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Practical Asymmetric Synthesis of Trifluoromethyl-Containing Aminoester Using a Modified Davis Protocol

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Abstract:

Practical synthesis of aminoester 1 starting from 1,1,1-trifluoro-3-iodopropane is presented. Use of Ti(O*i*-Pr)$_4$ as a Lewis acid for condensation of intermediate aldehyde 8 with (*S*)-(+)-*p*-toluenesulfinamide was found to be critical. Conditions for a reproducible and high-yielding Wittig reaction of aldehyde hydrate with phosphorus ylide 4, that appear to have general applicability, are described.

Introduction

L-Bis(trifluoromethyl)valine methyl ester (**1**) (Scheme 1), an unnatural amino acid derivative, is an intermediate of interest for Medicinal Chemistry programs,[1] as it offers the possibility to introduce a biologically unique and metabolically stable pharmacophore. Figure 1

The synthesis of **1** has been described.[1b] The reported approach provides for the preparation of **1** in 2.5% overall yield,[2] allowing access to milligram quantities of the substrate. As quick access to multigram quantities of ester **1** was needed, rapid development of a more practical and scaleable protocol allowing larger-scale synthesis was required.

During our studies of the synthesis of this intermediate we have observed a lack of critical information in the synthetic literature on parameters influencing several key steps of our selected approach, which relies on seemingly well-established transformations. Among the issues encountered were the following: developing a protocol for efficient condensation of an aldehyde with a sulfinamide chiral auxiliary under milder-than-reported conditions, developing a practical protocol for the selective Wittig reaction of a phosphorus ylide with an aldehyde hydrate, and determining critical parameters affecting the conversion of a phosphonium halide to an α-phosphanilydene ester reproducibly.

This communication describes our findings in these areas that led to the development of a practical, industrially applicable synthesis of L-bis(trifluoromethyl)valine methyl ester. A discussion of critical parameters affecting key transformations, and reproducibility and scaleability of the preparation of **1** is provided.

Results and Discussion

The presence of trifluoroethyl substituents in **1** imposes limitations on synthetic approaches to the target. The strong electron-withdrawing nature of a trifluoromethyl group significantly deactivates trifluoroethyl halides or triflates towards nucleophilic substitution by corresponding enolates. At the same time, the instability of trifluoroethyl metal species hinders possible cross-coupling approaches with dibromodehydroamino acid derivatives followed by asymmetric hydrogenation. An approach relying on condensation or Wittig olefination of 1,1,1,5,5,5-hexafluoropentan-3-one was also considered and ruled out. Although the ketone is a known compound,[3] its reported synthesis relies on the isolation of a minor component of a mixture for a key intermediate, requires specialized equipment, and poses potential safety concerns. Therefore, the decision was made to use the reported sequence,[1b] relying on conversion of ester **6** to 2-(2,2,2-trifluoroethyl)-4,4,4-trifluorobutyl alcohol and further to aldehyde **8** as a starting point for development of a scaleable synthesis.

The low-yielding sequence of steps in the reported approach,[1b] reduction of ester **6** to alcohol, oxidation of alcohol to aldehyde **8**, and formation of sulfinimine, was perceived to be due to volatility of the intermediate alcohol and the aldehyde. The synthetic scheme was therefore modified to avoid the alcohol intermediate and use the higher-boiling Weinreb amide **7** instead. The synthesis used to access ester **1** is shown in Scheme 1.

α-Phosphanilydene Ester Preparation. Interestingly, on larger scale, the conversion of iodide **2** to phosphonium salt **3** did not proceed in the reported high yield under the described conditions (toluene, 110 °C),[1b] giving only 40–45% yield of **3**. Such an outcome was presumably a result of substrate loss over the reaction time (28 h) due to its low boiling point (55 °C) relative to the reaction temperature. This issue could be resolved either by utilizing a sealed vessel, or by accelerating the reaction by increasing the concentration of the less expensive reagent, Ph_3P. Not surprisingly, linear dependence between number of equivalents of Ph_3P and the yield of phosphonium salt was observed, with **3** forming in 92–96% yield when 3 equiv of Ph_3P were used.

