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Practical Enantioselective Synthesis of a 3-Aryl-3-trifluoromethyl-2-aminopropanol Derivative

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Abstract:

Development of a large-scale enantioselective synthesis of a lead compound containing a 3-aryl-3-trifluoromethyl-2-aminopropanol core is described. A single isomer of 3,3-disubstituted acrylic acid derivative was prepared via Perkin condensation or Horner−Wadsworth−Emmons olefination, followed by hydrolysis. The acid was converted to a chiral acryloxazolidinone derivative. Hydrogenation of the latter on Pd/C in the presence of $MgBr_2$ proceeded via a chelation-controlled conformation to yield the desired isomer with high selectivity. Subsequent Evans azidation, hydrogenation, reductive cleavage of the chiral auxiliary, and sulfonylation afforded the target compound as a single isomer in high overall yield.

Introduction

In a recent Medicinal Chemistry program, a trifluoromethyl-containing aminoalcohol derivative **1** was identified as a compound of interest. Early milligram-scale batches of **1** were prepared via a short synthesis involving Schöllkopf olefination[1] and hydride reduction, followed by chiral preparative HPLC separation of a mixture of all four possible isomers. The desired isomer was obtained in 4% overall yield (Scheme 1). As kilogram quantities of the target compound were needed for further studies, a stereoselective and practical synthesis of **1** was required.

Route Selection. The evaluated possible routes to **1** are shown in Scheme 2. Since alcohol **1** has two adjacent stereocenters, asymmetric hydrogenation of an appropriate isomer of a tetrasubstituted olefin, e.g., a dehydroalanine derivative, would potentially offer a shorter and more efficient synthesis (Route I) by setting both stereocenters in one step.

Routes II and III represent the stepwise introduction of stereocenters. Asymmetric 1,4-addition of organocuprates to α,β-unsaturated acyl derivatives containing chiral oxazolidinone auxiliary has been studied,[2] and examples of arylcuprate addition to 4,4,4-trifluoromethylbutenoyl derivatives such as **7** with up to 90% *de* for electron-rich aromatic derivatives have been reported (72% *de* was reported for phenylcuprate).[3] The conjugate addition would then be followed by Evans azidation. However, the enantiomer of the chiral auxiliary needed for the introduction of correct stereochemistry at the β-position would not be useful for direct α-amination since it would yield the (2*R*,3*R*)-isomer instead of the required (2*S*,3*R*). That, in turn, would necessitate a chiral auxiliary exchange before the amination and lengthen the synthesis. The indirect approach through α-bromination followed by nucleophilic substitution with an azide with inversion of configuration was not desirable. Apart from safety considerations related to the use of nucleophilic sources of azide (sodium azide or tetramethylguanidinium azide) on large scale, internal reports on related chemistry highlighted that elimination of HBr under nucleophilic substitution conditions due to the presence of both β-CF_3- and β-aryl-groups was a concern.[4] For these reasons Route II (Scheme 2) was not pursued.

Alternatively, **1** can be accessed from acrylic acid derivative **9** via asymmetric hydrogenation followed by Evans azidation. Either isomer of **9** can potentially be used, provided a single isomer is available.

Tetrasubstituted Olefins: Isomerization Studies. For a successful asymmetric hydrogenation, the *E*-isomer of the tetrasubstituted olefin was required. A number of olefins were therefore prepared starting from trifluoromethyl ketone **2** (Scheme 3).

Schöllkopf olefination of ketone **2** afforded a single isomer of olefin **3a** or **3b**,[1] but unfortunately this was the *Z*-isomer (confirmed by NOESY). Horner−Wadsworth−Emmons olefination of phosphonates derived from either glycine derivatives[5] or hydantoin[6] afforded olefins **11** and **12**, respectively, both as 2:1 mixtures of isomers. Conversion of ketone **2** to azalactone **13** proceeded stereoselectively,[7] but again afforded predomi-

