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# One-Pot Preparation of Enantiopure Fluorinated β-Amino Acid Precursors

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*Dedicated to Dr. Cliff Soll on the occasion of his untimely passing*

**Keywords:** Domino reactions / Fluorine / Amino acids / Organocatalysis / Synthetic methods

Chiral β-fluoro amines and β,β-difluoro amines are common substructures in medicinal compounds. Industrial syntheses typically use enantiopure starting materials, chiral auxiliaries, or the resolution of enantiomeric or diastereomeric mixtures to install these functionalities in enantiopure form. With the goal of improving access to these substructures, we recently developed the first catalytic enantioselective olefin aminohalogenation reaction, which produced chiral β-fluoro amines in a single flask from achiral enal starting materials. This paper describes the extension of this method to the preparation of β-amino-α,α-difluoro carbonyl compounds. Specifically, carbon–nitrogen and carbon–fluorine bond-forming reactions were combined in an organocascade reaction to produce β-amino-α,α-difluoro carbonyl compounds containing alkyl substituents at the β-position. As such, this method is mechanistically distinct from, and complementary to, existing one-pot catalytic enantioselective methods for the preparation of fluorinated β-amino acid precursors.

## Introduction

In 2007, nine of the 20 top-selling drugs in the world contained at least one fluorine atom.[1] This statistic reflects the trend in recent years of increasing incorporation of fluorine into medicinal compounds.[2] This trend is due to the many and varied effects of fluorine, the most electronegative element, on the properties of medicinal compounds. For example, the introduction of one or more fluorine atoms vicinal to an amine, as seen in the compounds in Figure 1, decreases the basicity of the amine.[3] This can have the result of increasing the biological activity,[4] bioavailability,[5] and/or lipophilicity (log D)[6] of a drug.

In addition to their influence on the biological activity of amines, the incorporation of proximal fluorine atoms can also modulate the activity of pharmacophoric carbonyl groups. As an example of this effect, the introduction of a *gem*-difluoromethylene group adjacent to a carbonyl group increases the propensity of the carbonyl group to adopt its tetrahedral hydrate form, which can increase the inhibitory activity of certain carbonyl compounds against proteases and esterases.[7] As an example of both of these effects, Daiichi pharmaceuticals developed fluorinated rhodopeptin analogue **4**, which retained the antifungal activity but had a maximum tolerated dose (MTD) more than twice that of non-fluorinated analogs of rhodopeptin.[8] In addition, three fluorinated Docetaxel analogs of type **5**, also developed by Daiichi pharmaceuticals, were more potent than Paclitaxel in terms of both their $GI_{50}$ against the five cancer cell lines assayed and their inhibition ($IC_{50}$) of microtubule assembly.[9]

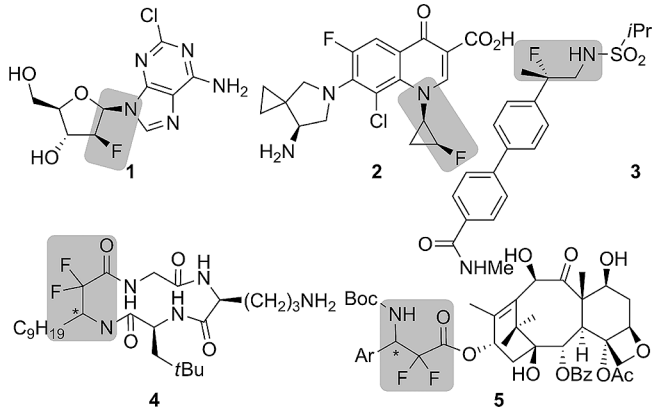


Figure 1. Fluorinated amine drugs.

While the impact of these chiral β-fluoroamine and β,β-difluoroamine moieties on the therapeutic parameters of drugs can be impressive, the synthetic methods used in industry for their introduction are rather unremarkable. Often, the use of enantiopure starting materials or a chiral auxiliary is required to enable diastereoselective C–F bond-forming reactions, as occurred in the synthesis of Sanofi–Aventis chemotherapeutic **1** and Daiichi Pharmaceuticals antibiotic **2**, respectively.[10,11] It is also a common strategy

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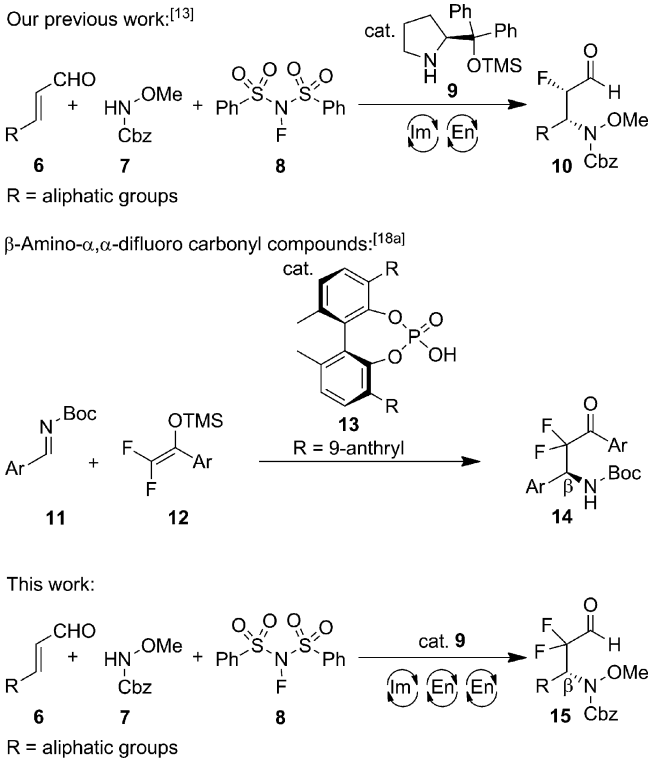
to use non-asymmetric bond-forming reactions followed by a resolution of the resulting enantiomeric or diastereomeric mixture, as occurred in the Eli Lilly synthesis of AMPA potentiator **3**, and in the Daiichi Pharmaceuticals syntheses of **4** and **5**.[8,9,12]

In contrast, catalytic enantioselective methods for producing chiral β-fluoro amines and β,β-difluoro amines would be more flexible and efficient than syntheses that are restricted to substrates available from the chiral pool, those that use a stoichiometric chiral auxiliary, and those that necessitate the disposal of an undesired stereoisomer. Towards this end, we recently reported an organocatalytic enantioselective olefin aminofluorination reaction that produced α-fluoro-β-amino acid precursors (Scheme 1).[13] Ours was the first example of a catalytic enantioselective olefin aminohalogenation reaction.[14] Among alternative catalytic methods to produce enantiopure β-fluoro amines from achiral starting materials, several examples involve asymmetric hydrogenation of fluoroenamines,[15] and thus require that the carbon–nitrogen and carbon–fluorine bonds be intact prior to the enantiodetermining step. Other one-pot methods generate β-fluoro amines that contain only a single stereocenter,[16] or that cannot be readily transformed into diastero- or enantiopure fluorinated amino acids.[14f,17]

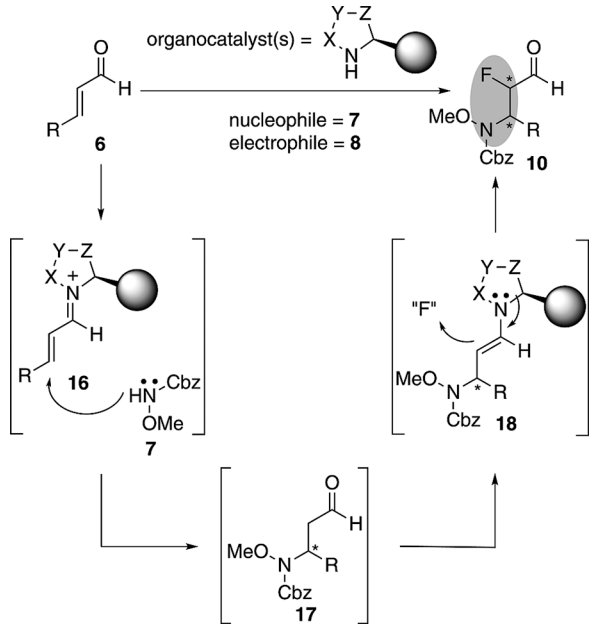



Scheme 1. Catalytic asymmetric synthesis of fluorinated β-amino acid precursors. Cbz = benzyloxycarbonyl; Boc = *tert*-butoxycarbonyl; TMS = trimethylsilyl.