Conversion of phosphonium salt **3** to ylide **4** was reported to proceed with 80% yield. Surprisingly, under controlled conditions using the reported protocol (sequential addition of LiHMDS and ethyl chloroformate at −78 °C) alkoxycarbonylation proceeded with variable yields on larger scale, typically

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(2) Estimated 80% ee.

(3) (a) Van Der Puy, M. *J. Org. Chem.* **1997**, *62*, 6466. (b) Van Der Puy, M. U.S. Patent 6,072,088; *Chem. Abstr.* 2000, *130*, 15138. (c)) Van Der Puy, M.; Madhavan, G. V. B.; Bemmin, T. R. U.S. Patent 5,395,997; *Chem. Abstr.* 1995, *122*, 239173.

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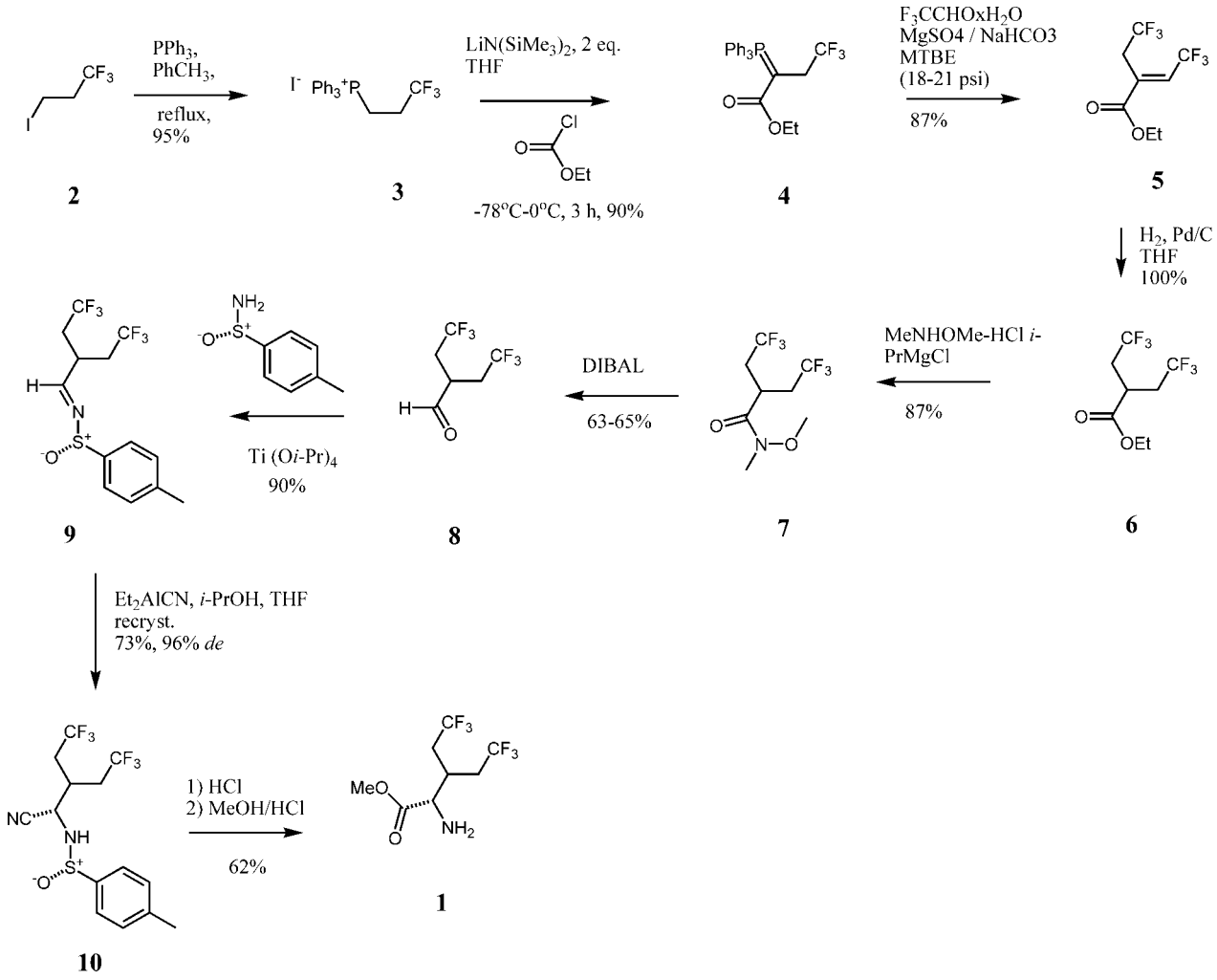
Scheme 1



