5 | **5b** (1) | 90 | 91 | 79 |
| 6 | **5b** (2) | 88 | 88 | 72 |
| 7 | **5b** (3) | 86 | 88 | 75 |
| 8 | **5b** (4) | 86 | 83 | 83 |
| 9 | **5c** (1) | 98 | 89 | 99 |
| 10 | **5c** (2) | 96 | 87 | 90 |
| 11 | **5c** (3) | 90 | 89 | 92 |
| 12 | **5c** (4) | 90 | 85 | 92 |
| 13 | **5c** (5) | 89 | 87 | 88 |

[a] The reaction was carried out at 0.2 mmol scale with 2.0 equiv of $Cl_3SiH$ and 10 mol % of the catalyst in the beginning at room temperature for 16 h. [b] Isolated yield. [c] The absolute configuration was established by comparison of the optical rotation (measured in $CHCl_3$) with the literature data (see the Experimental Section) and/or by HPLC via comparison with authentic samples; all samples were (*S*)-configured. [d] Determined by chiral HPLC.

(entries 13 and 14) and good enantioselectivity was achieved even for the reduction of the very bulky imine **1h** (entry 15). It is pertinent to note that the background, uncatalyzed reaction is very slow, as less than 5% conversion was observed in the absence of the catalyst at room temperature over 24 h.[11]

**Asymmetric Reduction of Ketimines with $Cl_3SiH$ Catalyzed by Chiral Fluorous Formamides 5a−c.** As explained above, the enantioselectivity previously observed by us for the *p*-methoxyanilide **4** (85% ee; entry 22)[11] set the scene for the development of a fluorous catalyst, in which the fluorous tag[14] was to be appended through an ether link in the 4-position (**5a**); it was also hoped that addition of bulky 3,5-substituents would lead to a similar enhancement of enantioselectivity as in the previous instance. Indeed, **5a** exhibited enantioselectivity comparable with that of **4** (≤84% ee; entries 23−25), and an increase to ≤92% ee was observed for the 3,5-alkylated catalysts **5b**,**c** (entries 26−32). Importantly, these experiments have demonstrated that the fluorous tag did not affect the performance of the catalyst and that conversions and enantioselectivities match those obtained with untagged catalysts. Note that the octyl derivative **5d** did not exhibit any deviation from the behavior of the fluorous catalysts **5a−c** (entry 33).

The workup of the reactions that employed the fluorous catalysts was carried out in the same manner as that for the untagged catalysts, described previously (aqueous $NaHCO_3$). However, the catalyst separation from the product was simplified in that the crude product, dissolved in a MeOH−$H_2O$ mixture (4:1), was filtered through a pad of fluorous silica, which eluted the pure amine; continued elution with pure MeOH then released the catalyst. Hence, the rather more demanding classical column chromatography, required for the untagged catalysts, was avoided.

The regenerated fluorous catalysts **5a−c** were then repeatedly used for the reduction of imine **1b** to probe the sustainability of the process (Table 2). Naturally, the catalyst recycling was not quantitative, so that every new batch actually used less catalyst than the previous one. This, however, had only a marginal effect on both the reactivity and selectivity, especially in the case of the diisopropyl catalyst **5c** (Table 2, entries 9−13).

## Conclusions

We have refined our new valine-derived[11] organocatalysts for the asymmetric reduction of *N*-aryl ketimines with $Cl_3SiH$. The introduction of bulky groups into the anilide moiety of the catalyst (**3c**,**d**)[29] resulted in an increase of enantioselectivity not only in the aromatic realm (i.e., for **1a−h**, derived from aromatic ketones) but also for the nonaromatic imines (**1i−k**). The enantioselectivity attained with Sigamide **3d** (91−95% ee in most cases) matches the level reported for the methods employing transition metal catalysts.[2−4] Formation of (*S*)-amines **2** was observed for the L-valine-derived catalysts **3**, whereas those based on proline, picolinic, and piperazine carboxylic acid of the same configuration have been shown by Matsumura[16] and Sun[17] to produce (*R*)-**2**, which renders these two systems complementary, thereby avoiding the need to employ the unnatural enantiomers of the starting amino acids. Our catalytic process is also complementary to the Cu-catalyzed hydrosilylation developed by Lipshutz,[3f,g] which favors 1,4-addition to α,β-unsaturated imines, whereas our system is 1,2-selective, as demonstrated by the reduction of **1k** (Table 1, entry 21). Since the reduction exhibits high enantioselectivities at room temperature and normal pressure, it compares favorably with its alternatives, such as catalytic hydrogenation[2] or the reduction with Hantzsch dihydropyridine.[8−10] Finally, the catalyst loading can be reduced to 1 mol % (Table 1, entry 12), which is rather uncommon in the area of organocatalysis in general.

Trichlorosilane, employed here as the stoichiometric reducing agent, serves as a starting material in the silicon industry and is manufactured in bulk, so that its price is reduced almost to the level typical for common organic solvents. Although $Cl_3SiH$ is sensitive to water, the implications are rather modest and the reagent can be easily handled by using standard procedures for moisture-sensitive materials with minimum precautions (in principle, a $CaCl_2$ drying tube could be used instead of an inert atmosphere of nitrogen or argon). Since toluene was identified as an optimal solvent[11] and the workup of the reaction with aqueous $NaHCO_3$ produces innocuous inorganic materials, namely NaCl and silica, this protocol represents a relatively low environmental risk. In conjunction with the low catalyst loading, all these features suggest that the organocatalyzed reductions with $Cl_3SiH$ developed by us and by Matsumura[16] and Sun[17] may become an attractive alternative to the established industrial technologies for the synthesis of chiral amine building blocks.

The practicality of the reaction has now been considerably enhanced by fluorous tagging of the catalyst (**5b**,**c**), which allows a very easy isolation of the product and an undemanding recovery of the catalyst that can be used in the next cycle. The fluorous catalysts operate in the solution and the difference between their efficiency and that of their untagged predecessors (**3a−d**) is negligible. Therefore, this technology appears to be particularly suited to the small-scale parallel chemistry.

## Experimental Section

**Formamide (*S*)-(−)-3c.** Trifluoroacetic acid (5 mL) was added dropwise to a solution of BOC derivative **15c** (380 mg, 0.97 mmol) in dichloromethane (5 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. The solvent was then removed under reduced pressure and the residue was coevaporated with toluene (3 × 5

(29) For other structural requirements in the catalyst, see our previous papers.[11]

mL) to afford a TFA salt of the deprotected amide as a colorless solid, which was used in the following step without further purification. The crude amide was dissolved in formic acid (3.0 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (1.5 mL, 15.9 mmol) was added dropwise and the reaction mixture was allowed to stir at room temperature overnight, and then evaporated to dryness. The traces of acids were removed by coevaporation with toluene (3 × 5 mL) and the residue was purified by column chromatography on silica gel with a petroleum ether−ethyl acetate mixture (2:1, $R_f$ 0.46/0.24) to afford (*S*)-(−)-**3c** (307 mg, 99%) as a colorless solid: mp 102−104 °C; $[\alpha]_D$ −193.6 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 6.5:1 ratio; the signals for the minor rotamer are marked with an *) $\delta$ 0.91 (d, $J$ = 6.6 Hz, 3H), 1.06 (d, $J$ = 6.5 Hz, 3H), 1.22 (d, $J$ = 6.9 Hz, 12H), 2.40−2.56 (m, 1H), 2.85 (hept, $J$ = 6.9 Hz, 2H), 2.93* (s, 0.4H), 3.0 (s, 2.6H), 3.54* (d, $J$ = 10.4 Hz, 0.13H), 4.43 (d, $J$ = 11.3 Hz, 0.87H), 6.83 (br s) and 6.86* (br s, 1H), 7.22* (d, $J$ = 1.5 Hz) and 7.24 (d, $J$ = 1.5 Hz, 2H), 8.0* (br s) and 8.13 (br s, 1H), 8.15 (s) and 8.28* (s, 1H); $^{13}$C NMR $\delta$ 18.53 ($CH_3$), 18.85* ($CH_3$), 19.60 ($CH_3$), 19.87* ($CH_3$), 23.93 ($CH_3$), 25.19 ($CH_3$), 26.64* ($CH_3$), 27.25* (CH), 31.47 (CH), 34.22 (CH), 63.02 (CH), 69.26* (CH), 115.43 (CH), 115.64* (CH), 120.98 (CH), 121.41* (CH), 137.24* (C), 137.59 (C), 149.84 (C), 149.91* (C), 163.53* (CHO), 163.93 (CHO), 166.77* (CO), 166.98 (CO); IR (KBr) $\nu$ 3320, 3295, 2962, 1686, 1650, 1615, 1562, 1084, 867 cm$^{-1}$; MS (EI) *m*/*z* (%) 318 ($M^{\bullet+}$, 25), 177 (20), 142 (43), 114 (100), 83 (40); HRMS (EI) 318.2305 ($C_{19}H_{30}O_2N_2$ requires 318.2307).