Similarly, only two catalytic enantioselective methods for the direct preparation of enantiopure β-amino-α,α-difluoro carbonyl compounds are known (Scheme 1).[18] Both methods involve an asymmetric Mannich reaction using difluoroenol silyl ethers **12**. One method used chiral phosphoric acid organocatalyst **13**,[18a] and the other used a chiral Zn catalyst.[18b] While the organocatalytic method gave yields of up to 91% and *ee*s of up to 93% using imines derived from aromatic aldehydes, a 0% yield was obtained using an imine derived from an aliphatic aldehyde. In this paper, we review our original organocatalytic enantioselective olefin aminofluorination reaction, and present the extension of this method to the synthesis of β-amino-α,α-difluoro carbonyl compounds (Scheme 1).

## Results and Discussion

We initially envisioned that an organocascade reaction (Scheme 2) would be an efficient means of producing enantiopure α-fluoro-β-amino acid precursors.[19] At that time, no single organocatalyst had proven to be effective in both iminium-catalyzed aza-Michael additions (**16** → **17**) and enamine-catalyzed α-fluorinations of aldehydes (**18** → **10**). We therefore anticipated that different organocatalysts might be required for the iminium- and enamine-catalyzed steps of the cascade reaction, which is known as cycle-specific organocascade catalysis.[20]



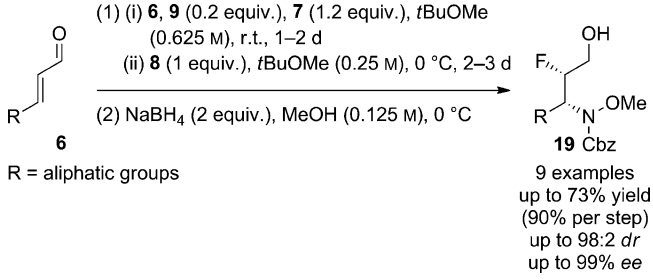

Scheme 2. Organocascade reaction to generate α-fluoro-β-amino aldehydes.

A key observation in the development of this cascade reaction, however, was that the diastereoselectivity reversed from 1:3 *syn*/*anti* to 3:1 *syn*/*anti* upon running the fluorination step at –10 °C and at room temp., respectively. These results indicated that different catalysts were operating in the enamine-catalyzed α-fluorination step at low and at high temperatures, and suggested that catalyst **9** could, in fact, catalyze the entire cascade reaction.

This key observation, in conjunction with extensive reaction optimization, led to the realization of this cascade reaction as an efficient one-pot process. As mentioned earlier, this process represents the first example of a catalytic enan-

tioselective olefin aminohalogenation reaction (Scheme 3). A variety of enals with aliphatic R groups gave the desired products in isolated yields of up to 73%, with *dr*s up to 98:2 and *ee*s up to 99%. Acrolein (R = H), however, along with cinnamaldehyde and *p*-nitrocinnamaldehyde (R = Ar) did not give any olefin aminofluorination product under the reaction conditions.




Scheme 3. Organocatalytic enantioselective aminofluorination of olefins.

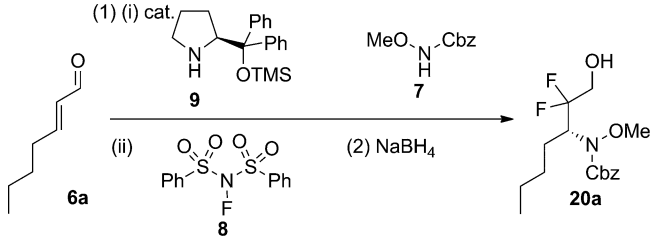
We envisioned that our organocatalyic enantioselective olefin aminofluorination reaction could be adapted to directly produce enantiopure β-amino-α,α-difluoro carbonyl compounds by combining an iminium-catalyzed (Im) aza-Michael addition with *two* consecutive enamine-catalyzed (En) fluorinations in a single flask. The use of successive carbon–nitrogen and carbon–fluorine bond-forming reactions in a cascade reaction would thus be distinct from the two existing catalytic asymmetric methods to form enantiopure β-amino-α,α-difluoro carbonyl compounds,[18] both of which involve a carbon–carbon bond-forming (Mannich) reaction (Scheme 1). Moreover, our approach would generate enantiopure β-amino-α,α-difluoro carbonyl compounds **15** containing aliphatic groups at the β-position, and thus would be complementary to the organocatalytic method shown in Scheme 1, which produces enantiopure β-amino-α,α-difluoro carbonyl compounds **14** containing aromatic groups at that position.

Using our initial cascade reaction conditions, but increasing the number of equivalents of *N*-fluorobenzenesulfonimide (NFSI; **8**) from one to two,[16a] and running the fluorination step at room temp. (as opposed to 0 °C, because no difluorination was observed in the original cascade reaction at that temperature), resulted in a dismal 17% yield of **20a** after in situ reduction (Table 1, Entry 1). Extensive reexamination of the individual steps of the cascade reaction and exhaustive optimization of the one-pot cascade reaction, detailed in the Supporting Information, ultimately provided improved product yields. A few key observations are summarized in Table 1.

The presence of multiple silyl peaks in the $^1$H NMR spectra during monitoring of the cascade reaction suggested possible decomposition of catalyst **9**. Therefore, fresh catalyst was added for the fluorination step, and this resulted in a significant increase in the product yield (Table 1, Entry 2).