giving **4** in 32–47% yield.[4] A significant amount of urethane was formed as a byproduct.

Although conversion of iodide **3** to ylide **4** is a one-pot process, there are several successive individual processes that have to occur in sequence for the transformation to proceed to completion (Scheme 2), including: deprotonation to form intermediate ylide **11**, nucleophilic substitution of ethyl chloroformate to form intermediate salt **12**, and deprotonation of **12** with **11** (transylidation) or LiHMDS. Interestingly, incomplete dissolution of **3** even after prolonged time was observed in low-yielding cases, which pointed to solubility as a potential cause of yield irreproducibility. Poor solubility of salt **3** would cause inefficient deprotonation and incomplete conversion to the intermediate ylide **11**, which would translate into incomplete conversion to ylide **4**. Unreacted LiHMDS remaining in the system would then slowly react with ethyl chloroformate, forming the urethane byproduct after hydrolysis. The efficiency of intermediate **11** formation was found to be dependent on the temperature of initial deprotonation.

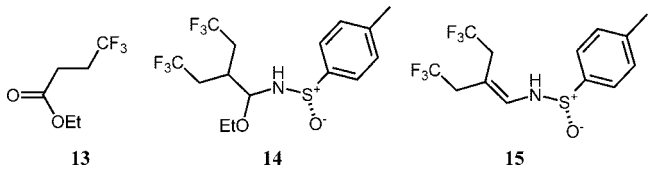
Simply raising the temperature of deprotonation to −5 to 5 °C range ensured complete consumption of **3** (can be monitored by complete dissolution).[5] Subsequent addition of ethyl chloroformate at −78 °C afforded ester **4**, now reproducibly in up to 89% yield on ∼200 g scale.

The reproducibility issue described above may possibly be unnoticed during smaller-scale experiments, when the rate of LiHMDS addition (exothermic process) and, consequently, internal temperature, are not carefully controlled (uncontrolled exotherm during initial deprotonation may inadvertently drive the reaction to completion). However, on larger-scale experiments, when strict control over reaction parameters is always exercised, exact determination of the parameters is crucial for successful conversion.

Wittig Olefination of Trifluoroacetaldehyde Hydrate. The following Wittig olefination of ylide **4** with commercially available trifluoroacetaldehyde hydrate in a sealed vessel in THF at 100 °C indeed proceeded to yield the desired olefin **5**.[1b] However, 25–30% of a byproduct, ethyl trifluorobutyrate **13**, forms along with **5** under these conditions, as determined by NMR.

(4) In one instance 81% was observed on a smaller, 5-g scale.

(5) (a) Ullmannn, J.; Hanack, M. *Synthesis* **1989**, 685. (b) Morimoto, Y.; Shirahama, H. *Tetrahedron* **1996**, *52*, 10631. (c) Bestman, H. J.; Schulz, H. *Liebigs Ann. Chem.* **1964**, *674*, 11. (d) Isler, O.; Gutmann, H.; Montavon, M.; Ruegg, R.; Ryser, G.; Zeller, P. *Helv. Chim. Acta* **1957**, *40*, 1242.