**Formamide (*S*)-(−)-3d.** Trifluoroacetic acid (14 mL) was added dropwise to a solution of BOC derivative **15d** (1.19 g, 2.85 mmol) in dichloromethane (14 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. The solvent was then removed under reduced pressure and the residue was coevaporated with toluene (3 × 5 mL) to afford a TFA salt of the deprotected amide as a colorless solid, which was used in the following step without further purification. The crude amide was dissolved in formic acid (8.6 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (4.3 mL, 45.5 mmol) was added dropwise and the reaction mixture was allowed to stir at room temperature overnight, and then evaporated to dryness. The traces of acids were removed by coevaporation with toluene (3 × 5 mL) and the residue was purified by column chromatography on silica gel with a petroleum ether−ethyl acetate mixture (75:25, $R_f$ 0.56/0.29) to afford (*S*)-(−)-**3d** (985 mg, 99%) as a colorless solid: mp 167−169 °C; $[\alpha]_D$ −178.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 5.7:1 ratio; the signals for the minor rotamer are marked with an *) $\delta$ 0.92 (d, $J$ = 6.6 Hz, 3H), 1.06 (d, $J$ = 6.5 Hz, 3H), 1.30 (s, 18H), 2.40−2.57 (m, 1H), 2.94* (s, 0.45H), 3.0 (s, 2.55H), 3.55* (d, $J$ = 10.4 Hz, 0.15H), 4.46 (d, $J$ = 11.2 Hz, 0.85H), 7.18 (t, $J$ = 1.6 Hz) and 7.20* (t, $J$ = 1.6 Hz, 1H), 7.39* (d, $J$ = 1.6 Hz) and 7.41 (d, $J$ = 1.6 Hz, 2H), 8.01* (br s) and 8.13 (br s, 1H), 8.15 (s) and 8.30* (s, 1H); $^{13}$C NMR $\delta$ 18.53 ($CH_3$), 18.86* ($CH_3$), 19.63 ($CH_3$), 19.92* ($CH_3$), 25.21 ($CH_3$), 26.63* ($CH_3$), 27.26* (CH), 31.35 ($CH_3$), 31.42 (CH), 34.91 (C), 62.96 (CH), 69.33* (CH), 114.28 (CH), 114.49* (CH), 118.63 (CH), 119.03* (CH), 136.77* (C), 137.13 (C), 151.66 (C), 151.75* (C), 163.55* (CHO), 163.90 (CHO), 166.74* (CO), 166.97 (CO); IR (KBr) $\nu$ 3318, 2963, 1649, 1615, 1566, 1083, 870, 711 cm$^{-1}$; MS (EI) *m*/*z* (%) 346 ($M^{\bullet+}$, 24), 205 (36), 142 (47), 114 (100), 83 (39), 57 (19); HRMS (EI) 346.2618 ($C_{21}H_{34}O_2N_2$ requires 346.2620).

**Formamide (*S*)-(−)-5a.** The BOC derivative **13a** (340 mg, 0.51 mmol) was dissolved in trifluoroacetic acid (2 mL) at room temperature. After 1 h the acid was evaporated under reduced pressure and the residue was coevaporated with toluene (2 × 5 mL) to afford a TFA salt of the deprotected amine as a brownish oil, which was used in the following step without further purification. The crude salt was dissolved in formic acid (1.5 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (0.7 mL, 7.42 mmol) was added dropwise and the mixture was allowed to stir at room temperature for 18 h. The volatiles were then removed under reduced pressure and the residue (347 mg) was dissolved in $CH_2Cl_2$ (25 mL) and washed with a saturated solution of $NaHCO_3$ (3 × 10 mL) and brine (10 mL). The organic solution was dried over $MgSO_4$ and evaporated. The residue (272 mg) was purified by chromatography on a column with silica gel (70 g) with a mixture of $CH_2Cl_2$ and MeOH (209:1) to afford formamide (*S*)-(−)-**5a** (228 mg, 73%) as a yellowish wax: $R_f$ 0.45/0.22 ($CH_2Cl_2$−MeOH, 49:1); $[\alpha]_D$ −42.4 (*c* 0.5, EtOH); $^1$H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 4:1 ratio; the signals for the minor rotamer are marked with an *) $\delta$ 0.91 (d, $J$ = 6.6 Hz, 3H), 1.05 (d, $J$ = 6.3 Hz, 3H), 2.40−2.52 (m, 1H), 2.60 (tt, $J_{H-H}$ = 6.8 Hz, $J_{H-F}$ = 18.4 Hz, 2H), 2.93 (s, 0.44H*), 3.01 (s, 2.44H), 3.63 (d, $J$ = 10.4 Hz, 0.17H*), 4.24 (t, $J$ = 6.6 Hz, 2H), 4.43 (d, $J$ = 11.3 Hz, 0.83H), 6.83−6.86 (m, 2H), 7.44−7.48 (m, 2H), 8.15 (s, 0.83H), 8.31 (s, 0.84H), 8.38 (s, 0.23H*), 8.50 (s, 0.2H*); $^{13}$C NMR $\delta$ 18.58 ($CH_3$), 19.52 ($CH_3$), 25.39 (CH), 31.23 (t, $J$ = 21.4 Hz, $CH_2$), 31.63 ($CH_3$), 60.31 ($CH_2$), 63.01 (CH), 114.88 (CH), 121.62 (CH), 131.62 (C), 154.80 (C), 163.93 (CHO), 167.07 (CO); IR (KBr) $\nu$ 3467, 1658, 1606, 1546, 1512, 1472, 1239, 1145, 835, 809, 698 cm$^{-1}$; $^{19}$F NMR ($CCl_3F$) $\delta$ −81.23 (t, $J_{F-F}$ = 10.3 Hz, 3F), −113.82 (m, 2F), −122.37 (m, 2F), −123.36 (m, 2F), −124.07 (m, 2F), −126.65 (m, 2F); MS (CI) *m*/*z* (%) 597 ($[MH]^{\bullet+}$, 38), 596 (58), 595 (16), 567 (14), 524 (13), 494 (12), 455 (48), 454 (11), 115 (100), 88 (82); HRMS (CI) 597.1425 ($C_{21}H_{22}O_3N_2F_{13}$ requires 597.1423).

**Formamide (*S*)-(−)-5b.** Trifluoroacetic acid (3 mL) was added dropwise to a solution of BOC derivative **13b** (382 mg, 0.55 mmol) in $CH_2Cl_2$ (3 mL) at 0 °C and the stirring and cooling were continued for 1 h. The acid was removed under reduced pressure and the residue was coevaporated with toluene (2 × 5 mL) to afford a TFA salt of the deprotected amide as a brownish oil, which was used in the following step without further purification. The crude amine salt was dissolved in formic acid (1.7 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (1.3 mL) was then added dropwise and the mixture was allowed to stir at room temperature for 18 h. The volatiles were then evaporated and the residue was coevaporated with toluene (3 × 5 mL). The residue (341 mg) was purified by chromatography on a column of silica gel (70 g) with a mixture of $CH_2Cl_2$ and MeOH (209:1) to afford formamide (*S*)-(−)-**5b** (278 mg; 82%) as a white solid: mp 25−26 °C; $R_f$ 0.50/0.29 ($CH_2Cl_2$−MeOH, 49:1); $[\alpha]_D$ −37.1 (*c* 0.5, EtOH); $^1$H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 4:1 ratio; the signals for the minor rotamer are marked with an *) $\delta$ 0.91 (d, $J$ = 6.6 Hz, 3H), 1.04 (d, $J$ = 6.6 Hz, 3H), 2.24 (s, 6H), 2.40−2.51 (m, 1H), 2.61 (tt, $J_{H-H}$ = 6.7 Hz, $J_{H-F}$ = 18.7 Hz, 2H), 2.95 (s, 0.46H*), 3.00 (s, 2.46H), 3.65 (d, $J$ = 10.6 Hz, 0.15H*), 3.99 (t, $J$ = 6.6 Hz, 2H), 4.39 (d, $J$ = 11.4 Hz, 0.83H), 7.20 (s, 1.34 H), 7.22 (s, 0.66H*), 8.14 (s, 0.80H), 8.17 (s, 0.81H), 8.38 (s, 0.15H*), 8.42 (s, 0.15H*); $^{13}$C NMR $\delta$ 16.24 ($CH_3$), 18.55 ($CH_3$), 19.53 ($CH_3$), 25.21 (CH), 31.56 ($CH_3$), 31.78 (t, $J$ = 22.0 Hz, $CH_2$), 63.16 (CH), 63.75 ($CH_2$), 120.42 (CH), 131.39 (C), 133.58 (C), 151.89 (C), 163.99 (CHO), 167.07 (CO); $^{19}$F NMR $\delta$ −81.29 (t, $J_{F-F}$ = 10.3 Hz, 3F), −113.77 (m, 2F), −122.35 (m, 2F), −123.34 (m, 2F), −124.06 (m, 2F), −126.61 (m, 2F); IR (KBr) $\nu$ 3444, 1658, 1615, 1556, 1487, 1241, 1145, 874, 808, 697 cm$^{-1}$; MS (CI) *m*/*z* (%) 647 ($[MNa]^+$, 100), 624 (55), 597 (11), 483 (36), 115 (87), 88 (76); HRMS (CI) 647.1546 ($C_{23}H_{25}O_3N_2NaF_{13}$ ($[MNa]^{\bullet+}$ requires 647.1555).

**Formamide (*S*)-(−)-5c.** Trifluoroacetic acid (2.3 mL) was added dropwise to a solution of BOC derivative **13c** (350 mg, 0.46 mmol) in $CH_2Cl_2$ (3.5 mL) at 0 °C and the stirring and cooling were continued for 1 h. The acid was removed under reduced pressure and the residue was coevaporated with toluene (2 × 10 mL) to afford a TFA salt of the deprotected amide as a brownish oil, which was used in the following step without further purification. The crude amine salt was dissolved in formic acid (2.6 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (1.9 mL) was then added dropwise and the mixture was allowed to stir at room temperature for 26 h. The volatiles were then evaporated and

the residue was coevaporated with toluene (3 × 5 mL). The residue (352 mg) was purified by chromatography on a column of silica gel (50 g) with a mixture of $CH_2Cl_2$ and MeOH (260:1) to afford formamide (*S*)-(−)-**5c** (250 mg; 78%) as a white solid: mp 46−48 °C; $R_f$ 0.70/0.50 ($CH_2Cl_2$−MeOH, 49:1); $[\alpha]_D$ −33.6 (*c* 0.5, EtOH); $^1$H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 4:1 ratio; the signals for the minor rotamer are marked with an *) $\delta$ 0.92 (d, $J$ = 6.6 Hz, 3H), 1.06 (d, $J$ = 6.6 Hz, 3H), 1.21 (d, $J$ = 6.8 Hz, 6H), 1.23 (d, $J$ = 6.8 Hz, 6H), 2.42−2.52 (m, 1H), 2.65 (tt, $J_{H-H}$ = 6.7 Hz, $J_{H-F}$ = 18.7 Hz, 2H), 2.97 (s, 0.32H*), 3.00 (s, 2.68H), 3.22 (hept, $J$ = 6.8 Hz, 2H), 3.61 (d, $J$ = 10.7 Hz, 0.18H*), 3.98 (t, $J$ = 6.8 Hz, 2H), 4.40 (d, $J$ = 11.3 Hz, 0.82H), 7.27 (s, 1.70 H), 7.32 (s, 0.25 H*), 7.97 (s, 0.82H), 8.15 (s, 0.84H), 8.43 (s, 0.13H*); $^{13}$C NMR $\delta$ 18.58 ($CH_3$), 19.70 ($CH_3$), 23.90 ($CH_3$), 25.20 (CH), 26.81 (CH), 31.55 ($CH_3$), 31.99 (t, $J$ = 21.6 Hz, $CH_2$), 63.12 (CH), 66.17 ($CH_2$), 115.99 (CH), 134.70 (C), 142.47 (C), 149.31 (C), 164.03 (CHO), 166.92 (CO); $^{19}$F NMR $\delta$ −81.25 (t, $J_{F-F}$ = 10.1 Hz, 3F), −113.84 (m, 2F), −122.37 (m, 2F), −123.40 (m, 2F), −124.08 (m, 2F), −126.64 (m, 2F); IR (KBr) $\nu$ 3455, 2967, 1660, 1607, 1554, 1468, 1242, 1206 cm$^{-1}$; MS (EI) *m*/*z* (%) 680 (M$^{\bullet+}$, 62), 539 (72), 192 (56), 114 (100), 86 (35), 55 (11); HRMS (EI) 680.2281 ($C_{27}H_{33}O_3N_2F_{13}$ requires 680.2284).