Furthermore, it was conceivable that the product of the first α-fluorination was mismatched for the second enamine-catalyzed fluorination using **9**. Subjecting 2-fluorotridecanal to the fluorination conditions in the absence of an amine catalyst provided no difluorinated product after 20 h. Furthermore, subjecting 2-fluorotridecanal to the fluorination conditions in the absence of **9**, but in the presence of a stoichiometric amount of DBU, provided traces of the difluorinated product after 20 h. Taken together, these results suggest that in the cascade reaction, difluorination probably does not proceed via an enol intermediate, neither does it involve basic catalysis or transfer fluorination, but rather it occurs by two successive enamine-catalyzed α-fluorinations. Moreover, resubjecting pure **10** (R = Et), as a 2:1 *syn*/*anti* diastereomeric mixture, to the fluorination conditions revealed that **9** converted approximately 60% of the minor diastereomer and none of the major diastereomer

Table 1. Reaction development.[a]




| Entry | Cat. in step (ii) | Equiv. **7** | Equiv. **8** | *T* of step (ii) | Yield of **20a** [%][b] |
|---|---|---|---|---|---|
| 1 | – | 1.2 | 2 | r.t. | 17 |
| 2 | **9** (10 mol-%) | 1.2 | 2 | r.t. | 30 |
| 3 | *rac*-**9** (10 mol-%) | 1.2 | 2 | r.t. | 39 |
| 4[c] | *rac*-**9** (20 mol-%) | 1.2 | 2 | r.t. | 52 |
| 5[c,d] | *rac*-**9** (20 mol-%) | 1.2 | 2 | 0 °C | 35 |
| 6[c] | *rac*-**9** (20 mol-%) | 1.2 | 3 | r.t. | 20 |
| 7 | *rac*-**9** (20 mol-%) | 2.0 | 2 | r.t. | 54 |

[a] Reaction conditions: (1) (i) **6a** (0.25 mmol), **7** (equiv.), **9** (0.05 mmol), *t*BuOMe (0.4 mL), room temp., 1 d; (ii) **8** (equiv.), cat. (equiv.), temp, 2 d; (2) $NaBH_4$ (2.5 equiv.), $CH_2Cl_2$/EtOH (2:1), room temp. [b] Isolated yield. [c] Reaction time for step (i) 2 d. [d] Reaction time for step (ii) 3 d.

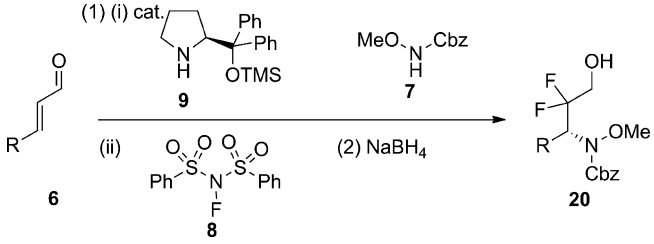
  

into the corresponding difluorinated aldehyde (i.e., **15**) within 2 min, as indicated by $^1$H NMR spectroscopy. Within the same timeframe, the enantiomer of **9** (i.e., *ent*-**9**) converted approximately 25% of the major diastereomer, but none of the minor diastereomer. Subsequent monitoring of this reaction by $^1$H NMR spectroscopy revealed that this trend continued. In the light of these results, racemic **9** (*rac*-**9**) was added for the fluorination step in the cascade reaction, and this further improved the product yield (Table 1, Entry 3). Further increasing the amount of *rac*-**9** added in the fluorination step increased the product yield to useful levels (Table 1, Entry 4).

Running the fluorination step at lower temperatures or in the presence of increased amounts of **8** was detrimental (Table 1, Entries 5 and 6). However, increasing the amount of **7** increased the conversion of **6** to **17**, which slightly increased the product yield while decreasing the overall reaction times, and thus provided the optimal reaction conditions (Table 1, Entry 7 vs. Entry 4).

Having established the optimal reaction conditions for the one-pot cascade reaction, a variety of α,β-unsaturated aldehydes were examined in this transformation (Table 2). Enals with unbranched aliphatic R groups provided β-amino-α,α-difluoro alcohols in excellent yields (≥79% average yield per step) and with excellent *ee*s (Table 2, Entries 1–4). Importantly, this cascade reaction was readily scaled up tenfold to give identical product yields and *ee*s (Table 2, Entries 4 and 5). Branching at the ε- (**20e**) and δ-positions (**20f**) of the enals was tolerated in this transformation (Table 2, Entries 6 and 7). Notably, even a very hindered substrate with branching at the γ-position gave the corresponding β-amino-α,α-difluoro alcohol (i.e., **20g**) in 40% isolated yield and with 90% *ee* (Table 2, Entry 8). Interestingly, this substrate gave a lower isolated yield (24%) and *ee* (80%) in the organocatalytic enantioselective olefin aminofluorination reaction.[13] This transformation also tolerates isolated olefins (Table 2, Entry 9), ether protecting groups (Table 2, Entry 10), and remote reactive functionality, such as ester groups (Table 2, Entry 11). An alternative nitrogen nucleophile, BnONHCbz, was also effective in this cascade reaction, giving results comparable to those obtained with **7** (Table 2, Entries 5 and 12). Under the reaction conditions, cinnamaldehyde and 3-methylcrotonaldehyde were unreactive in the aza-Michael step of the cascade reaction.

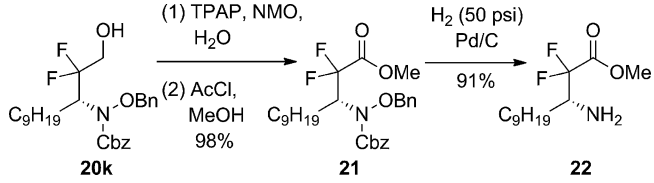
Table 2. Substrate scope.[a]




| Entry | **20** | R | Yield of **20** [%][b,c] | *ee* of **20** [%][d] |
|---|---|---|---|---|
| 1 | **20a** | *n*Bu | 54 (81) | 91 |
| 2 | **20b** | Et | 57 (83) | 90 |
| 3 | **20c** | *n*Pr | 52 (80) | 98 |
| 4 | **20d** | $C_9H_{19}$ | 49 (79) | 92 |
| 5[e] | **20d** | $C_9H_{19}$ | 49 (79) | 92 |
| 6 | **20e** | $CH_2Bn$ | 43 (75) | 93 |
| 7 | **20f** | *i*Bu | 49 (79) | 88 |
| 8 | **20g** | *i*Pr | 40 (73) | 90 |
| 9 | **20h** | $(CH_2)_3CHCH_2$ | 47 (78) | 91 |
| 10 | **20i** | $CH_2OBn$ | 44 (76) | 92 |
| 11 | **20j** | $(CH_2)_7CO_2Me$ | 47 (78) | 90 |
| 12[f] | **20k** | $C_9H_{19}$ | 54[g] (81) | 89[h] |

[a] Reaction conditions: (1) (i) **6** (0.25 mmol), **7** (0.5 mmol), **9** (0.05 mmol), *t*BuOMe (0.4 mL), room temp., 1 d; (ii) **8** (0.5 mmol), *rac*-**9** (0.05 mmol), *t*BuOMe (0.6 mL), room temp., 2–3 d; (2) $NaBH_4$ (2.5 equiv.), $CH_2Cl_2$/EtOH (2:1), room temp. [b] Isolated yield. [c] The number in parentheses corresponds to the average yield per step in the three-step sequence. [d] Determined by chiral-phase HPLC of the alcohol. [e] Reaction run on a 2.5 mmol scale. [f] BnONHCbz used instead of **7**. [g] Yield determined by $^1$H NMR spectroscopy using an internal standard. [h] *ee* of ester **21** (Scheme 4).

Cascade product **20k** was transformed in three steps into β-amino-α,α-difluoro amino ester **22** (Scheme 4), an intermediate in the synthesis of fluorinated rhodopeptin analogue **4**.[8] Quantitative oxidation of alcohol **20k** directly to the corresponding carboxylic acid followed by methyl ester formation provided **21** in 98% overall yield with 89% *ee* (Table 2, Entry 12). Lastly, *N*-deprotection gave **22** in 89% overall yield from **20k**.




Scheme 4. Transformation of cascade product into an intermediate in the synthesis of **4**. TPAP = tetrapropylammonium perruthenate; NMO = *N*-methylmorpholine *N*-oxide.