13 14 15

Figure 1. **Byproducts in the formation of 5, 9.**

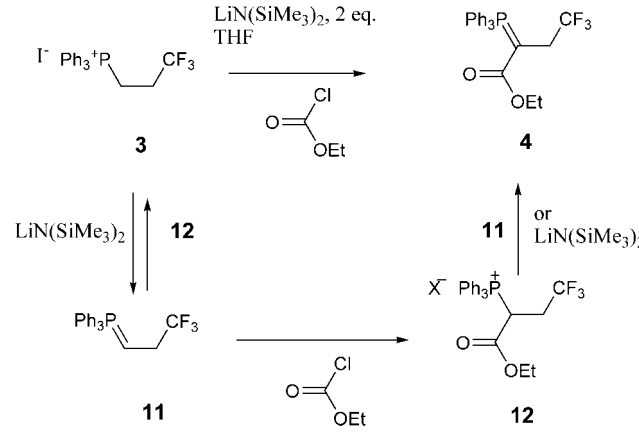
Phosphorus ylides are known to be susceptible to hydrolysis,[6] which is catalyzed by acids. Such a hydrolysis would result in formation of impurity **13**. It should be noted that trifluoroacetaldehyde, being a gas in its pure form at room temperature, is commercially available as its acetal (hydrate). Dissociation of the acetal to form free aldehyde is needed for the Wittig reaction to proceed, hence necessitating high temperature and use of a sealed vessel. Water produced from the acetal is responsible for ylide hydrolysis. Interestingly, it was found that commercial trifluoroacetaldehyde hydrate (acetal) contains not only water of the hydrate but also unbound water as well as residual HCl and HF, which would catalyze formation of impurity **13**. Therefore, critical for this transformation is efficient removal of water and any acidic impurities from the reaction medium.

It was found that by incorporating pretreatment of trifluoroacetaldehyde hydrate with $NaHCO_3$ and $MgSO_4$, running the Wittig reaction in the presence of a water-consuming agent ($MgSO_4$), and switching solvents to the less water-miscible MTBE (to increase $MgSO_4$ efficiency), one could generate acid-free anhydrous trifluoroacetaldehyde in situ.[7] This, in turn, suppressed formation of impurity **13** to a level below 2%, yielding **5** reproducibly in 87% isolated yield.

Hydrogenation of olefin **5** afforded saturated ester **6**, which was used further without isolation as a THF solution. As the direct reduction of ester **6** to the aldehyde was not selective, **6** was converted to Weinreb amide **7** using the standard protocol.[8] DIBAL reduction to aldehyde **8** proceeded cleanly at −70 °C. The dichloromethane solution of **8**, after phase split and aqueous wash, was dried and used further as such due to volatility concern. The yield of aldehyde **8** was determined by NMR after adding a known amount of mesitylene as an internal standard to the stock solution and integrating corresponding peaks.

Sulfinimine Formation. With aldehyde **8** available, the introduction of chiral auxiliary was studied. Conversion of aldehydes to *p*-toluenesulfinimines is well documented.[9] However, using standard conditions described in literature ((*S*)-*p*-toluenesulfinamide and $Ti(OEt)_4$ in CH_2Cl_2 or Et_2O), sulfinimine **9** could only be obtained in 13–34% yield, along with numerous byproducts, regardless of temperature or concentration, and

Scheme 2



corresponding to results reported for this substrate.[1b] Alternative reported methods of preparation of sulfinimines (4 Å molecular sieves, Py-TsOH)[7] did not offer any advantages. It should be noted that such a low yield is not due to aldehyde volatility, instability, or incomplete consumption. Aldehyde **8** was found to be stable as a CH_2Cl_2 solution at room temperature for weeks, and was fully consumed under condensation conditions.

Examination of the product mixture by LC/MS suggested formation of **14** and **15** as major byproducts of condensation, present in up to 31% and 6%, respectively. The amount of both of these byproducts increased with reaction temperature and time.