**Formamide (*S*)-(−)-5d.** Trifluoroacetic acid (5.6 mL) was added dropwise to a solution of BOC derivative **13d** (580 mg, 1.12 mmol) in $CH_2Cl_2$ (9 mL) at 0 °C and the stirring and cooling were continued for 1 h. The acid was removed under reduced pressure and the residue was coevaporated with toluene (2 × 10 mL) to afford a TFA salt of the deprotected amide as a brownish oil, which was used in the following step without further purification. The crude amine salt was dissolved in formic acid (6.3 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (4.8 mL) was then added dropwise and the mixture was allowed to stir at room temperature for 19 h. The volatiles were then evaporated and the residue was coevaporated with toluene (3 × 5 mL). The residue (540 mg) was purified by chromatography on a column of silica gel (50 g) with a mixture of $CH_2Cl_2$ and MeOH (260:1) to afford formamide (*S*)-(−)-**5d** (302 mg; 60%) as a colorless oil: $R_f$ 0.72/0.42 ($CH_2Cl_2$−MeOH, 49:1); $[\alpha]_D$ −48.2 (*c* 0.5, EtOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.87−0.92 (m, 3H), 0.91 (t, $J$ = 6.4 Hz, 3H partly overlapped with the latter multiplet), 1.06 (d, $J$ = 6.5 Hz, 3H), 1.20 (d, $J$ = 6.9 Hz, 6H), 1.21 (d, $J$ = 6.9 Hz, 3H), 1.29−1.37 (m, 8H), 1.44−1.52 (m, 2H), 1.76−1.83 (m, 2H), 2.40−2.55 (m, 1H), 2.96 (s, 0.49H*), 3.00 (s, 2.51H), 3.28 (hept, 2H, $J$ = 6.9 Hz), 3.61 (d, $J$ = 10.5 Hz, 0.17H), 3.67 (t, $J$ = 6.6 Hz, 2H), 4.42 (d, $J$ = 11.2 Hz, 0.84H), 7.26 (s, 1.75H), 7.29 (s, 0.25H*), 8.03 (s, 0.74H), 8.14 (s, 0.86H), 8.42 (s, 0.14H*); $^{13}$C NMR $\delta$ 14.09 ($CH_3$), 18.53 ($CH_3$), 19.64 ($CH_3$), 22.64 ($CH_2$), 23.95 ($CH_3$), 25.18 (CH), 26.03 ($CH_2$), 26.53 (CH), 29.24 ($CH_2$), 29.44 ($CH_2$), 30.34 ($CH_2$), 31.49 ($CH_3$), 31.83 ($CH_2$), 62.91 (CH), 75.03 ($CH_2$), 115.77 (CH), 133.96 (C), 142.55 (C), 150.09 (C), 163.92 (CO), 166.74 (CO); IR (KBr) $\nu$ 3425, 2962, 1659, 1606, 1551, 1466, 1244, 1207 cm$^{-1}$; MS (EI) *m*/*z* (%) 446 (M$^{\bullet+}$, 100), 339 (10), 305 (100), 219 (12), 193 (93), 142 (100), 114 (100), 86 (85), 43 (49); HRMS (EI) 446.3510 ($C_{27}H_{46}O_3N_2$ requires 446.3508).

**3,5-Diisopropylnitrobenzene 7.** Ice (12 g) was added to a solution of 3,6-diisopropyl-4-nitroaniline[21] **6** (1.33 g, 6 mmol) in acetic acid (28 mL) and the resulting suspension was cooled to 0 °C. A solution of sodium nitrite (456 mg, 6.6 mmol) in water (1 mL) was slowly added dropwise and the reaction mixture was stirred at 0 °C for 30 min. The resulting clear solution of the diazo salt was slowly added dropwise to a solution of $FeSO_4 \cdot 7H_2O$ (1.67 g, 6 mmol) in dimethylformamide (20 mL), pre-cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for another 30 min, then diluted with water (200 mL) and the product was extracted into dichloromethane (3 × 75 mL). The organic phase was washed with a 10% aqueous NaOH solution (2 × 50 mL), dried ($MgSO_4$), and evaporated. The residue was filtered through a short pad of silica gel (2.5 × 3.5 mL), eluting with petroleum ether (300 mL), and the filtrate was evaporated to afford **7** (0.782 g, 63%) as a yellowish oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.29 (d, $J$ = 6.9 Hz, 12H), 2.99 (hept, $J$ = 6.9 Hz, 2H), 7.39 (t, $J$ = 1.6 Hz, 1H), 7.91 (d, $J$ = 1.6 Hz, 2H); $^{13}$C NMR $\delta$ 23.77 ($CH_3$), 34.08 (CH), 118.85 (CH), 131.47 (CH), 148.59 (C), 150.59 (C); IR (neat) $\nu$ 2966, 1531, 1350, 891 cm$^{-1}$; MS (EI) *m*/*z* (%) 207 (M$^{\bullet+}$, 19), 192 (62), 91 (26), 84 (54), 49 (100); HRMS (EI) 207.1260 ($C_{12}H_{17}NO_2$ requires 207.1259).

**3,5-Diisopropylaniline 8.** Tin(II) chloride dihydrate (4.20 g, 18.62 mmol) was added to a solution of 1,3-diisopropyl-5-nitrobenzene **7** (772 mg, 3.72 mmol) in ethanol (20 mL) and the mixture was heated under reflux for 1.5 h. The reaction mixture was cooled to room temperature, then poured into ice (150 g), and the resulting suspension was made alkaline by an addition of solid NaOH. The aqueous phase was extracted with dichloromethane (3 × 25 mL), and the organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel with a petroleum ether−ethyl acetate mixture (8:2, $R_f$ 0.28) to afford **8** (651 mg, 99%) as a yellowish oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.23 (d, $J$ = 6.9 Hz, 12H), 2.80 (hept, $J$ = 6.9 Hz, 2H), 3.58 (br s, 1H), 6.41 (d, $J$ = 1.4 Hz, 2H), 6.52 (t, $J$ = 1.4 Hz, 1H); $^{13}$C NMR $\delta$ 23.96 ($CH_3$), 34.12 (CH), 110.85 (CH), 115.51 (CH), 146.17 (C), 150.08 (C); IR (neat) $\nu$ 3448, 3367, 2962, 1604, 1531, 1458, 852 cm$^{-1}$; MS (EI) *m*/*z* (%) 177 (M$^{\bullet+}$, 100), 162 (81), 149 (22), 134 (30), 120 (62), 106 (18), 91 (22), 77 (16); HRMS (EI) 177.1518 ($C_{12}H_{19}N$ requires 177.1517).

**Ether 12a.**[26] A 28% aqueous solution of NaOH (6 mL) was slowly added dropwise to a mixture of *p*-fluoronitrobenzene **11** (5.30 g, 37.6 mmol), 1,1,2,2-tetrahydroperfluorooctanol **7** (2.00 g, 5.5 mmol), and tetrabutylammonium iodide (520 mg, 1.4 mmol) and the mixture was stirred at 45 °C for 48 h. After this time water (30 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 40 mL). The organic phase was dried over $MgSO_4$ then the solvent was evaporated to give a mixture of white solid and brown oil (7.39 g). The crude product was purified by chromatography on a column of silica gel (180 g) with a mixture of petroleum ether and $CH_2Cl_2$ (6:1) to afford ether **12a** (2.14 g, 80%) as a yellowish oil, which became a solid after cooling in a fridge: mp 26−27 °C; $R_f$ 0.30 (petroleum ether−dichloromethane, 4:1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.69 (tt, $J_{H-H}$ = 6.6 Hz, $J_{H-F}$ = 18.1 Hz, 2H), 4.37(t, $J$ = 6.6 Hz, 2H), 6.98 (br d, $J$ = 9.3 Hz, 2H), 8.22 (br d, $J$ = 9.3 Hz, 2H); $^{13}$C NMR $\delta$ 31.13 (t, $J$ = 21.9 Hz, $CH_2$), 60.74 ($CH_2$), 114.45 (CH), 125.97 (CH), 142.09 (C), 162.88 (C); $^{19}$F NMR $\delta$ −81.24 (t, $J_{F-F}$ = 9.2 Hz, 3F), −113.77 (m, 2F), −122.32 (m, 2F), −123.34 (m, 2F), −123.99 (m, 2F), −126.61 (m, 2F); MS (CI) *m*/*z* (%) 486 ([MH]$^{\bullet+}$, 100), 469 (94), 124 (19), 71 (42); HRMS (CI) 486.0377 ($C_{14}H_9O_3NF_{13}$ [MH]$^{\bullet+}$ requires 486.0375).