In the synthesis of fluorinated rhodopeptin analogue **4**, **22** was generated as a racemic mixture. This mixture was carried through nine subsequent steps, ultimately generating diastereomers that were separated by flash column chromatography four steps from the completion of **4**. In contrast, the organocascade reaction described in this paper allows an asymmetric synthesis of **22**, avoiding a cumbersome separation of diastereomers and the resulting loss of half of the material.

## Conclusions

Previously, we had developed an organocascade reaction that generated α-fluoro-β-amino aldehydes, and which was the first example of a catalytic enantioselective olefin aminofluorination reaction. This organocascade reaction was readily adapted to produce β-amino-α,α-difluoro aldehydes from achiral enals *in a single flask* in good yields and with excellent *ee*s. This new organocascade reaction represents a new approach to β-amino-α,α-difluoro carbonyl compounds, and moreover, it produces compounds

not directly accessible by existing organocatalytic methods. Further investigations into other cascade reactions involving organocatalytic fluorinations are underway in our laboratory, and the results will be reported shortly.

## Experimental Section

**General Remarks:** All reactions were run in oven-dried glassware under argon. Solvents were dried and kept air-free in a solvent-purification unit. Enals were distilled before use. NMR spectroscopic data were acquired using $CDCl_3$ as the solvent and internal reference ($^1H$: $\delta$ = 7.26 ppm; $^{13}C$: $\delta$ = 77.0 ppm; unreferenced for $^{19}F$). Multiplicities are reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets, qd = quartet of doublets. Enantiomeric excesses were determined by comparison with a racemic sample (prepared using the corresponding racemic catalyst), using chiral-phase HPLC with Chiralpak AD-H (0.46 × 25 cm) and Chiralpak AS-H (0.46 × 25 cm) columns. Optical rotations were determined using a Jasco P-1020 polarimeter (589 nm, 23 °C). IR spectra were collected using an FTIR instrument. HRMS data were acquired using a TOF spectrometer. Silica gel chromatography was carried out using SiliaFlash F60 40–63 μm silica and SiliaPlate $F_{254}$ glass TLC plates.

**Preparation of Catalysts (9, *rac*-9), Starting Enals (6e, 6f–6j), and Amine Nucleophiles (7, 7a):** Catalysts **9** and *rac*-**9** were prepared according to literature procedures from the corresponding diarylprolinols.[21–23] Non-commercially available enals **6e**,[24] **6f**,[25] **6g**,[26] **6h**,[27] **6i**,[28] and **7j**[29] were prepared according to known procedures. Amine nucleophiles **7** and **7a** were prepared according to literature procedures.[30]

**General Procedure for the Aminodifluorination:** Enal **6a** (0.25 mmol, 1 equiv.) was added to a solution of catalyst **9** (0.05 mmol, 0.2 equiv.) and amine **7** (0.5 mmol, 2 equiv.) in MTBE (methyl *tert*-butyl ether; 0.4 mL). After $^1H$ NMR spectroscopy showed ≥95% consumption of enal **6a** (1 d), the reaction mixture was diluted with MTBE (0.6 mL), then NFSI (0.5 mmol, 2 equiv.) and then catalyst *rac*-**9** (0.05 mmol, 0.2 equiv.) were added. The mixture was stirred vigorously until $^1H$ NMR spectroscopy showed >85% (or, in some cases, complete) consumption of the intermediate β-aminoaldehyde and α-fluoro-β-aminoaldehyde (2 d). The reaction mixture was then diluted with $Et_2O$ (2 mL), cooled to –78 °C, and filtered through silica gel (5 cm in a pipette), eluting with a cold (–50 °C) mixture of $Et_2O/CH_2Cl_2$ (9:1; 30 mL). $Me_2S$ (0.2 mL) was added to the eluted solution at room temp. The mixture was stirred for 15 min, then it was transferred to a separatory funnel, and washed with satd. aq. $NaHCO_3$ (2 × 50 mL) and brine. The organic phase was dried with $MgSO_4$ and concentrated. The resulting residue was dissolved in $CH_2Cl_2$/EtOH (2:1; 2 mL), and then $NaBH_4$ (0.625 mmol, 2.5 equiv.) was added in one portion. The mixture was stirred for 30 min, then it was cooled to 0 °C, and quenched by the slow addition of satd. aq. $NH_4Cl$ (5 mL). The mixture was then warmed to room temp. and stirred vigorously for 30 min. The mixture was extracted with $CH_2Cl_2$ (2 × 50 mL), and the combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated. Purification on silica gel was achieved (unless otherwise noted) using $CH_2Cl_2$/petroleum ether (19:1), until the excess of unreacted amine nucleophile had been eluted, then switching to $CH_2Cl_2/Et_2O$ (19:1) to elute the difluoroamino alcohols.

**Benzyl (*R*)-(2,2-Difluoro-1-hydroxyheptan-3-yl)(methoxy)carbamate (20a):** Pale yellow liquid (44.3 mg, 54% yield, 91% *ee*). $[\alpha]_D^{23}$ = +2.8 ($c$ = 1.8, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3454, 2959, 2927, 2859, 1713, 1457, 1403, 1320, 1286, 1219, 1139, 1079, 1007, 912, 758, 736 cm$^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.44–7.31 (m, 5 H), 5.26 (q, $J$ = 12.2 Hz, 2 H), 4.52–4.39 (m, 1 H), 3.89–3.65 (m, 5 H), 3.10 (s, 1 H), 2.05–1.88 (m, 1 H), 1.81–1.64 (m, 1 H), 1.44–1.14 (m, 4 H), 0.88 (t, $J$ = 7.1 Hz, 3 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 158.4, 135.5, 128.7 (2 C), 128.5, 128.1 (2 C), 121.4 (t, $J$ = 249.3 Hz, 1 C), 68.6, 63.5, 62.9–61.8 (m, 1 C), 59.8, 28.0, 22.7, 22.3, 13.8 ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –113.4 (d, $J_{F,F}$ = 258.6 Hz, 1 F), –118.9 (d, $J$ = 262.6 Hz, 1 F) ppm. HPLC (AD-H column; *n*-hexane/*i*PrOH, 95:5; 0.3 mL/min): major $t_R$ = 42.4 min, minor $t_R$ = 56.1 min. HRMS: calcd. for $C_{16}H_{23}F_2NO_4$ $[M + H]^+$ 331.1595; found 331.1595.

**Benzyl (*R*)-(2,2-Difluoro-1-hydroxypentan-3-yl)(methoxy)carbamate (20b):** Colorless liquid (43.3 mg, 57% yield, 90% *ee*). $[\alpha]_D^{23}$ = +10.9 ($c$ = 2.1, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3453, 2975, 2944, 1712, 1457, 1402, 1359, 1314, 1263, 1214, 1143, 1077, 1028, 756 cm$^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37 (h, $J$ = 4.9 Hz, 5 H), 5.26 (q, $J$ = 12.2 Hz, 2 H), 4.46–4.31 (m, 1 H), 3.92–3.62 (m, 5 H), 3.07 (s, 1 H), 1.97 (ddt, $J$ = 18.7, 14.4, 7.3 Hz, 1 H), 1.88–1.73 (m, 1 H), 0.96 (t, $J$ = 7.3 Hz, 3 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 158.6, 135.5, 128.7 (2 C), 128.5, 128.1 (2 C), 121.4 (t, $J$ = 249.3 Hz, 1 C), 68.6, 63.6, 62.8–61.9 (m, 1 C), 61.9–61.0 (m, 1 C), 16.5, 10.6 ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –113.5 (d, $J_{F,F}$ = 257.6 Hz, 1 F), –118.7 (d, $J_{F,F}$ = 263.3 Hz, 1 F) ppm. HPLC (AS-H column; *n*-hexane/*i*PrOH, 95:5; 0.3 mL/min): major $t_R$ = 34.2 min, minor $t_R$ = 31.5 min. HRMS: calcd. for $C_{14}H_{19}F_2NO_4$ $[M + H]^+$ 303.1282; found 303.1279.