The presence of impurity **14** pointed to involvement of $Ti(OEt)_4$ in the byproduct formation. The $Ti(OEt)_4$ additive plays a dual role in aldehyde condensation with sulfinamide, acting as a water-consuming agent and as a Lewis acid to activate the aldehyde towards nucleophilic addition. However, $Ti(OEt)_4$ activates condensation product **9** towards nucleophilic addition as well, while also acting as a source of ethoxide nucleophile to generate byproduct **14**. It was reasoned that pivotal for the success of this condensation would be an additive possessing all following characteristics: being a water-consuming agent; being a Lewis acid, but a less active one than $Ti(OEt)_4$; and, if such an additive is a metal alkoxide, having a bulkier and less nucleophilic alkoxide group. Indeed, the use of $Ti(O\textit{i}\text{-Pr})_4$ offered significant advantage, allowing to obtain sulfinimine **9** in 90% isolated yield as a single product. Other critical parameters for this reaction include temperature (40 °C) and concentration (~0.1 M). At high concentrations alkoxide addition byproduct would be formed even with $Ti(O\textit{i}\text{-Pr})_4$.

Impurity **15** was presumably formed by tautomerization of **9** under prolonged reaction conditions, and its formation was suppressed using the newly developed protocol.

Strecker reaction using $Et_2AlCN-\textit{i}\text{-PrOH}$ proceeded as expected,[10] giving **10** in 90% yield as a 9:1 mixture of diastereomers, which was improved to a 98:2 ratio by recrys-

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(11) For an explanation of the sense of stereoinduction, see refs 10a and b.

(12) Ester **1** was converted to several pharmacologically active derivatives of interest in two steps. Enantiomeric purity was determined for one of the derivatives purified by recrystallization and was found to be >99% ee by chiral HPLC.

tallization (73% yield).[11] Subsequent hydrolysis and esterification in MeOH/HCl afforded **1** in 10 steps and 17% overall yield.[12]

Conclusions

In summary, milder and more practical protocols were established for condensation of aldehyde **8** with a sulfinamide chiral auxiliary, and for selective Wittig reaction of phosphorus ylide **4** with an aldehyde hydrate. Both protocols appear to have general applicability. Critical parameters affecting key steps of described synthesis were determined. As a result, a scaleable and industrially applicable selective synthesis of ester **1** was developed, allowing easy access to multigram quantities of the substrate.

Experimental Section

(3,3,3-Trifluoropropyl)triphenylphosphonium Iodide (3). A solution of 1,1,1-trifluoro-3-iodopropane **2** (223.96 g, 1 mol) and triphenylphosphine (786.87 g, 3 mol) was prepared in toluene (800 mL). This solution was stirred at reflux for 12 h. The solid product precipitated from the reaction mixture throughout the course of the reaction. The reaction was allowed to cool to ambient temperature and then cooled to ~5 °C in an ice bath. The solid precipitate was isolated by filtration and dried in vacuo at 25 °C to give a white powder (461.94 g, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90–7.85 (m, 9H), 7.78–7.74 (m, 6H), 4.09–4.01 (m, 2H), 2.71–2.57 (m, 2H). Anal. Calcd for $C_{21}H_{19}F_3IP$: C, 51.87; H, 3.94. Found C, 51.99; H, 3.90.

4,4,4-Trifluoro-2-(triphenyl-λ^5-phosphanylidene)butyric Acid Ethyl Ester (4). A suspension of (3,3,3-trifluoropropyl)triphenylphosphonium iodide **3** (194.5 g, 0.4 mol) in tetrahydrofuran (anhydrous, 800 mL) was cooled to −5 °C in an ice/brine bath under nitrogen. To this suspension, lithium bis(trimethylsilyl)amide (1.0 M in THF, 800 mL, 0.8 mol) was added dropwise over 2 h. The temperature was maintained below 5 °C throughout the addition. The reaction mixture was then cooled to −75 °C in a dry ice/acetone bath. To this solution, ethylchloroformate (76.5 mL, 0.8 mol) was added dropwise over 30 min. The reaction was stirred at −75 °C for an additional hour and allowed to warm to room temperature overnight. The reaction mixture was poured onto brine (1.5 L) and stirred for 30 min. The layers were separated, and the organic layer was washed with brine (200 mL). The aqueous layer was washed with methylene chloride (2 × 200 mL), and the combined organics were concentrated to a residue. This residue was redissolved in methylene chloride (500 mL), dried over $MgSO_4$, and filtered through a plug of magnesol. The solvent was reduced to a minimum (~100 mL) in vacuo, and the product was precipitated with hexanes (250 mL). The solvent was completely removed in vacuo, and the solid product was triturated in hexanes (500 mL). The solid was isolated by filtration and dried overnight in vacuo at 25 °C to give a beige powder (152.8 g, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$, for two rotamers) δ 7.66–7.45 (m, 15H), 4.05 and 3.70 (q, 2H, J = 7.2 Hz), 2.81–2.64 (m, 2H), 1.21 and 0.41 (t, 3H, J = 7.2 Hz); MS (M + H): 431. Anal. Calcd: C, 66.97; H, 5.15. Found: C, 66.37; H, 5.28.