**Ether 12b.**[25] Triphenylphosphine (690 mg, 2.63 mmol), 1,1,2,2-tetrahydroperfluorooctanol **7** (0.6 mL, 2.75 mmol), and diethylazodicarboxylate (0.42 mL, 2.6 mmol) were added successively to a stirred solution of 2,6-dimethyl-4-nitrophenol **9b** (370 mg, 2.2 mmol) in THF (5 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 18 h. The mixture was partitioned between brine (20 mL) and ethyl acetate (40 mL), the organic phase was dried over $MgSO_4$ and concentrated, and then ether (40 mL) was added to induce the precipitation of triphenylphosphine oxide, which was separated by filtration. The filtrate was evaporated and the residue (1.9 g) was purified by chromatography on a column of silica gel (60 g) with a mixture of petroleum ether and dichloromethane (6:1, $R_f$ 0.25) to afford ether **12b** (470 mg, 41%) as a white solid: mp 53−54 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.36 (s, 6H), 2.68 (tt, $J_{H-H}$ = 6.6 Hz, $J_{H-F}$ = 18.5 Hz, 2H), 4.11 (t, $J$ = 6.6 Hz, 2H), 7.94 (s, 2H); $^{13}$C NMR $\delta$ 16.46 ($CH_3$) 31.81 (t, $J$ = 22.0 Hz, $CH_2$), 63.95 ($CH_2$), 124.36 (CH), 132.35 (C), 143.89 (C), 160.41 (C); $^{19}$F NMR $\delta$ −81.26 (t, $J_{F-F}$ = 10.3 Hz, 3F), −113.70 (m, 2F), −122.30 (m, 2F), −123.31 (m, 2F), −123.99 (m, 2F), −126.59 (m, 2F); MS (CI) *m*/*z* (%) 514 ([MH]$^{\bullet+}$, 100), 497 (41), 152 (10), 71 (18); HRMS (CI) 514.0696 ($C_{16}H_{13}O_3NF_{13}$ [MH]$^{\bullet+}$ requires 514.0688).

**Ether 12c.**[25] Triphenylphosphine (1.38 g, 5.26 mmol), 1,1,2,2-tetrahydroperfluorooctanol **10** (1.2 mL, 5.5 mmol), and diethylazodicarboxylate (0.84 mL, 5.3 mmol) were added successively to a stirred solution of 2,6-diisopropyl-4-nitrophenol **9c** (1.00 g, 4.5 mmol) in THF (10 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 20 h. The mixture was partitioned between brine (40 mL) and ethyl acetate (80 mL), the organic phase was dried over $MgSO_4$, and a solvent was evaporated affording 4.21 g of a residue. The residue was purified by chromatography on a column of silica gel (100 g) with a mixture of petroleum ether and ethyl acetate (6:1) to afford ether **12c** (840 mg, 33%) as a white solid: mp 58−59 °C; $R_f$ 0.60 (petroleum ether−dichloromethane, 5:1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.28 (d, $J$ = 6.9 Hz, 12H), 2.71 (tt, $J_{H-H}$ = 6.7 Hz, $J_{H-F}$ = 18.4 Hz, 2H), 3.28 (hept, $J$ = 6.9 Hz, 2H), 4.07 (t, $J$ = 6.6 Hz, 2H), 8.01 (s, 2H); $^{13}$C NMR $\delta$ 23.66 ($CH_3$) 27.08 (CH), 31.91 (t, $J$ = 22.5 Hz, $CH_2$), 66.43 ($CH_2$), 120.16 (CH), 143.65 (C), 145.27 (C), 157.93 (C); $^{19}$F NMR $\delta$ −81.26 (t, $J_{F-F}$ = 10.1 Hz, 3F), −113.73 (m, 2F), −122.28 (m, 2F), −123.31 (m, 2F), −123.97 (m, 2F), −126.58 (m, 2F); MS (EI) *m*/*z* (%) 569 ($M^{\bullet+}$, 100), 554 (90), 511 (17), 221 (77), 208 (40), 164 (36), 82 (27), 43 (14); HRMS (EI) 569.1230 ($C_{20}H_{20}O_3NF_{13}$ requires 569.1236).

**Ether 12d.** Potassium carbonate (1.00 g, 7.23 mmol) and iodooctane (1.00 mL, 5.50 mmol) were consequently added to a stirred solution of 2,6-diisopropyl-4-nitrophenol **9c** (0.53 g, 2.37 mmol) in dry acetone (11 mL). A mixture was heated at 45 °C for 19 h followed by evaporation of the solvent. Ether (50 mL) and water (20 mL) were added to a residue and after separation an organic phase was additionally washed with water (20 mL). The organic solution was dried over $MgSO_4$ and evaporation of the solvent afforded a crude product (1.52 g). The crude product was purified on a column of silica gel (50 g) with a mixture of petroleum ether and dichloromethane (8:1) to give ether **12d** (750 mg, 94%) as a colorless oil; $R_f$ 0.52 (petroleum ether−dichloromethane, 5:1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.88−0.92 (m, 3H), 1.26 (d, $J$ = 6.9 Hz, 12H), 1.29−1.41 (m, 8H), 1.47−1.53 (m, 2H), 1.81−1.88 (m, 2H), 3.33 (hept, $J$ = 6.9 Hz, 2H), 3.77 (t, 2H, $J$ = 6.6 Hz), 7.98 (s, 2H); $^{13}$C NMR $\delta$ 14.09 ($CH_3$), 22.65 ($CH_2$), 23.74 ($CH_3$), 25.95 ($CH_2$), 26.90 (CH), 29.23 ($CH_2$), 29.39 ($CH_2$), 30.30 ($CH_2$), 31.82 ($CH_2$), 75.38 ($CH_2$), 120.00 (CH), 143.71 (C), 144.69 (C), 159.22 (C); MS (EI) *m*/*z* (%) 335 ($M^{\bullet+}$, 18), 223 (99), 208 (82), 71 (38), 57 (53), 43 (56); HRMS (EI) 335.2461 ($C_{20}H_{33}O_3N$ requires 335.2460).

**Aniline 13a.**[26] Tin(II) chloride dihydrate (2.59 g, 11.47 mmol) was added to a solution of nitroether **12a** (1.40 g, 2.89 mmol) in ethanol (22 mL) and the mixture was refluxed for 12 h; no trace of starting material was detected by the TLC after this period. The mixture was cooled and a satd solution of $NaHCO_3$ (40 mL) was added to reach pH 10. The solution was extracted with ether (3 × 120 mL) and the organic phase was dried over $MgSO_4$ and evaporated to furnish a brownish solid (1.25 g). The latter solid was purified by chromatography on a column of silica gel (75 g) with a mixture of petroleum ether and $CH_2Cl_2$ (1:1) to afford aniline **13a** (1.09 g, 83%) as a white solid: mp 47−48 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.58 (tt, $J_{H-H}$ = 6.8 Hz, $J_{H-F}$ = 18.5 Hz, 2H), 3.45 (br s, 1.71H), 4.20 (t, $J$ = 6.9 Hz, 2H), 6.65 (d, $J$ = 8.8 Hz, 2H), 6.75 (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR $\delta$ 31.27 (t, $J$ = 21.9 Hz, $CH_2$), 60.80 ($CH_2$), 115.94 (CH), 116.34 (CH), 140.74 (C), 151.11 (C); $^{19}$F NMR $\delta$ −81.26 (t, $J_{F-F}$ = 10.3 Hz, 3F), −113.82 (m, 2F), −122.39 (m, 2F), −123.39 (m, 2F), −124.09 (m, 2F), −126.64 (m, 2F); MS (CI) *m*/*z* (%) 456 ($[MH]^{\bullet+}$, 96), 455 (100), 454 (22), 109 (79), 94 (17); HRMS (CI) 456.0628 ($C_{14}H_{11}ONF_{13}$ requires 456.0633).

**Aniline 13b.**[26] Tin(II) chloride dihydrate (2.18 g, 9.66 mmol) was added to a solution of nitroether **12b** (1.00 g, 1.95 mmol) in ethanol (14 mL) and the mixture was refluxed for 10 h. The mixture was then cooled and a saturated aqueous solution of $NaHCO_3$ (45 mL) was added to reach pH 10 and the product was extracted with ether (3 × 90 mL). The organic phase was dried over $MgSO_4$ and evaporated and the yellow oily residue (1.05 g) was purified by chromatography on a column of silica gel (90 g) with a petroleum ether−$CH_2Cl_2$ mixture (1:1, $R_f$ 0.2) to afford aniline **13b** (0.72 g, 76%) as a white solid: mp 69−70 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.20 (s, 6H), 2.61 (tt, $J_{H-H}$ = 6.8 Hz, $J_{H-F}$ = 18.8 Hz, 2H), 3.98 (t, $J$ = 6.8 Hz, 2H), 6.36 (s, 2H); $^{13}$C NMR $\delta$ 16.17 ($CH_3$), 31.81 (t, $J$ = 21.9 Hz, $CH_2$), 63.86 ($CH_2$), 115.32 (CH), 131.42 (C), 142.52 (C), 147.89 (C); $^{19}$F NMR $\delta$ −81.26 (t, $J_{F-F}$ = 10.3 Hz, 3F), −113.70 (m, 2F), −122.30 (m, 2F), −123.31 (m, 2F), −123.99 (m, 2F), −126.58 (m, 2F); MS (CI) *m*/*z* (%) 484 ($[MH]^{\bullet+}$, 98), 483 (100), 482 (19), 137 (85), 121 (31); HRMS (CI) 484.0961 ($C_{16}H_{15}ONF_{13}$ $[MH]^{+}$, requires 484.0946).