**Benzyl (*R*)-(2,2-Difluoro-1-hydroxyhexan-3-yl)(methoxy)carbamate (20c):** Pale yellow liquid (40.9 mg, 52% yield, 98% *ee*). $[\alpha]_D^{23}$ = +3.8 ($c$ = 1.2, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3462, 2962, 2875, 1712, 1457, 1402, 1299, 1239, 1139, 1078, 1016, 914, 757 cm$^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.43–7.29 (m, 5 H), 5.25 (q, $J$ = 12.2 Hz, 2 H), 4.55–4.41 (m, 1 H), 3.90–3.63 (m, 5 H), 3.08 (s, 1 H), 2.05–1.90 (m, 1 H), 1.73–1.62 (m, 1 H), 1.52–1.37 (m, 1 H), 1.34–1.20 (m, 1 H), 0.92 (t, $J$ = 7.4 Hz, 3 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 158.4, 135.5, 128.7 (2 C), 128.5, 128.1 (2 C), 121.4 (t, $J$ = 249.3 Hz, 1 C) 68.6, 63.6, 62.8–61.9 (m, 1 C), 59.5 (t, $J$ = 26.7 Hz, 1 C), 25.0, 19.1, 13.6 ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –113.4 (d, $J_{F,F}$ = 257.8 Hz, 1 F), –118.8 (d, $J_{F,F}$ = 278.3 Hz, 1 F) ppm. HPLC (AD-H column; *n*-hexane/*i*PrOH, 95:5; 0.3 mL/min): major $t_R$ = 42.4 min, minor $t_R$ = 62.9 min. HRMS: calcd. for $C_{15}H_{21}F_2NO_4$ $[M + H]^+$ 317.1439; found 317.1438.

**Benzyl (*R*)-(2,2-Difluoro-1-hydroxydodecan-3-yl)(methoxy)carbamate (20d):** Chromatography (acetone/petroleum ether, 3:97) gave a yellow liquid (49.5 mg, 49% yield, 92% *ee*). $[\alpha]_D^{23}$ = +7.5 ($c$ = 2.6, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3462, 2927, 2855, 1713, 1457, 1401, 1304, 1085, 911, 756 cm$^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42–7.31 (m, 5 H), 5.26 (q, $J$ = 12.2 Hz, 2 H), 4.55–4.37 (m, 1 H), 3.90–3.62 (m, 5 H), 3.10 (s, 1 H), 2.05–1.87 (m, 1 H), 1.79–1.60 (m, 1 H), 1.41–1.20 (m, 14 H), 0.88 (t, $J$ = 6.9 Hz, 3 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 158.6, 135.6, 128.7 (2 C), 128.6, 128.2 (2 C), 121.6 (t, $J$ = 249.2 Hz, 1 C), 68.6, 63.6, 62.9–62.0 (m, 1 C), 59.9 (t, $J$ = 23.9 Hz, 1 C), 32.0, 29.6, 29.5, 29.4, 29.3, 26.0, 23.2, 22.8, 14.2 ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –113.4 (d, $J_{F,F}$ = 261.0 Hz, 1 F), –118.9 (d, $J_{F,F}$ = 266.2 Hz, 1 F) ppm. HPLC (AD-H column; *n*-hexane/*i*PrOH, 97:3; 0.3 mL/min): major $t_R$ = 41.6 min, minor $t_R$ = 48.6 min. HRMS: calcd. for $C_{21}H_{33}F_2NO_4$ $[M + H]^+$ 401.2378; found 401.2376.

**Benzyl (*R*)-(2,2-Difluoro-1-hydroxy-5phenylpentan-3-yl)(methoxy)-carbamate (20e):** Colorless liquid (41.1 mg, 43% yield, 93% *ee*). $[\alpha]_D^{23}$ = +13.8 ($c$ = 1.0, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3461, 3029,

2944, 1712, 1497, 1455, 1402, 1309, 1214, 1170, 1102, 1077, 1018, 913, 752 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42–7.10 (m, 10 H), 5.38–5.17 (m, 2 H), 4.53–4.39 (m, 1 H), 3.88–3.60 (m, 5 H), 3.14 (s, 1 H), 2.78 (ddd, $J$ = 14.0, 9.7, 4.5 Hz, 1 H), 2.54 (dt, $J$ = 13.8, 8.3 Hz, 1 H), 2.39–2.24 (m, 1 H), 2.13–2.01 (m, 1 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 158.4, 140.7, 135.5, 128.8 (2 C), 128.7, 128.6 (2 C), 128.5 (2 C), 128.3 (2 C), 126.4, 121.50 (t, $J$ = 249.6 Hz, 1 C), 68.8, 63.8, 63.2–61.3 (m, 1 C), 59.3 (t, $J$ = 28.5 Hz, 1 C), 32.1, 25.0 ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –113.4 (d, $J_{F,F}$ = 263.1 Hz, 1 F), –119.1 (d, $J_{F,F}$ = 270.0 Hz, 1 F) ppm. HPLC (AD-H column; *n*-hexane/*i*PrOH, 95:5; 0.5 mL/min): major $t_R$ = 42.4 min, minor $t_R$ = 50.9 min. HRMS: calcd. for $C_{20}H_{23}F_2NO_4$ $[M + H]^+$ 379.1595; found 379.1595.

**Benzyl (*R*)-(2,2-Difluoro-1-hydroxy-5-methylhexan-3-yl)(methoxy)-carbamate (20f):** Colorless liquid (40.8 mg, 49% yield, 88% *ee*). $[\alpha]_D^{23}$ = +7.3 ($c$ = 1.2, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3460, 2959, 2872, 1712, 1456, 1402, 1305, 1244, 1085, 1002, 912, 755 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.43–7.30 (m, 5 H), 5.26 (q, $J$ = 12.2 Hz, 2 H), 4.64–4.49 (m, 1 H), 3.89–3.66 (m, 5 H), 3.20 (s, 1 H), 2.01 (ddd, $J$ = 14.7, 11.6, 3.4 Hz, 1 H), 1.67–1.55 (m, 1 H), 1.41 (t, $J$ = 12.4 Hz, 1 H), 0.95 (d, $J$ = 6.6 Hz, 3 H), 0.86 (d, $J$ = 6.5 Hz, 3 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 158.3, 135.4, 128.6 (2 C), 128.5, 128.1 (2 C), 121.6 (t, $J$ = 249.4 Hz, 1 C), 68.6, 63.6, 62.8–61.6 (m, 1 C), 57.7, 31.7, 24.4, 23.5, 21.1 ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –113.2 (d, $J_{F,F}$ = 257.4 Hz, 1 F), –119.0 (d, $J_{F,F}$ = 260.1 Hz, 1 F) ppm. HPLC (AD-H column; *n*-hexane/*i*PrOH, 95:5; 0.3 mL/min): major $t_R$ = 31.6 min, minor $t_R$ = 47.8 min. HRMS: calcd. for $C_{16}H_{23}F_2NO_4$ $[M + H]^+$ 331.1595; found 331.1594.