4,4,4-Trifluoro-2-(2,2,2-trifluoroethyl)-but-2-enoic Acid Ethyl Ester (5). Trifluoroacetaldehyde hydrate (150 g, technical grade, pH 1) was stirred with anhydrous sodium bicarbonate (15 g, powder) to result in a mildly foaming suspension. Anhydrous magnesium sulfate powder (60 g) was added, followed by addition of MTBE (300 mL) to result in a mildly exothermic reaction. The suspension was kept in a water bath at 10 °C for 10 min, filtered through a fluted filter funnel, and washed with MTBE (2 × 250 mL). The filtrate (pH 7.2) was charged into a 2 L "Parr" pressure reactor containing the starting ylide **4** (204 g, 0.474 mol). To the mixture was added anhydrous magnesium sulfate powder (60 g). The reaction vessel was heated to 70−75 °C with stirring for 15 h. The pressure in the "Parr" reactor rose to 18–21 psi. The reaction was cooled to room temperature, and the mixture was filtered. The filter cake was washed with MTBE. The filtrate was distilled at 60–70 mm/Hg to remove most of the MTBE in the first fraction, and the remainder was collected in the second fraction. The pressure for the second fraction was reduced to 20 mm/Hg to yield 121.7 g. The second fraction (121.7 g) was redistilled at 20 mm/Hg with a bath temperature at 80 °C to yield a main fraction of a low viscosity liquid (103.5 g, yield 87%, bp 53–55 °C at 20 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (q, 1 H, J = 8 Hz), 4.33 (q, 2 H, J = 7.3 Hz), 3.50 (q, 2 H, J = 9.9 Hz), 1.35 (t, 3 H, J = 7.3 Hz). MS (M + H): 251.

4,4,4-Trifluoro-2-(2,2,2-trifluoroethyl)butyric Acid Ethyl Ester (6). 4,4,4-Trifluoro-2-(2,2,2-trifluoroethyl)but-2-enoic acid ethyl ester **5** (225 g, 0.9 mol) was dissolved in tetrahydrofuran (700 mL) and treated with 5% Pd/C (17 g). The mixture was reduced by hydrogenation in a "Parr" shaker in a 2.5 L pressure bottle at 50 psi. The reaction is exothermic to 45 °C and is controlled by interrupting the shaking motion of the "Parr" shaker. The reaction was completed in approximately 2 h (as judged by NMR). The reaction mixture was filtered through a 2-in. bed of "Solka Floc"/magnesium sulfate to give a clear, colorless solution of the title compound (225 g in 1182 g of tetrahydrofuran, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.14 (q, 2 H, J = 7.2 Hz), 2.99–2.89 (m, 1 H), 2.68–2.48 (m, 2 H), 2.4–2.21 (m, 2 H), 1.22 (t, 3H, J = 7.2 Hz). MS (M + H): 253.