**Aniline 13c.**[26] Tin(II) chloride dihydrate (1.30 g, 5.76 mmol) was added to a solution of nitroether **12c** (0.82 g, 1.44 mmol) in ethanol (10 mL) and the mixture was refluxed for 19 h. The mixture was then cooled and a saturated aqueous solution of $NaHCO_3$ (21 mL) was added to reach pH 10 and the product was extracted with ether (3 × 60 mL). The organic phase was dried over $MgSO_4$ and evaporated and the residue (0.74 g) was purified by chromatography on a column of silica gel (50 g) with a petroleum ether−$CH_2Cl_2$ mixture (3:2, $R_f$ 0.30) to afford aniline **13c** (0.61 g, 79%) as a white solid: mp 41−43 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.20 (d, $J$ = 6.9 Hz, 12H), 2.64 (tt, $J_{H-H}$ = 6.9 Hz, $J_{H-F}$ = 18.7 Hz, 2H), 3.19 (hept, $J$ = 6.9 Hz, 2H), 3.96 (t, $J$ = 6.9 Hz, 2H), 4.17 (br s, 1.62H), 6.49 (s, 2H); $^{13}$C NMR $\delta$ 23.93 ($CH_3$), 26.61 (CH), 31.97 (t, $J$ = 21.5 Hz, $CH_2$), 66.13 ($CH_2$), 111.55 (CH), 141.95 (C), 142.50 (C), 145.92 (C); $^{19}$F NMR $\delta$ −81.29 (t, $J_{F-F}$ = 9.6 Hz, 3F), −113.73 (m, 2F), −122.35 (m, 2F), −123.35 (m, 2F), −124.04 (m, 2F), −126.60 (m, 2F); MS (EI) *m*/*z* (%) 539 ($M^{\bullet+}$, 22), 192 (62), 150 (9), 44 (22); HRMS (EI) 539.1495 ($C_{20}H_{22}ONF_{13}$ requires 539.1494).

**Aniline 13d.**[26] Tin(II) chloride dihydrate (2.50 g, 11.08 mmol) was added to a solution of nitroether **12d** (0.93 g, 2.77 mmol) in ethanol (19 mL) and the mixture was refluxed for 20 h. The mixture was then cooled and a saturated aqueous solution of $NaHCO_3$ (40 mL) was added to reach pH 10 and the product was extracted with ether (3 × 120 mL). The organic phase was dried over $MgSO_4$ and evaporated and the residue (0.81 g) was purified by chromatography on a column of silica gel (70 g) with a mixture of petroleum ether and $CH_2Cl_2$ (3:2) to afford aniline **13d** (0.62 g, 74%) as a slightly orange oil: $R_f$ 0.37 (petroleum ether−$CH_2Cl_2$, 1:1); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.88−0.91 (m, 3H), 1.19 (d, $J$ = 6.9 Hz, 12H), 1.30−1.34 (m, 8H), 1.44−1.51 (m, 2H), 1.75−1.82 (m, 2H), 3.26 (hept, $J$ = 6.9 Hz, 2H), 3.65 (t, $J$ = 6.6 Hz, 2H), 6.54 (s, 2H); $^{13}$C NMR $\delta$ 14.10 ($CH_3$), 22.66 ($CH_2$), 24.05 ($CH_3$), 26.09 ($CH_2$), 26.37 (CH), 29.27 ($CH_2$), 29.48 ($CH_2$), 30.39 ($CH_2$), 31.85 ($CH_2$), 75.04 ($CH_2$), 111.22 (CH), 141.79 (C), 142.56 (C), 146.41 (C); MS (EI) *m*/*z* (%) 305 ($M^{\bullet+}$, 35), 192 (100), 150 (17), 122 (4), 106 (3), 57 (4), 43 (11); HRMS (EI) 305.2718 ($C_{20}H_{35}$-ON requires 305.2719).

**BOC-*N*-Methyl (*S*)-(−)-Valine (*S*)-(−)-(14).** Sodium hydride (2.21 g, 0.092 mol) was added in small portions to a stirred solution of BOC-protected L-valine (2.00 g, 9.21 mmol) and methyl iodide (13.20 g, 0.092 mol) in THF (40 mL) at 0 °C. The mixture was allowed to stir at room temperature for 24 h under an argon atmosphere and the reaction was then quenched with water (15 mL). Ethyl acetate (15 mL) was added and the mixture was evaporated in vacuum. The concentrate was diluted with water (200 mL) and extracted with ethyl acetate (3 × 40 mL). The aqueous solution was acidified to pH 3.5 with a 5% solution of citric acid and extracted with ethyl acetate (3 × 50 mL). The extract was washed with brine, dried over $MgSO_4$, and evaporated in vacuum to give (*S*)-(−)-**14** (1.89 g, 88%) as a yellow oil: $[\alpha]_D$ −85 (*c* 0.5, EtOH), identical with an authentic sample.[11]

**Amide (*S*)-(−)-15c.** Triethylamine (0.31 mL, 2.25 mmol) was added to a solution of (*S*)-**14** (347 mg, 1.50 mmol) and 3,5-diisopropylaniline **8** (319 mg, 1.80 mmol) in dry dichloromethane (15 mL) at 0 °C. To the resulting clear solution were consecutively added 1-hydroxybenzotriazole hydrate (HOBt; 310 mg, ca. 1.95 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydro-

chloride (EDCI; 374 mg, 1.95 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The mixture was then diluted with ethyl acetate (75 mL) and washed successively with water (30 mL), cold 0.5 M HCl (2 × 30 mL), saturated $NaHCO_3$ (2 × 30 mL), and brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification by column chromatography on silica gel with a petroleum ether−ethyl acetate mixture (24:1, $R_f$ 0.21) afforded (*S*)-(−)-**15c** (413 mg, 71%) as an off-white solid: mp 102−104 °C; $[\alpha]_D$ −111.8 (*c* 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.92 (d, $J$ = 6.6 Hz, 3H), 1.03 (d, $J$ = 6.4 Hz, 3H), 1.23 (d, $J$ = 6.9 Hz, 12H), 1.49 (s, 9H), 2.30−2.43 (m, 1H), 2.83 (s, 3H), 2.85 (hept, $J$ = 7.0 Hz, 2H), 4.13 (d, $J$ = 10.9 Hz, 1H), 6.83 (s, 1H), 7.22 (s, 2H), 8.18 (br s, 1H); $^{13}$C NMR $\delta$ 18.58 ($CH_3$), 19.93 ($CH_3$), 23.92 ($CH_3$), 25.83 ($CH_3$), 28.36 ($CH_3$), 30.34 (CH), 34.20 (CH), 65.98 (CH), 80.60 (C), 115.28 (CH), 120.67 (CH), 137.99 (C), 149.79 (C), 157.46 (CO), 168.61 (CO); IR (KBr) $\nu$ 3321, 2964, 1691, 1659, 1614, 1557, 1156, 883, 861 cm$^{-1}$; MS (EI) *m*/*z* (%) 390 ($M^{\bullet+}$, 15), 177 (61), 130 (100), 86 (73), 57 (54); HRMS (EI) 390.2883 ($C_{23}H_{38}O_3N_2$ requires 390.2882).

**Amide (*S*)-(−)-15d.** Triethylamine (0.63 mL, 4.50 mmol) was added to a solution of (*S*)-**14** (694 mg, 3.0 mmol) and 3,5-di-*tert*-butylaniline (739 mg, 3.60 mmol) in dry dichloromethane (30 mL) at 0 °C. To the resulting clear solution were consecutively added 1-hydroxybenzotriazole hydrate (HOBt; 620 mg, ca. 3.9 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 747 mg, 3.90 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The mixture was then diluted with ethyl acetate (150 mL) and washed successively with water (60 mL), cold 0.5 M HCl (2 × 60 mL), saturated $NaHCO_3$ (2 × 60 mL), and brine (60 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification by column chromatography on silica gel with a petroleum ether−ethyl acetate mixture (22:1, $R_f$ 0.26) afforded (*S*)-(−)-**15d** (1.197 g, 95%) as an off-white solid: mp 138−140 °C; $[\alpha]_D$ −118.7 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.92 (d, $J$ = 6.6 Hz, 3H), 1.04 (d, $J$ = 6.4 Hz, 3H), 1.31 (s, 18H), 1.49 (s, 9H), 2.31−2.44 (m, 1H), 2.83 (s, 3H), 4.14 (d, $J$ = 11.2 Hz, 1H), 7.17 (s, 1H), 7.37 (s, 2H), 8.19 (br s, 1H); $^{13}$C NMR $\delta$ 18.60 ($CH_3$), 19.97 ($CH_3$), 25.80 ($CH_3$), 28.36 ($CH_3$), 30.91 (CH), 34.89 (C), 65.97 (CH), 80.59 (C), 114.22 (CH), 118.28 (CH), 137.50 (C), 151.60 (C), 157.49 (CO), 168.59 (CO); IR $\nu$ 3339, 2964, 1692, 1666, 1612, 1558, 1155 cm$^{-1}$; MS (EI) *m*/*z* (%) 418 ($M^{\bullet+}$, 14), 205 (78), 158 (16), 130 (100), 86 (76), 57 (61); HRMS (EI) 418.3198 ($C_{25}H_{42}O_3N_2$ requires 418.3195).