**Benzyl (*R*)-(2,2-Difluoro-1-hydroxy-4-methylpentan-3-yl)(methoxy)-carbamate (20g):** Colorless liquid (31.4 mg, 40% yield, 90% *ee*). $[\alpha]_D^{23}$ = +1.0 ($c$ = 0.9, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3480, 2968, 2946, 2879, 1712, 1457, 1394, 1350, 1305, 1277, 1213, 1148, 1075, 1004, 912, 756 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.44–7.31 (m, 5 H), 5.32–5.18 (m, 2 H), 4.21 (d, $J$ = 17.4 Hz, 1 H), 3.97–3.64 (m, 5 H), 2.92 (s, 1 H), 2.39 (d, $J$ = 6.9 Hz, 1 H), 1.11 (dd, $J$ = 6.3, 3.1 Hz, 3 H), 1.04 (d, $J$ = 6.7 Hz, 3 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 158.5, 135.5, 128.7 (2 C), 128.5, 128.1 (2 C), 122.4 (t, $J$ = 251.0 Hz, 1 C), 68.6, 64.6, 63.8–63.1 (m, 1 C), 63.1, 26.1, 20.6, 19.8 (d, $J$ = 6.2 Hz, 1 C) ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –105.3 to –117.1 (m, 2 F) ppm. HPLC (AS-H column; *n*-hexane/*i*PrOH, 97:3; 0.3 mL/min): major $t_R$ = 35.4 min, minor $t_R$ = 50.9 min. HRMS: calcd. for $C_{15}H_{21}F_2NO_4$ $[M + H]^+$ 317.1439; found 317.1440.

**Benzyl (*R*)-(2,2-Difluoro-1-hydroxyoct-7-en-3-yl)(methoxy)carbamate (20h):** Yellow liquid (40.8 mg, 47% yield, 91% *ee*). $[\alpha]_D^{23}$ = +8.4 ($c$ = 1.7, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3458, 2942, 1712, 1456, 1401, 1316, 1213, 1165, 1080, 1016, 913, 755 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42–7.32 (m, 5 H), 5.75 (ddt, $J$ = 16.9, 10.2, 6.7 Hz, 1 H), 5.26 (q, $J$ = 12.2 Hz, 2 H), 5.05–4.93 (m, 2 H), 4.54–4.40 (m, 1 H), 3.88–3.67 (m, 5 H), 3.05 (s, 1 H), 2.13–1.90 (m, 3 H), 1.81–1.67 (m, 1 H), 1.57–1.44 (m, 1 H), 1.43–1.28 (m, 1 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 158.3, 137.9, 135.4, 128.7 (2 C), 128.5, 128.1 (2 C), 121.4 (t, $J$ = 249.4 Hz, 1 C), 115.1, 68.6, 63.6, 62.4 (dd, $J$ = 32.8, 30.1 Hz, 1 C), 60.8–58.6 (m, 1 C), 33.2, 25.1, 22.5 ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –113.4 (d, $J_{F,F}$ = 257.4 Hz, 1 F), –118.7 (d, $J_{F,F}$ = 246.6 Hz, 1 F) ppm. HPLC (AD-H column; *n*-hexane/*i*PrOH, 95:5; 0.3 mL/min): major $t_R$ = 42.2 min, minor $t_R$ = 60.0 min. HRMS: calcd. for $C_{17}H_{23}F_2NO_4$ $[M + H]^+$ 343.1595; found 343.1594.

**Benzyl (*R*)-[1-(Benzyloxy)-3,3-difluoro-4-hydroxybutan-2-yl](methoxy)carbamate (20i):** Chromatography (EtOAc/petroleum ether, 1:7 to 1:4) gave a colorless liquid (43.6 mg, 44% yield, 92% *ee*). $[\alpha]_D^{23}$ = +6.9 ($c$ = 1.8, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3461, 2926, 1716, 1455, 1396, 1303, 1120, 1067, 1028, 910, 737 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42–7.28 (m, 10 H), 5.32–5.20 (m, 2 H), 4.86 (dtd, $J$ = 17.8, 9.3, 4.3 Hz, 1 H), 4.56 (s, 2 H), 4.04 (t, $J$ = 9.8 Hz, 1 H), 3.90–3.71 (m, 6 H), 2.90 (s, 1 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 158.3, 137.5, 135.5, 128.6 (2 C), 128.4 (2 C), 128.1 (2 C), 127.8 (2 C), 127.7 (2 C), 121.1 (t, $J$ = 249.6 Hz, 1 C), 73.3, 68.6, 63.7, 63.3, 62.6 (t, $J$ = 31.1 Hz, 1 C), 59.5 (t, $J$ = 25.8 Hz, 1 C) ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –113.0 (d, $J_{F,F}$ = 253.9 Hz, 1 F), –115.8 (d, $J_{F,F}$ = 273.0 Hz, 1 F) ppm. HPLC (AD-H column; *n*-hexane/*i*PrOH, 90:10; 1.0 mL/min): major $t_R$ = 17.6 min, minor $t_R$ = 20.0 min. HRMS: calcd. for $C_{20}H_{23}F_2NO_5$ $[M + H]^+$ 395.1544; found 395.1545.

**Methyl (*R*)-9-{[(Benzyloxy)carbonyl](methoxy)amino}-10,10-difluoro-11-hydroxyundecanoate (20j):** Chromatography (EtOAc/petroleum ether, 1:7 to 1:4) gave a colorless liquid (50.5 mg, 47% yield, 90% *ee*). $[\alpha]_D^{23}$ = +3.2 ($c$ = 2.8, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3999, 2941, 2858, 1737, 1456, 1399, 1303, 1213, 1171, 1115, 1079, 1015, 912, 756 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.41–7.31 (m, 5 H), 5.25 (q, $J$ = 12.2, 11.4 Hz, 2 H), 4.53–4.38 (m, 1 H), 3.91–3.64 (m, 8 H), 3.11 (s, 1 H), 2.29 (t, $J$ = 7.5 Hz, 2 H), 2.01–1.90 (m, 1 H), 1.69 (s, 1 H), 1.63–1.56 (m, 2 H), 1.45–1.16 (m, 8 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 174.6, 158.8, 135.8, 129.0 (2 C), 128.9, 128.5 (2 C), 121.8 (t, $J$ = 249.3 Hz, 1 C), 68.9, 63.9, 63.2–62.2 (m, 1 C), 60.9–60.0 (m, 1 C), 51.8, 34.4, 29.3, 29.3, 29.3, 26.1, 25.2, 23.2 ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –113.4 (d, $J_{F,F}$ = 258.3 Hz, 1 F), –118.8 (d, $J_{F,F}$ = 259.9 Hz, 1 F) ppm. HPLC (AD-H column; *n*-hexane/*i*PrOH, 90:10; 1.0 mL/min): major $t_R$ = 12.8 min, minor $t_R$ = 15.6 min. HRMS: calcd. for $C_{21}H_{31}F_2NO_6$ $[M + H]^+$ 431.2119; found 431.2119.

**Benzyl (*R*)-Benzyloxy(2,2-difluoro-1-hydroxydodecan-3-yl)carbamate (20k):** Prepared according to the general procedure (3.0 mmol scale), using *N*-OBn protected amine nucleophile **7a**. Chromatography (EtOAc/petroleum ether, 7.5:92.5 to 15:85) of the crude cascade product gave an inseparable mixture of alcohol **20k** and the unreacted amine nucleophile in an approximate 2:3 ratio. The yield was determined by NMR spectroscopy, using cyclohexene as an internal standard (54% yield). Full characterization of the corresponding methyl ester (**21**) was achieved and is described below.