4,4,4-Trifluoro-*N*-methoxy-*N*-methyl-2-(2,2,2-trifluoroethyl)butyramide (7). *N*,*O*-Dimethylhydroxylamine hydrochloride (90 g, 0.92 mol) was added to a solution of 4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butyric acid ethyl ester **6** (116.28 g, 0.46 mol) in tetrahydrofuran (610.8 g weight of the solution). The mixture was cooled to −15 to −20 °C with a dry ice/acetone bath. To the reaction mixture was added dropwise a solution of *i*-propylmagnesium chloride (924 mL, 2 M in tetrahydrofuran, 1.848 mol) over a period of 1 h, keeping the temperature at −15 to −20 °C. After the addition, the reaction was stirred at that temperature for 30 min. The reaction was quenched by adding dropwise hydrochloric acid (2 N, 600 mL, 1.2 mol). The reaction proceeds at a very rapid rate, accompanied by a large exothermic temperature excursion during addition of the first 50 mL. The temperature did not exceed 3 °C resulting in a thick suspension first, subsequently becoming a clear solution with two layers. The mixture was extracted with

MTBE (1.5 L). The aqueous phase was re-extracted with MTBE (0.5 L). The combined organic extracts were washed with brine (2 × 0.5 L). The organic phase was dried over anhydrous magnesium sulfate powder and filtered, and the filtrate was concentrated in vacuo at max. 35 °C to provide 121 g of an oil. The oil was distilled at 15 mmHg/bp 64–68 °C to give the title compound as oil (120 g, yield 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.735 (s, 3 H), 3.6–3.5 (m, 1 H), 3.22 (s, 3 H), 2.76–2.60 (m, 2 H), 2.35–2.2 (m, 2 H). MS (M + H): 268.

4,4,4-Trifluoro-2-(2,2,2-trifluoroethyl)butyraldehyde (8). To a solution of 4,4,4-trifluoro-*N*-methoxy-*N*-methyl-2-(2,2,2-trifluoroethyl)-butyramide (53.4 g, 0.2 mol) in dichloromethane (300 mL) was added diisobutylaluminum hydride (58 mL, 0.32 mol) over 20 min at −68 to −62 °C. The reaction mixture was stirred at −70 °C for 1 h and then poured into 1.5 L of ice containing 500 mL of 6 N HCl. The phases were split, and the aqueous phase was extracted with 300 mL of dichloromethane. The combined organic phase was washed with 1 N HCl and dried over $MgSO_4$. The solution was filtered through a 2.5-cm pad of silica gel. The silica gel pad was washed with dichloromethane. The total volume of the solution: 2 L. NMR analysis of the solution using an internal standard (mesitylene) indicated formation of the title product in 62.5% yield. The solution was stored over 4 Å molecular sieves and used as such for further transformations. ^{1}H NMR (300 MHz, $CDCl_3$; solvent and mesitylene peaks excluded): δ 9.74 (d, 2 H, J = 1.2 Hz), 3.02–2.98 (m, 1 H), 2.80–2.62 (m, 2 H), 2.46–2.36 (m, 2 H).

(*S*)-4-Methyl-*N*-[(1*Z*)-4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butylidene]benzenesulfinamide (9). To a dichloromethane solution of 4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butyraldehyde **8** (1000 mL; contains 62.5 mmol of the aldehyde; prepared as described above; dried over 4 Å molecular sieves) were added titanium isopropoxide (95 mL, 314.4 mmol, 97% pure) and (*S*)-(+)-*p*-toluenesulfinamide (11.86 g, 76.4 mmol, 1.2 equiv). The reaction mixture was stirred at 40 °C for 5.5 h, cooled to rt, and poured into ice–water (400 mL) at 0 °C. The mixture was stirred at room temperature for 1 h, then filtered through Celite. Phases were separated, the aqueous phase was extracted with dichloromethane. The combined organic fraction was washed with brine and dried over $MgSO_4$. The resultant mixture was filtered through a 5-cm pad of silica gel and concentrated to afford 19.2 g (90%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, 1 H, J = 3.8 Hz), 7.53 (d, 2 H, J = 8.2 Hz), 7.31 (d, 2 H, J = 8.2 Hz), 3.28–3.15 (m, 1 H), 2.7–2.53 (m, 2 H), 2.52–2.32 (m, 5 H). MS (M + H): 346.