**Amide (*S*)-(−)-16a.** Triethylamine (0.45 mL, 3.27 mmol) was added to a solution of (*S*)-**14** (0.5 g, 2.16 mmol) in dry $CH_2Cl_2$ (15 mL) at 0 °C. To the resulting clear solution were consequently added aniline **13a** (890 mg, 1.95 mmol), 1-hydroxybenzotriazole hydrate (HOBt; 430 mg, 2.75 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 530 mg, 2.76 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 24 h. The mixture was then diluted with ethyl acetate (110 mL) and washed successively with water (45 mL), cold 0.5 M HCl (2 × 45 mL), saturated $NaHCO_3$ (2 × 45 mL), and brine (45 mL), dried over $MgSO_4$, filtered, and evaporated. The residue (1.18 g) was purified by chromatography on a column of silica gel (50 g) with a hexane−ethyl acetate mixture (19:1, 600 mL), which eluted impurities. Continued elution with the same mixture in 14:1 ratio afforded pure (*S*)-(−)-**16a** (880 mg, 68%) as a slightly yellowish oil: $R_f$ 0.3 (petroleum ether−ethyl acetate, 9:1); $[\alpha]_D$ −59.6 (*c* 0.5, EtOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.91 (d, $J$ = 6.6 Hz, 3H), 1.02 (d, $J$ = 6.3 Hz, 3H), 1.48 (s, 9H), 2.33−2.42 (m, 1H), 2.61 (tt, $J_{H-H}$ = 6.8 Hz, $J_{H-F}$ = 18.5 Hz, 2H), 2.83 (s, 3H), 4.09 (d, $J$ = 11.4 Hz, 1H), 4.25 (t, $J$ = 6.8 Hz, 2H), 6.85 (d, $J$ = 9.0 Hz, 2H), 7.43 (d, $J$ = 9.0 Hz, 2H), 8.20 (br s, 1H); $^{13}$C NMR $\delta$ 18.57 ($CH_3$), 19.83 ($CH_3$), 25.96 ($CH_3$), 28.33 ($CH_3$), 30.89 (CH), 31.20 (t, $J$ = 21.5 Hz, $CH_2$), 60.31 ($CH_2$), 65.95 (CH), 80.65 (C), 114.90 (CH), 121.37 (CH), 131.99 (C), 154.55 (C), 157.43 (CO), 168.61 (CO); $^{19}$F NMR ($CCl_3F$) $\delta$ −81.27 (t, $J_{F-F}$ = 9.7 Hz, 3F), −113.82 (m, 2F), −122.37 (m, 2F), −123.37 (m, 2F), −124.07 (m, 2F), −126.64 (m, 2F); MS (CI) *m*/*z* (%) 669 ($[MH]^{\bullet+}$, 27), 668 (42), 613 (47), 569 (45), 456 (100), 455 (100), 131 (49), 88 (49), 59 (48); HRMS (CI) 669.1997 ($C_{25}H_{30}O_4N_2F_{13}$ $[MH]^{\bullet+}$ requires 669.1998).

**Amide (*S*)-(−)-16b.** Triethylamine (0.19 mL, 1.39 mmol) was added to a solution of (*S*)-**14** (217 mg, 0.94 mmol) in dry dichloromethane (9 mL) at 0 °C. To the resulting clear solution were consequently added aniline **13b** (540 mg, 1.12 mmol), 1-hydroxybenzotriazole hydrate (HOBt; 190 mg, 1.22 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 234 mg, 1.22 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 18 h. The mixture was then diluted with ethyl acetate (50 mL) and washed successively with water (20 mL), cold 0.5 M HCl (2 × 20 mL), saturated $NaHCO_3$ (2 × 20 mL), and brine (20 mL) then dried over $MgSO_4$ and evaporated. The residue (540 mg) was purified by chromatography on a column of silica gel (90 g) with a petroleum ether−ethyl acetate mixture (12:1) to afford pure amide (*S*)-(−)-**16b** (380 mg, 58%) as a yellowish oil: $R_f$ 0.32 (petroleum ether−dichloromethane, 12:1); $[\alpha]_D$ −45.2 (*c* 0.5, EtOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.91 (d, $J$ = 6.6 Hz, 3H), 1.01 (d, $J$ = 6.3 Hz, 3H), 1.47 (s, 9H), 2.24 (s, 6H), 2.31−2.40 (m, 1H), 2.61 (tt, $J_{H-H}$ = 6.5 Hz, $J_{H-F}$ = 18.6 Hz, 2H), 2.84 (s, 3H), 3.99 (t, $J$ = 6.8 Hz, 2H), 4.10 (d, $J$ = 10.8 Hz, 1H), 7.18 (s, 2H), 8.21 (br s, 0.75H); $^{13}$C NMR $\delta$ 16.22 ($CH_3$), 18.57 ($CH_3$), 19.80 ($CH_3$), 25.99 ($CH_3$), 28.33 ($CH_3$), 30.44 (CH), 31.78 (t, $J$ = 22 Hz, $CH_2$), 63.73 ($CH_2$), 65.91 (CH), 80.61 (C), 120.20 (CH), 131.28 (C), 134.03 (C), 151.61 (C), 157.40 (CO), 168.75 (CO); $^{19}$F NMR $\delta$ −81.28 (t, $J_{F-F}$ = 10.3 Hz, 3F), −113.75 (m, 2F), −122.34 (m, 2F), −123.30 (m, 2F), −124.05 (m, 2F), −126.60 (m, 2F); MS (CI) *m*/*z* (%) 719 ($[MNa]^{\bullet+}$, 56), 597 (38), 595 (16), 484 (100), 483 (100), 131 (100), 88 (100), 59 (94); HRMS (CI) 719.2124 ($C_{27}H_{33}O_4N_2F_{13}Na$ $[MNa]^{\bullet+}$ requires 719.2130).

**Amide (*S*)-(−)-16c.** Triethylamine (0.30 mL, 2.18 mmol) was added to a solution of (*S*)-**14** (350 mg, 1.51 mmol) in dry dichloromethane (10 mL) at 0 °C. To the resulting clear solution were consequently added aniline **13c** (730 mg, 1.35 mmol), 1-hydroxybenzotriazole hydrate (HOBt; 270 mg, 1.75 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 330 mg, 1.72 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The mixture was then diluted with ethyl acetate (60 mL) and washed successively with water (30 mL), cold 0.5 M HCl (2 × 30 mL), saturated $NaHCO_3$ (2 × 40 mL), and brine (30 mL) then dried over $MgSO_4$ and evaporated. The residue (1.05 g) was purified by chromatography on a column of silica gel (50 g) with a petroleum ether−ethyl acetate mixture (25:1 for the first 250 mL and then 19:1) to afford pure amide (*S*)-(−)-**16c** (810 mg, 80%) as a white solid: $R_f$ 0.60 (petroleum ether− thyl acetate, 9:1); mp 94−96 °C; $[\alpha]_D$ −52.2 (*c* 0.5, EtOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.92 (d, $J$ = 6.6 Hz, 3H), 1.03 (d, $J$ = 6.4 Hz, 3H), 1.20−1.24 (m, 12 H), 1.49 (s, 9H), 2.32−2.42 (m, 1H), 2.65 (tt, $J_{H-H}$ = 6.8 Hz, $J_{H-F}$ = 18.6 Hz, 2H), 2.83 (s, 3H), 3.22 (hept, $J$ = 6.8 Hz, 2H), 3.98 (t, $J$ = 6.8 Hz, 2H), 4.12 (d, $J$ = 10.2 Hz, 1H), 7.25 (s, 2H), 8.19 (br s, 0.92H); $^{13}$C NMR $\delta$ 18.61 ($CH_3$), 19.97 ($CH_3$), 23.86 ($CH_3$), 25.84 (CH), 26.72 (CH), 28.35 ($CH_3$), 30.38 ($CH_3$), 31.92 (t, $J$ = 21.8 Hz, $CH_2$), 66.11 (CH and $CH_2$), 80.67 (C), 115.80 (CH), 135.06 (C), 142.31 (C), 148.98 (C), 157.52 (CO), 168.53 (CO); $^{19}$F NMR $\delta$ −81.27 (t, $J_{F-F}$ = 10.4 Hz, 3F), −113.79 (m, 2F), −122.37 (m, 2F), −123.38 (m, 2F), −124.06 (m, 2F), −126.62 (m, 2F); MS (EI) *m*/*z* (%) 752 ($M^{\bullet+}$, 35), 539 (92), 192 (66), 158 (65), 130 (100), 86 (62), 69 (60), 57 (55); HRMS (EI) 752.2853 ($C_{31}H_{41}O_4N_2F_{13}$ requires 752.2859).

**Amide (*S*)-(−)-16d.** Triethylamine (0.30 mL, 2.18 mmol) was added to a solution of (*S*)-**14** (370 mg, 1.60 mmol) in dry dichloromethane (7 mL) at 0 °C. To the resulting clear solution were consequently added aniline **13d** (440 mg, 1.44 mmol) in DCM (3 mL), 1-hydroxybenzotriazole hydrate (HOBt; 280 mg, 1.83 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hy-

drochloride (EDCI; 350 mg, 1.83 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 16 h. The mixture was then diluted with ethyl acetate (70 mL) and washed successively with water (35 mL), cold 0.5 M HCl (2 × 35 mL), saturated $NaHCO_3$ (2 × 45 mL), and brine (35 mL) then dried over $MgSO_4$ and evaporated. The residue (0.81 g) was purified by chromatography on a column of silica gel (70 g) with a petroleum ether−ethyl acetate mixture (24:1) to afford pure amide (*S*)-(−)-**15d** (620 mg, 83%) as a yellowish oil: $R_f$ 0.62 (petroleum ether−ethyl acetate, 9:1); $[\alpha]_D$ −58.6 (*c* 0.5, EtOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.87−0.92 (m, 3H), 0.91 (t, $J$ = 6.5 Hz, 3H, partly overlapped with the multiplet), 1.03 (d, $J$ = 6.4 Hz, 3H), 1.19−1.22 (m, 12H), 1.30−1.35 (m, 8H), 1.45−1.54 (m, 11H), 1.76−1.83 (m, 2H), 2.32−2.41 (m, 1H), 2.82 (s, 3H), 3.28 (hept, $J$ = 6.9 Hz, 2H), 3.67 (t, $J$ = 6.6 Hz, 2H), 4.12 (d, $J$ = 10.7 Hz, 1H), 7.23 (s, 2H), 8.12 (br s, 1.32H); $^{13}$C NMR $\delta$ 14.09 ($CH_3$), 18.59 ($CH_3$), 19.96 ($CH_3$), 22.64 ($CH_2$), 23.95 ($CH_3$), 25.83 (CH), 26.04 ($CH_2$), 26.51 (CH), 28.35 ($CH_3$), 29.25 ($CH_2$), 29.44 ($CH_2$), 30.35 ($CH_2$ and $CH_3$), 31.83 ($CH_2$), 65.87 (CH), 75.02 ($CH_2$), 80.58 (C), 115.64 (CH), 134.35 (C), 142.44 (C), 149.83 (C), 157.45 (CO), 168.39 (CO); MS (EI) *m*/*z* (%) 518 ($M^{\bullet+}$, 19), 305 (75), 192 (54), 130 (64), 86 (99), 57 (51), 44 (21); HRMS (EI) 518.4081 ($C_{31}H_{54}O_4N_2$ requires 518.4084).