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(1) Enders, D.; Chen, Z.-X.; Raabe, G. *Synthesis* **2005**, 306.
(2) (a) Han, Y.; Liao, S.; Qui, W.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **1997**, *38*, 5135. (b) Liao, S.; Han, Y.; Qui, W.; Bruck, M.; Hruby, V. J. *Tetrahedron Lett.* **1996**, *37*, 7917.
(3) Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Fluorine Chem.* **1999**, *97*, 91.
(4) Caggiano, T. Wyeth internal report on related substrates.
(5) (a) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487. (b) Su, G.; Pan, C.; Wang, H.; Zeng, L. *Synth. Commun.* **2004**, *34*, 665.
(6) Meanwell, N. A.; Roth, H. R.; Smith, E. C. R.; Wedding, D. L.; Wright, J. J. K. *J. Org. Chem.* **1991**, *56*, 6897.
(7) (a) Konkel, J. T.; Fan, J.; Jayachandran, B.; Kirk, K. L. *J. Fluorine Chem.* **2002**, *115*, 27. (b) Kolycheva, M. T.; Yagupol'skii, Yu., L.; Zaitsev, L. M.; Gerus, I. J.; Kukhar', V. P.; Klebanov, B. M. *Khim.-Farm. Zh.* **1988**, *22*, 159.

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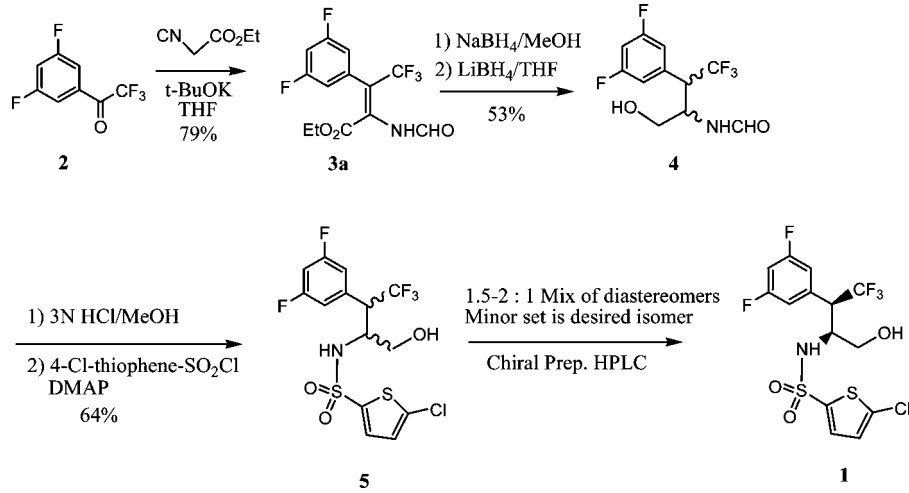
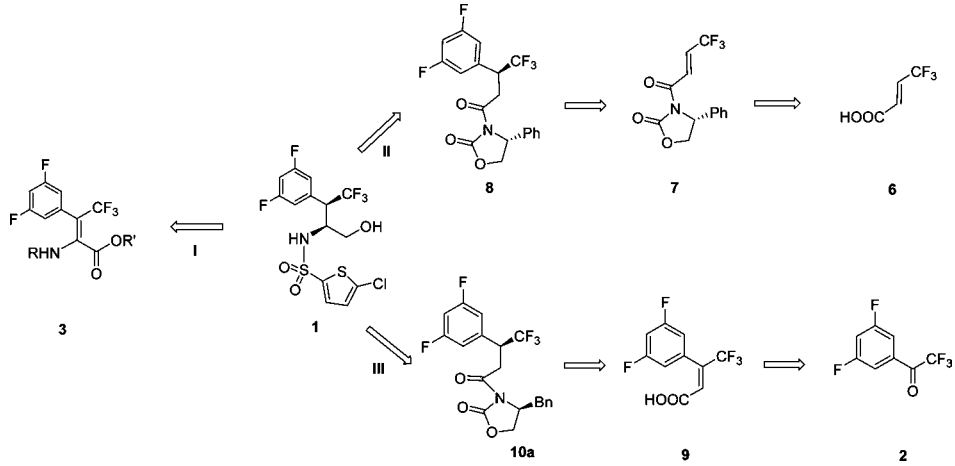
Scheme 1. **Medicinal Chemistry synthesis of 1**



2 **3a** **4** **5** **1**

Scheme 2. **Possible routes to 1**



3 **1** **8** **7** **6** **10a** **9** **2**

nantly the *Z*-isomer (*Z*:*E* = 94:6) as determined by NOESY of the solvolyzed derivative **14**.