4-Methyl-*N*-[(1*S*)-1-cyano-4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butyl]-(*S*)-benzenesulfinamide (10). To a mixture of THF (110 mL) and diethylaluminum cyanide (112 mL of 1 M toluene solution, 112 mmol) was added isopropanol (8.7 mL, 113 mmol) over 5 min at 2−4 °C. The mixture was stirred at that temperature for 1 h and then cooled to −65 °C. A solution of (*S*)-4-methyl-*N*-[(1*Z*)-4,4,4-trifluoro-2-(2,2,2-trifluoroethyl-)butylidene]benzenesulfinamide **9** (18.5 g, 56.2 mmol) in THF (250 mL) was added over 30 min at −65 to −60 °C. The reaction mixture was stirred at that temperature for 15 min and then allowed to slowly warm up to 0 °C. The mixture was stirred at 0 °C for 3 h and then poured onto ice–water (1200 mL) containing NH_4Cl (150 g). The resultant suspension was filtered through Celite. The Celite pad was washed with MTBE. The phases were separated, and the aqueous phase was extracted with MTBE. The combined organic fraction was dried over $MgSO_4$ and filtered through 2.5-cm pad of silica gel. The silica gel pad was washed with MTBE. The combined solution was concentrated to an oil, which was treated with heptane. The resultant white solid was filtered and washed with heptane to afford 17.2 g of the title product as a 9:1 mixture of diastereomers (90% yield). The crude material was recrystallized from 25 mL of hot MTBE and 70 mL of heptane, filtered, washed with heptane to afford 14 g of the title product (95% de, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$; major diastereomer): δ 7.56 (d, 2 H, J = 8.2 Hz), 7.37 (d, 2 H, J = 8.2 Hz), 5.6 (d, 1 H, J = 8.6 Hz), 4.33 (dd, 1 H, J = 8.6, 4.3 Hz), 2.77–2.55 (m, 2 H), 2.5–2.2 (m, 6 H). MS (M + H): 373.

(2*S*)-2-Amino-5,5,5-trifluoro-3-(2,2,2-trifluoroethyl)pentanoic Acid Methyl Ester (1). 4-Methyl-*N*-[(1*S*)-1-cyano-4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butyl]-(*S*)-benzenesulfinimide **10** (10 g, 29 mmol) was dissolved in concentrated hydrochloric acid (200 mL), and the mixture was heated under reflux for 15 h. The reaction was cooled to room temperature. A byproduct, toluene-4-thiosulfonic acid *S*-*p*-tolyl ester, separated from the aqueous solution as a white crystalline solid and was filtered off. The aqueous filtrate was concentrated in vacuo to a sticky white solid. The crude amino acid was taken up in concentrated hydrochloric acid (200 mL) and extracted with toluene (2 × 50 mL). The aqueous phase was concentrated in vacuo, coevaporating with toluene (4 × 70 mL) to give a solid compound. The aminoacid was dissolved in methanol (400 mL), treated with anhydrous hydrochloric acid (4 N, 100 mL), and refluxed for 72 h. The reaction was evaporated in vacuo to a foam (60% ester conversion by NMR). The reaction mixture was dissolved in methanol (300 mL) and treated with ethereal hydrochloric acid (2 N, 100 mL) and refluxed for 24 h. The solution was concentrated to a solid (80% ester conversion by NMR). The crude mixture was dissolved in water and extracted with MTBE. The aqueous phase was basified with solid sodium bicarbonate and extracted with MTBE (2 × 100 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to give the title compound as a solid. (4.6 g, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 3 H), 3.75 (d, 1 H, J = 2.2 Hz), 2.66–2.52 (m, 2 H), 2.35–2.20 (m, 1 H), 2.18–2.06 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.28, 126.67 (q, J = 278 Hz), 126.45 (q, J = 278 Hz), 54.91, 52.58, 34.58 (q, J = 29 Hz), 33.41 (q, J = 29 Hz), 31.40. Anal. Calcd for $C_8H_{11}F_6NO_2$: C 35.96, H 4.15, N 5.24; found: C 36.18, H 4.20, N 5.27. HRMS (for M + H) calcd: 268.07668; found: 268.07582. $[\alpha]_D$ +11.2 (c = 1, MeOH).

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Supporting Information Available

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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