**General Procedure for the Synthesis of Imines 1f−h,j.** Molecular sieves (12.5 g, 5 Å) were added to a solution of the corresponding ketone (10 mmol) and aniline (12.5 mmol) in dry toluene (50 mL) and the reaction mixture was heated under reflux for 24 h, then cooled and filtered through a pad of Celite. The pad was rinsed with dichloromethane and the filtrate was evaporated to afford crude imines **1**; the yields and purification details are give below.

**Imine 1f.** Purified by distillation to afford **1f** (41%) as an yellow oil: bp 96−98 °C (0.1 mmHg); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 2.25 (s, 3H), 2.37 (s, 3H), 6.60 (d, $J$ = 7.6 Hz, 1H), 6.64 (s, 1H), 6.91 (d, $J$ = 7.6 Hz, 1H), 7.24 (t, $J$ = 7.6 Hz, 1H) in agreement with literature data;[30] $^{13}$C NMR $\delta$ 17.35 ($CH_3$), 21.47 ($CH_3$), 116.30 (CH), 119.94 (CH), 123.92 (CH), 127.11 (CH), 128.31 (CH), 128.74 (CH), 130.36 (CH), 138.71 (C), 139.51 (C), 151.66 (C), 165.21 (C); MS (EI) *m*/*z* (%) 209 ($M^{\bullet+}$, 51), 194 (100), 132 (11), 91 (46), 65 (27); HRMS (EI) 209.1203 ($C_{15}H_{15}N$ requires 209.1204).

**Imine 1g.** Purified by distillation to afford **1g** (53%) as a yellow oil: bp 114−115 °C (0.1 mmHg); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 2.24 (s, 3H), 2.32 (s, 6H), 6.43 (s, 2H), 6.74 (s, 1H), 7.42−7.47 (m, 3H), 7.96−7.99 (m, 2H); $^{13}$C NMR $\delta$ 17.33 ($CH_3$), 21.35 ($CH_3$), 116.94 (CH), 124.78 (CH), 127.08 (CH), 128.28 (CH), 130.28 (CH), 138.50 (C), 139.56 (C), 151.67 (C), 164.98 (C); IR (neat) $\nu$ 3028, 2953, 1635, 1592, 1276, 846, 763, 692 cm$^{-1}$; MS (EI) *m*/*z* (%) 223 ($M^{\bullet+}$, 54), 208 (100), 105 (23), 77 (28); HRMS (EI) 223.1362 ($C_{16}H_{17}N$ requires 223.1361).

**Imine 1h.** Purified by flash chromatography on silica gel (15 g), treated with $NEt_3$ (3 mL) in petroleum ether−toluene (1:1, 30 mL) overnight, with petroleum ether−toluene (1:1) mixture to afford **1h** (71%) as a yellowish solid: mp 65−66 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 1.33 (s, 18H), 2.26 (s, 3H), 6.64 (d, $J$ = 1.7 Hz, 2H), 7.14 (t, $J$ = 1.7 Hz, 1H), 7.42−7.46 (m, 3H), 7.98−8.01 (m, 2H); $^{13}$C NMR $\delta$ 17.33 ($CH_3$), 31.48 ($CH_3$), 34.90 (C), 113.77 (CH), 117.11 (CH), 127.11 (CH), 128.31 (CH), 130.27 (CH), 139.69 (C), 150.89 (C), 151.42 (C), 165.02 (C); IR (KBr) $\nu$ 2954, 1648, 1594, 718, 699 cm$^{-1}$; MS (EI) *m*/*z* (%) 307 ($M^{\bullet+}$, 100), 292 (84), 236 (13), 125 (11), 84 (39); HRMS (EI) 307.2303 ($C_{22}H_{29}N$ requires 307.2300).

**Imine 1j.** Purified by vacuum distillation to afford **1j** [mixture of (*E*/*Z*) isomers (~6:1), 38%] as an yellow oil: bp 59 °C (0.1 mmHg); $^1$H NMR (400 MHz, $CDCl_3$, major isomer) $\delta_H$ 1.19 (d, $J$ = 6.9 Hz, 6H), 1.75 (s, 3H), 2.62 (hept, $J$ = 6.9 Hz, 1H), 3.79 (s, 3H), 6.60−6.64 (m, 2H), 6.82−6.86 (m, 2H); $^{13}$C NMR (major isomer) $\delta$ 116.78 ($CH_3$), 19.86 ($CH_3$), 39.22 (CH), 55.37 ($CH_3$), 114.07 (CH), 120.42 (CH), 144.85 (C), 155.53 (C), 176.46 (C); IR (neat) $\nu$ 2968, 1656, 1608, 1513, 1239, 1036, 826 cm$^{-1}$; MS (EI) *m*/*z* (%) 191 ($M^{\bullet+}$, 16), 165 (21), 148 (100), 123 (50), 108 (78), 80 (25); HRMS (EI) 191.1312 ($C_{12}H_{17}NO$ requires 191.1310).

**General Procedure for the Catalytic Hydrosilylation of Imines 1a−k with Catalysts 3a−d, 4, and 5d.** Trichlorosilane (40 $\mu$L, 0.4 mmol) was added dropwise to a stirred solution of the imine **1a−k** (0.2 mmol) and the catalyst (0.02 mmol) in anhydrous toluene (2 mL) at room temperature, and the mixture was allowed to stir overnight at room temperature under an argon atmosphere. The reaction was quenched with a saturated solution of $NaHCO_3$ (10 mL) and the product was extracted with ethyl acetate (3 × 10 mL). The extract was washed with brine and dried over anhydrous $MgSO_4$ and the solvent was evaporated. Purification with column chromatography on silica gel (see below) afforded the product as an oil. The yields and enantioselectivities are given in Table 1.

**General Procedure for the Catalytic Hydrosilylation of Imines 1b−e with Fluorous Catalysts 5a−c.** Trichlorosilane (50 $\mu$L, 0.5 mmol) was added dropwise to a stirred solution of the imine **1b−e** (0.2 mmol) and the catalyst (0.02 mmol) in anhydrous toluene (2 mL) at room temperature (or at 10 °C; see Table 1), and the mixture was allowed to stir overnight at room temperature (or at 10 °C; see Table 1) under an argon atmosphere. The reaction was quenched with a saturated solution of $NaHCO_3$ (10 mL) and the product was extracted with ethyl acetate (3 × 30 mL). The extract was washed with brine and dried over anhydrous $MgSO_4$ and the solvent was evaporated. The residue was dissolved in a mixture of methanol and water (80:20) and the resulting solution was filtered through a column of fluorous silica gel (2.8 g) to afford pure amine **2b−e**. The yields and enantioselectivities are given in Table 1. The results of the reduction of **1b** with recycled catalyst are shown in Table 2.

**General Procedure for Recovery of the Fluorous Catalyst.** After elution of the product from the column of fluorous silica, methanol was employed to elute the fluorous catalyst. The methanolic eluate was evaporated, the residue was dissolved in $CH_2Cl_2$ (25 mL), and the resulting solution was dried over $MgSO_4$. The latter solution was then evaporated to afford the regenerated fluorous catalyst **5a−c**, which was used for the next catalytic reduction without further purification.

**Amine (*S*)-(−)-2b.** Purified by column chromatography on silica gel with hexane−ethyl acetate mixture (10:1, $R_f$ 0.3): $[\alpha]_D$ −4.0 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 1.50 (d, $J$ = 6.7 Hz, 3H), 3.70 (s, 3H), 3.79 (br s, 1H), 4.42 (q, $J$ = 6.7 Hz, 1H), 6.46−6.50 (m, 2H), 6.68−6.72 (m, 2H), 7.20−7.25 (m, 1H), 7.30−7.38 (m, 4H) in agreement with literature data;[8] chiral HPLC (Chiracel OD-H, hexane/2-propanol 99:1, 0.9 mL/min) showed 94% ee ($t_R$ = 21.6 min, $t_S$ = 24.4 min).

**Amine (*S*)-(+)-2c.** Purified by column chromatography on silica gel with petroleum ether−ethyl acetate mixture (9:1, $R_f$ 0.2): $[\alpha]_D$ +6.5 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 1.51 (d, $J$ = 6.7 Hz, 3H), 3.70 (s, 3H), 3.83 (br s, 1H), 4.46 (q, $J$ = 6.7 Hz, 1H), 6.41−6.45 (m, 2H), 6.67−6.71 (m, 2H), 7.48 (d, $J$ = 8.2 Hz, 2H), 7.57 (d, $J$ = 8.2 Hz, 2H) in agreement with literature data;[8] chiral HPLC (Chiracel OD-H, hexane/2-propanol 95:5, 0.9 mL/min) showed 92% ee ($t_R$ = 15.7 min, $t_S$ = 21.8 min).

**Amine (*S*)-(−)-2d.** Purified by column chromatography on silica gel with petroleum ether−ethyl acetate mixture (9:1, $R_f$ 0.18): $[\alpha]_D$ −16.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 1.47 (d, $J$ = 6.7 Hz, 3H), 3.70 (s, 3H), 3.78 (s, 3H), 4.37 (q, $J$ = 6.7 Hz, 1H), 6.46−6.70 (m, 2H), 6.67−6.71 (m, 2H), 6.84−6.87 (m, 2H), 7.25−7.29 (m, 2H) in agreement with literature data;[8] chiral HPLC (Chiracel OD-H, hexane/2-propanol 98:2, 0.6 mL/min) showed 91% ee ($t_R$ = 28.8 min, $t_S$ = 33.9 min).

**Amine (*S*)-(−)-2e.** Purified by column chromatography on silica gel with hexane−ethyl acetate mixture (10:1, $R_f$ 0.24): $[\alpha]_D$ −23.2 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 1.58 (d, $J$ = 6.7 Hz, 3H), 3.68 (s, 3H), 3.90 (br s, 1H), 4.57 (q, $J$ = 6.7 Hz, 1H), 6.50−6.54 (m, 2H), 6.66−6.70 (m, 2H), 7.41−7.52 (m, 3H), 7.79−

(30) Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570.