Isomerization of olefins **3**, **13**, and **14** was then studied under a variety of conditions. Interestingly, when treated with NaSMe, NaS-*t*-Bu, or DABCO in DMF, *Z*-**3a** isomerized to afford the desired *E*-**3a** as the major component, but in only 3:1 *E:Z* ratio. The *t*-Bu- analog **3b** afforded a 1.5:1 *E:Z* mixture under the same conditions. No isomerization was observed on treatment of **3a** with I_2 in $CHCl_3$ or NaOEt in EtOH. Attempted isomerization of azalactone **13** (HBr, AcOH, with or without $(PhCOO)_2$)[8] or ester **14** (DABCO or HBr, AcOH) afforded a 4:1 and a 1:1 *Z:E* mixtures, respectively.

As an alternative approach, we considered asymmetric hydrogenation of *Z*-**3a** with a possible subsequent chemoenzymatic inversion of stereochemistry at the α-position.[9] However, in contrast to *β*-methyl dehydroalanine ester derivatives described in the literature,[9a] the *β*-trifluoromethyl-containing *Z*-**3a** proved unreactive under asymmetric hydrogenation conditions at 450 psig H_2 on Rh or Ru catalysts using a variety of chiral ligands (*S*,*S*-MeDuphos, *R*,*R*-Et-BPE, Me-f-ketalphos, *R*-Binapine, *S*,*S*,*R*,*R*-Tangphos with $Rh(nbd)_2BF_4$, and [RuCl(*p*-cymene)C3-TunePhos]Cl). Olefin *Z*-**3a** could be hydrogenated non-enantioselectively on Pd/C in MeOH. Interestingly, when an *E/Z* mixture of **3a** was subjected to these conditions, we observed a significant rate difference for the hydrogenation of the isomers, with the *E*-isomer remaining virtually unchanged. Parallel route evaluations using trisubstituted olefins were showing promising results, so use of tetrasubstituted olefins as substrates was not evaluated further.

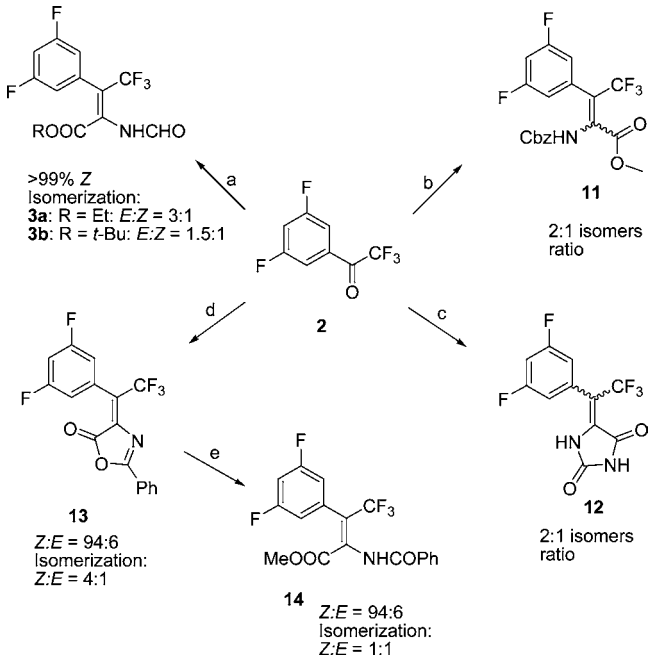
Trisubstituted Olefin Preparation and Reduction. Perkin condensation of ketone **2** with Ac_2O under conditions reported for aryl trifluoromethyl ketones (NaOAc, 140 °C)[10] afforded a 90:10 *E/Z*-mixture of acid **9**. The selectivity improved to 96:4 at 100 °C. Recrystallization from toluene−heptane afforded a single isomer of **9** in 85% yield (Scheme 4). Olefin stereochemistry was confirmed by NOESY. This method for selective preparation of acid **9** was used initially as it employed inexpensive reagents and could be run easily on >100 g scale. However, relatively low throughput due to the necessary aqueous quench of excess Ac_2O was considered a drawback for further scale-up, so an alternative preparation of **9** was developed.

(8) (a) Alias, M.; Lopez, M. P.; Cativiela, C. *Tetrahedron* **2004**, *60*, 885. (b) Schmidt, T.; Baumann, W.; Drexler, H.-J.; Arrieta, A.; Heller, D. *Organometallics* **2005**, *24*, 3842.