**Methyl (*R*)-3-{(Benzyloxy)[(benzyloxy)carbonyl]amino}-2,2-difluorododecanoate (21):** Prepared according to adapted literature procedures.[31] An inseparable mixture of difluoro amino alcohol **20k** (0.53 mmol, as determined by $^1H$ NMR spectroscopy with an internal standard) and the amine nucleophile (1.47 mmol) were dissolved in MeCN (10 mL, 0.2 M). NMO (2.34 g, 10 equiv.), $H_2O$ (360 μL, 10 equiv.), and TPAP (70.3 mg, 0.10 equiv.) were added, and the mixture was stirred at room temp. for 1.5 h. It was then quenched with *i*PrOH (5 mL), and stirred for a further 30 min. The crude mixture was filtered through silica gel (10 cm plug) with $CH_2Cl_2$/MeOH, 9:1 (150 mL), and the eluted solution was concentrated. The resulting crude residue was dissolved in $Et_2O$ (50 mL), and this solution was washed with satd. aq. $KHSO_4$ (2× 50 mL) to remove the excess NMO. The aqueous layer was re-extracted with $Et_2O$ (2× 20 mL). The combined organic extracts were washed with brine, dried with $Na_2SO_4$, and concentrated. Column chromatography (EtOAc/petroleum ether, 8:2, to EtOAc/MeOH, 9:1) gave the carboxylic acid in nearly quantitative yield (260 mg, 0.53 mmol) as a yellow oil.

This acid intermediate (260 mg, 0.53 mmol) was dissolved in methanol (4.0 mL) at 0 °C, and AcCl (377 μL, 10 equiv.) was added

dropwise. The mixture was warmed to room temp. and stirred for 2 h. After this time, TLC confirmed that the starting material had been consumed, and the mixture was concentrated. This crude residue was dissolved in EtOAc (50 mL). This solution was neutralized with satd. aq. $NaHCO_3$ (50 mL), washed with brine (50 mL), and dried with $MgSO_4$. Concentration provided pure methyl ester **21** (261 mg, 98% yield, 89% *ee*) as a colorless liquid. $[a]_D^{23}$ = +50.4 (*c* = 3.5, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3066, 3034, 2956, 2926, 2855, 1776, 1719, 1498, 1456, 1389, 1285, 1215, 1066, 751 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.47–7.28 (m, 10 H), 5.24 (s, 2 H), 4.99–4.81 (m, 2 H), 4.82–4.58 (m, 1 H), 3.76 (s, 3 H), 2.17–1.91 (m, 1 H), 1.73–1.52 (m, 1 H), 1.40–1.11 (m, 14 H), 0.94–0.81 (m, 3 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 163.9 (t, $J$ = 32.2 Hz, 1 C), 157.8, 135.6, 135.0, 129.4 (2 C), 128.6 (2 C), 128.5, 128.4, 128.4 (2 C), 128.2 (2 C), 114.7 (t, $J$ = 256.3 Hz, 1 C), 77.9, 68.5, 61.3 (t, $J$ = 25.8 Hz, 1 C), 53.4, 31.9, 29.4, 29.3, 29.3, 29.1, 25.3, 23.5, 22.7, 14.1 ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –109.9 (dd, $J_{F,F}$ = 259.7, $J_{F,H}$ = 9.4 Hz, 1 F), –115.3 (d, $J_{F,F}$ = 256.6 Hz, 1 F) ppm. HPLC (AD-H column; *n*-hexane/*i*PrOH, 99:1; 0.3 mL/min): major $t_R$ = 26.6 min, minor $t_R$ = 59.2 min. HRMS: calcd. for $C_{28}H_{37}F_2NO_5$ $[M + H]^+$ 506.2713; found 506.2712.

**Methyl (*R*)-3-Amino-2,2-difluorododecanoate (22):** Difluoro amino ester **21** (57 mg, 0.11 mmol) in MeOH (5 mL) was slowly added to a slurry of 5% Pd/C (47 mg, 20% Pd) in EtOH (0.5 mL) and hydrogenated (50 psi) at room temp. for 20 h. This crude mixture was filtered through cotton (EtOAc, 30 mL) and concentrated to give the pure free amino ester (**22**), as a yellow oil (27.3 mg, 91% yield). $[a]_D^{23}$ = +19.6 (*c* = 0.7, $CHCl_3$). IR (thin film, KBr): $\tilde{\nu}$ = 3407, 2956, 2926, 2856, 1764, 1459, 1441, 1378, 1316, 1196, 1097, 812, 723 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 3.89 (s, 3 H), 3.28–3.11 (m, 1 H), 1.66–1.50 (m, 2 H), 1.34–1.21 (m, 14 H), 0.88 (t, $J$ = 6.6 Hz, 3 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 164.72 (t, $J$ = 32.9 Hz, 1 C), 116.35 (t, $J$ = 253.3 Hz, 1 C), 54.32 (t, $J$ = 24.1 Hz, 1 C), 53.2, 31.9, 29.77 (t, $J$ = 2.5 Hz, 1 C), 29.5, 29.4, 29.4, 29.3, 25.8, 22.7, 14.1 ppm. $^{19}F$ NMR (188 MHz, $CDCl_3$): $\delta$ = –115.3 (dd, $J_{F,F}$ = 256.4, $J_{F,H}$ = 11.3 Hz, 1 F), –118.4 (dd, $J_{F,F}$ = 256.5, $J_{F,H}$ = 14.2 Hz, 1 F) ppm. HRMS: calcd. for $C_{13}H_{25}F_2NO_2$ $[M + H]^+$ 265.1926; found 265.1925.

**Assignment of Stereochemistry:** Stereochemistry was assigned based on the accepted model of stereochemical induction for catalyst **9**[32] and on the previously determined stereochemistry of the product of β-amination of substrate **6f** using catalyst **9**.[13]

**Supporting Information** (see footnote on the first page of this article): Peripheral discussion of cascade optimization, and copies of $^1H$ and $^{13}C$ NMR spectra and HPLC chromatograms for compounds **20a**–**20j**, **21** and **22**.

## Acknowledgments

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[1] X.-L. Qiu, X. Yue, F.-L. Qing in *Chiral Drugs: Chemistry and Biological Action* (Eds.: G.-Q. Lin, Q.-D. You, J.-F. Cheng), John Wiley & Sons, Inc., Hoboken, NJ, **2011**, pp. 195–252.

[2] For recent reviews of fluorine in medicinal chemistry, see: a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; c) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; d) R. Filler, R. Saha, *Future Med. Chem.* **2009**, *1*, 777–791.

[3] M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmeril, J. Schneider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100–1115.

[4] A. Donetti, E. Cereda, A. Ezhaya, R. Micheletti, *J. Med. Chem.* **1989**, *32*, 957–961.

[5] M. B. van Niel, I. Collins, M. S. Beer, H. B. Broughton, S. K. F. Cheng, S. C. Goodacre, A. Heald, K. L. Locker, A. M. MacLeod, D. Morrison, C. R. Moyes, D. O'Connor, A. Pike, M. Rowley, M. G. N. Russell, B. Sohal, J. A. Stanton, S. Thomas, H. Verrier, A. P. Watt, J. L. Castro, *J. Med. Chem.* **1999**, *42*, 2087–2104.

[6] H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643.