7.83 (m, 4H) in agreement with literature data;[8] chiral HPLC (Chiracel OD-H, hexane/2-propanol 99:1, 0.9 mL/min) showed 92% ee ($t_R$ = 27.4 min, $t_S$ = 33.4 min).

**Amine (+)-2f.** Purified by column chromatography on silica gel with petroleum ether−ethyl acetate mixture (24:1, $R_f$ 0.32): $[\alpha]_D$ +1.9 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 1.52 (d, *J* = 6.7 Hz, 3H), 2.23 (s, 3H), 3.99 (br s, 1H), 4.50 (q, *J* = 6.7 Hz, 1H), 6.33 (d, *J* = 7.8 Hz, 1H), 6.39 (s, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 7.21−7.26 (m, 1H), 7.32−7.40 (m, 4H) in agreement with the literature data;[31] chiral HPLC (Chiracel OD-H, hexane/2-propanol 99:1, 0.9 mL/min) showed 95% ee ($t_{major}$ = 10.0 min, $t_{minor}$ = 12.7 min). The absolute configuration of the prevailing enantiomer is assumed to be (*S*) in analogy with the rest of the series but has not been rigorously proven.

**Amine (−)-2g.** Purified by column chromatography on silica gel with petroleum ether−ethyl acetate mixture (24:1, $R_f$ 0.25): $[\alpha]_D$ −11.0 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 1.51 (d, *J* = 6.7 Hz, 3H), 2.16 (s, 6H), 3.93 (br s, 3H), 4.49 (q, *J* = 6.7 Hz, 1H), 6.18 (s, 2H), 6.33 (s, 1H), 7.22−7.26 (m, 1H), 7.31−7.40 (m, 4H) in agreement with literature data;[32] chiral HPLC (Chiracel OD-H, hexane/2-propanol 99:1, 0.7 mL/min) showed 92% ee ($t_{major}$ = 11.4 min, $t_{minor}$ = 13.4 min). The absolute configuration of the prevailing enantiomer is assumed to be (*S*) in analogy with the rest of the series but has not been rigorously proven.

**Amine (+)-2h.** Purified by column chromatography on silica gel with hexane−ethyl acetate mixture (24:1, $R_f$ 0.25): mp 67−69 °C; $[\alpha]_D$ +4.2 (*c* 1.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 1.22 (s, 18H), 1.53 (d, *J* = 6.7 Hz, 3H), 3.99 (br s, 1H), 4.47 (q, *J* = 6.7 Hz, 1H), 6.40 (s, 2H), 6.74 (s, 1H), 7.20−7.25 (m, 1H), 7.31−7.35 (m, 2H), 7.41−7.43 (m, 2H); $^{13}$C NMR $\delta$ 24.94 ($CH_3$), 31.35 ($CH_3$), 34.73 (C), 54.04 (CH), 108.10 (CH), 111.89 (CH), 125.96 (CH), 126.72 (CH), 128.55 (CH), 145.77 (C), 146.71 (C), 151.35 (C); IR (KBr) $\nu$ 3406, 2966, 1599, 708 $cm^{-1}$; MS (EI) *m/z* (%) 309 ($M^{\bullet+}$, 73), 294 (100), 278 (15), 205 (26), 190 (24), 105 (66), 57 (32); HRMS (EI) 309.2459 ($C_{22}H_{31}N$ requires 309.2457). For the ee determination, amine **2h** was converted into the corresponding acetyl derivative by heating at reflux with acetyl chloride (3 equiv), triethylamine (3 equiv), and DMAP (cat.) in $CHCl_3$ for 30 min. Aqueous workup, followed by purification with column chromatography on silica gel with a petroleum ether−ethyl acetate mixture (4:1, $R_f$ 0.45) afforded the acetamide derivative as a colorless solid (92%): mp 78−80 °C; $[\alpha]_D$ −5.6 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, CDCl3) $\delta_H$ 0.91−1.45 (br s, 18H), 1.39 (d, *J* = 7.2 Hz, 3H), 1.77 (s, 3H), 5.99 (br s, 0.5 H), 6.32 (d, *J* = 7.2 Hz, 1H), 6.90 (br s, 0.5H), 7.14−7.16 (m, 2H), 7.21−7.28 (m, 5H); $^{13}$C NMR $\delta$ 17.00 ($CH_3$), 23.41 ($CH_3$), 31.20 ($CH_3$), 34.63 (C), 51.59 (CH), 121.27 (CH), 124.57 (CH), 127.31 (CH), 127.99 (CH), 128.25 (CH), 137.99 (C), 141.31 (C), 151.33 (C), 170.20 (CO); IR (KBr) $\nu$ 2954,1648, 1594, 718 $cm^{-1}$; MS (EI) *m/z* (%) 351 ($M^{\bullet+}$, 6), 85 (100), 83 (100), 47 (83); HRMS (EI) 351.2559 ($C_{24}H_{33}ON$ requires 351.2562). Chiral HPLC (Whelk-O1, hexane/2-propanol 91:9, 0.9 mL/min) showed 70% ee ($t_{major}$ = 17.1 min, $t_{minor}$ = 19.0 min). The absolute configuration of the prevailing enantiomer is assumed to be (*S*) in analogy with the rest of the series but has not been rigorously proven.

**Amine (+)-2i.** Purified by column chromatography on silica gel with petroleum ether−ethyl acetate mixture (24:1, $R_f$ 0.3): $[\alpha]_D$ +11.2 (*c* 1, $CHCl_3$): $^1$H NMR (400 MHz, CDCl3) $\delta_H$ 0.99−1.28 (m, 5H), 1.09 (d, *J* = 6.5 Hz, 2H), 1.39−1.48 (m, 1H), 1.66−1.82 (m, 5H), 3.12 (br s, 1H), 3.19−3.26 (m, 1H), 3.74 (s, 3H), 6.52−6.56 (m, 2H), 6.75−6.79 (m, 2H) in agreement with literature data;[3c] chiral HPLC (Chiralpak IB, hexane/2-propanol 99:1, 0.5 mL/min) showed 85% ee ($t_{minor}$ = 11.5 min, $t_{major}$ = 12.2 min). The absolute configuration of the prevailing enantiomer is assumed to be (*S*) in analogy with the rest of the series but has not been rigorously proven.

**Amine (+)-2j.** Purified by column chromatography on silica gel with hexane−ethyl acetate mixture (24:1, $R_f$ 0.27): $[\alpha]_D$ +23.7 (*c* 1, $CHCl_3$): $^1$H NMR (400 MHz, CDCl3) $\delta_H$ 0.90 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 2H), 1.07 (d, *J* = 6.5 Hz, 2H), 1.83 (d × hept, *J* = 6.8 and 4.9 Hz, 1H), 3.20 (br s, 1H), 3.25 (d × q, *J* = 6.5 and 4.9 Hz, 1H), 3.74 (s, 3H), 6.53−6.57 (m, 2H), 6.75−6.79 (m, 2H) in agreement with literature data;[33] chiral HPLC (Chiralpak IB, hexane/2-propanol 99:1, 0.5 mL/min) showed 62% ee ($t_{minor}$ = 11.8 min, $t_{major}$ = 13.0 min). The absolute configuration of the prevailing enantiomer is assumed to be (*S*) in analogy with the rest of the series but has not been rigorously proven.

**Amine (−)-2k.** Purified by column chromatography on silica gel with petroleum ether−ethyl acetate mixture (20:1, $R_f$ 0.24): $[\alpha]_D$ −108.7 (*c* 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 1.40 (d, *J* = 6.6 Hz, 3H), 3.46 (br s, 1H), 3.74 (s, 3H), 4.04−4.11 (m, 1H), 6.22 (dd, *J* = 16.0 and 6.0 Hz, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.62−6.66 (m, 2H), 6.77−6.80 (m, 2H), 7.19−7.38 (m, 5H) in agreement with literature data.[34] For the ee determination, amine **2k** was converted into the acetyl derivative by heating at reflux with acetyl chloride (3 equiv), triethylamine (3 equiv), and DMAP (cat.) in $CHCl_3$ for 30 min. Aqueous workup followed by purification with column chromatography on silica gel with a petroleum ether−ethyl acetate mixture (7:3, $R_f$ 0.32) afforded the acetamide derivative as a colorless oil: $[\alpha]_D$ +44.9 (*c* 1, $CHCl_3$); $^1$H NMR (400 MHz, CDCl3) $\delta_H$ 1.22 (d, *J* = 6.9 Hz, 3H), 1.78 (s, 3H), 3.82 (s, 3H), 5.61 (d × pent, *J* = 6.9 and 1.0 Hz, 1H), 6.10 (dd, *J* = 16.0 and 6.9 Hz, 1H), 6.46 (dd, *J* = 16.0 and 1.0 Hz, 1H), 6.84−6.93 (m, 2H), 6.97−7.06 (m, 2H), 7.19−7.33 (m, 5H); $^{13}$C NMR $\delta$ 18.17 ($CH_3$), 23.24 ($CH_3$), 51.30 (CH), 55.38 ($CH_3$), 114.26 (CH), 126.36 (CH), 127.51 (CH), 128.49 (CH), 129.97 (CH), 131.04 (CH), 131.07 (CH), 132.05 (C), 136.90 (C), 159.13 (C), 170.39 (CO); IR (KBr) $\nu$ 2973, 1651, 1512, 1246, 1036, 968, 837, 752, 694 $cm^{-1}$; MS (EI) *m/z* (%) 295 ($M^{\bullet+}$, 24), 252 (13), 204 (14), 165 (16), 131 (100), 91 (33); HRMS (EI) 295.1574 ($C_{19}H_{21}NO_2$ requires 295.1572). Chiral HPLC (Whelk-O1, hexane/2-propanol 85:15, 0.75 mL/min) showed 81% ee ($t_{major}$ = 32.0 min, $t_{minor}$ = 68.9 min). The absolute configuration of the prevailing enantiomer is assumed to be (*S*) in analogy with the rest of the series but has not been rigorously proven.

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**Supporting Information Available:** General experimental methods and $^1$H and $^{13}$C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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