[7] a) M. H. Gelb, J. P. Svaren, R. H. Abeles, *Biochemistry* **1985**, *24*, 1813–1817; b) M. H. Gelb, *J. Am. Chem. Soc.* **1986**, *108*, 3146–3147; c) D. B. Damon, D. J. Hoover, *J. Am. Chem. Soc.* **1990**, *112*, 6439–6442.

[8] K. Nakayama, H. C. Kawato, H. Inagaki, R. Nakajima, A. Kitamura, K. Someya, T. Ohta, *Org. Lett.* **2000**, *2*, 977–980.

[9] K. Uoto, S. Ohsuki, H. Takenoshita, T. Ishiyama, S. Iimura, Y. Hirota, I. Mitsui, H. Terasawa, T. Soga, *Chem. Pharm. Bull.* **1997**, *45*, 1793–1804.

[10] U. Reichman, K. A. Watanabe, J. J. Fox, *Carbohydr. Res.* **1975**, *42*, 233–240.

[11] O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa, T. Akiba, S. Terashima, *Tetrahedron Lett.* **1992**, *33*, 3487–3490.

[12] N. A. Magnus, J. A. Aikins, J. S. Cronin, W. D. Diseroad, A. D. Hargis, M. E. LeTourneau, B. E. Parker, S. M. Reutzel-Edens, J. P. Schafer, M. A. Staszak, G. A. Stephenson, S. L. Tameze, L. M. H. Zollars, *Org. Process Res. Dev.* **2005**, *9*, 621–628.

[13] C. Appayee, S. E. Brenner-Moyer, *Org. Lett.* **2010**, *12*, 3356–3359.

[14] For other examples of catalytic enantioselective olefin aminohalogenation reactions, see: a) Y. Cai, X. Liu, Y. Hui, J. Jiang, W. Wang, W. Chen, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2010**, *49*, 6160–6164; *Angew. Chem.* **2010**, *122*, 6296–6300; b) Y. Cai, X. Liu, J. Jiang, W. Chen, L. Lin, X. Feng, *J. Am. Chem. Soc.* **2011**, *133*, 5636–5639; c) Y. Cai, X. Liu, J. Li, W. Chen, W. Wang, L. Lin, X. Feng, *Chem. Eur. J.* **2011**, *17*, 14916–14921; d) L. Zhou, J. Chen, C. K. Tan, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2011**, *133*, 9164–9167; e) D. Huang, H. Wang, F. Xue, H. Guan, L. Li, X. Peng, Y. Shi, *Org. Lett.* **2011**, *13*, 6350–6353; f) O. Lozano, G. Blessley, T. Martinez del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem. Int. Ed.* **2011**, *50*, 8105–8109; *Angew. Chem.* **2011**, *123*, 8255–8259; g) M. T. Bovino, S. R. Chemler, *Angew. Chem. Int. Ed.* **2012**, *51*, 3923–3927; *Angew. Chem.* **2012**, *124*, 3989–3993; h) J. Chen, L. Zhou, Y.-Y. Yeung, *Org. Biomol. Chem.* **2012**, *10*, 3808–3811; i) A. Alix, C. Lalli, P. Retailleau, G. Masson, *J. Am. Chem. Soc.* **2012**, *134*, 10389–10392; j) F. Chen, C. K. Tan, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2013**, *135*, 1232–1235; k) L. Zhou, D. W. Tay, J. Chen, G. Y. C. Leung, Y.-Y. Yeung, *Chem. Commun.* **2013**, *49*, 4412–4414; l) C. S. Brindle, C. S. Yeung, E. N. Jacobsen, *Chem. Sci.* **2013**, *4*, 2100–2104.

[15] a) A. Stumpf, M. Reynolds, D. Sutherlin, S. Babu, E. Bappert, F. Spindler, M. Welch, J. Gaudino, *Adv. Synth. Catal.* **2011**, *353*, 3367–3372; b) P. Zhang, C. Wang, L. Zhou, J. Sun, *Chin. J. Chem.* **2012**, *30*, 2636–2640; c) R.-N. Guo, X.-F. Cai, L. Shi, Z.-S. Ye, M.-W. Chen, Y.-G. Zhou, *Chem. Commun.* **2013**, *49*, 8537–8539.

[16] a) O. O. Fadeyi, C. W. Lindsley, *Org. Lett.* **2009**, *11*, 943–946; b) J. Wu, Y.-M. Wang, A. Drljevic, V. Rauniyar, R. J. Phipps, F. D. Toste, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 13729–13733.

  

[17] a) Y. Pan, Y. Zhao, T. Ma, Y. Yang, H. Liu, Z. Jiang, C.-H. Tan, *Chem. Eur. J.* **2010**, *16*, 779–782; b) H. P. Shunatona, N. Früh, Y.-M. Wang, V. Rauniyar, F. D. Toste, *Angew. Chem. Int. Ed.* **2013**, *52*, 7724–7727; *Angew. Chem.* **2013**, *125*, 7878–7881; c) J. A. Kalow, A. G. Doyle, *Tetrahedron* **2013**, *69*, 5702–5709.
[18] a) W. Kashikura, K. Mori, T. Akiyama, *Org. Lett.* **2011**, *13*, 1860–1863; b) Z. Yuan, L. Mei, Y. Wei, M. Shi, P. V. Kattamuri, P. McDowell, G. Li, *Org. Biomol. Chem.* **2012**, *10*, 2509–2513.
[19] For recent reviews of cascade reactions combining iminium- and enamine-catalyzed reactions, see: a) H. Pellissier, *Adv. Synth. Catal.* **2012**, *354*, 237–294; b) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390–2431.
[20] B. Simmons, A. M. Walji, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2009**, *48*, 4349–4353; *Angew. Chem.* **2009**, *121*, 4413–4417.
[21] I. Ibrahem, A. Cordova, *Chem. Commun.* **2006**, 1760–1762.
[22] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797; *Angew. Chem.* **2005**, *117*, 804–807.
[23] D. J. Mathre, T. K. Jones, L. C. Xavier, T. J. Blacklock, R. A. Reamer, J. J. Mohan, E. T. T. Jones, K. Hoogsteen, M. W. Baum, E. J. J. Grabowski, *J. Org. Chem.* **1991**, *56*, 751–762.
[24] A. A. Hartikka, P. I. P. Arvidsson, *J. Org. Chem.* **2007**, *72*, 5874–5877.
[25] J.-F. Fournier, S. Mathieu, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 13140–13141.
[26] Y.-S. Hon, L. Lu, R.-C. Chang, S.-W. Lin, P.-P. Sun, C.-F. Lee, *Tetrahedron* **2000**, *56*, 9269–9279.
[27] O. V. Singh, H. Han, *Org. Lett.* **2004**, *6*, 3067–3070.
[28] E. Piers, G. L. Jung, E. H. Ruediger, *Can. J. Chem.* **1987**, *65*, 670–682.
[29] D. Lin, J. Zhang, L. M. Sayre, *J. Org. Chem.* **2007**, *72*, 9471–9480.
[30] a) M. Kawase, T. Kitamura, Y. Kikugawa, *J. Org. Chem.* **1989**, *54*, 3394–3403; b) T. Kolasa, M. J. Miller, *J. Org. Chem.* **1987**, *52*, 4978–4984.
[31] a) A.-K. C. Schmidt, C. B. W. Stark, *Org. Lett.* **2011**, *13*, 4164–4167; b) R. Pragani, P. Stallforth, P. H. Seeberger, *Org. Lett.* **2010**, *12*, 1624–1627.
[32] J. Vesely, I. Ibrahem, R. Rios, G.-L. Zhao, Y. Xu, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 2193–2198.

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