(9) (a) Roff, G. J.; Lloyd, R. C.; Turner, N. J. *J. Am. Chem. Soc.* **2004**, *126*, 4098. (b) Enright, A.; Alexandre, F.-R.; Roff, G.; Fotheringham, I. G.; Dawson, M. J.; Turner, N. J. *Chem. Commun.* **2003**, 2636. (c) Alexandre, F.-R.; Pantaleone, D. P.; Taylor, P. P.; Fotheringham, I. G.; Ager, D. J.; Turner, N. J. *Tetrahedron Lett.* **2002**, *43*, 707.

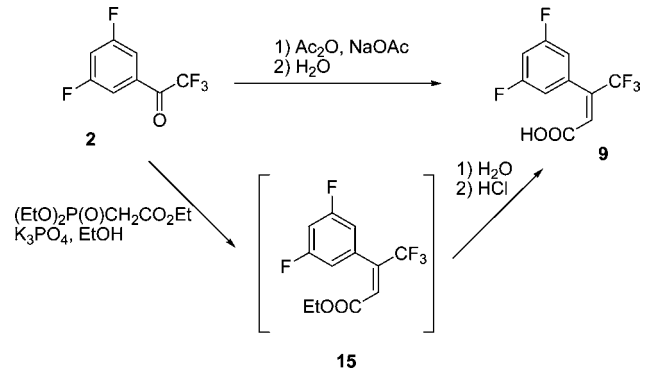
(10) Sevenard, D. V. *Tetrahedron Lett.* **2003**, *44*, 7119.

Scheme 3. **Preparation of tetrasubstituted olefins and isomerization results**[a]



[a] Reagents and conditions: a) $CNCH_2CO_2R$, *t*-BuOK; b) $CbzNHCH(PO(OMe)_2)CO_2Me$, DBU; c) i) hydantoin, Br_2, AcOH; ii) $P(OEt)_3$; iii) ketone **2**, LiOH; d) $PhCONHCH_2CO_2H$, AcOH, K_2CO_3; e) MeOH, NaOAc.

Scheme 4. **Selective olefination of ketone 2**



Horner−Wadsworth−Emmons olefination of ketone **2** with triethyl phosphonoacetate can be run at a higher concentration to afford ester **15**.

Interestingly, conflicting results are found in the literature on selectivity of Horner−Wadsworth−Emmons olefination of aryl trifluoromethyl ketones, with *E/Z* ratios ranging from 53:47 to 83:17 reported for the simplest analogue phenyl trifluoromethyl ketone using NaH as a base.[11] We have observed that, in the case of olefination of ketone **2** in ethanol using K_3PO_4 as a base, an 80:20 *E/Z* mixture of isomers of **15** forms after 0.5 h. However, equilibration to a ~95:5 *E/Z* mixture takes place in ethanol over 20 h.[12]

LC/MS examination of the reaction mixtures identified that ketal formation between ketone **2** and ethanol was a side reaction, albeit ketal formation occurred at a lower rate than that of the condensation. To avoid the side reaction and have addition control of the exotherm associated with the reaction, ketone **2** and triethyl phosphonoacetate were mixed as neat liquids. Safety testing did not identify any reaction between the two substrates when mixed neat. The resulting mixture was added slowly to a mixture of ethanol and K_3PO_4, followed by equilibration at room temperature. Addition of water to the mixture then ensured basic hydrolysis of intermediate ester **15** to afford acid **9**, which was isolated as a 98:2 *E/Z* mixture in 83% yield by filtration after ethanol distillation and acidification.

Asymmetric hydrogenation of olefin **9** was then studied. Screening of catalysts (Rh and Ru metal sources, Walphos, TangPhos, and Tunephos ligands) identified $Rh(nbd)_2BF_4$ and Walphos 8-1 as the optimal metal−ligand combination.[13] Further evaluation of catalyst loading, hydrogenation pressure, and temperature showed that the reduction can be done at room temperature at 45 psig H_2 using a 200:1 substrate:catalyst ratio to afford (*S*)-**16** in quantitative yield as a single enantiomer as detected by chiral HPLC (Scheme 5).

Acid **16** was converted to the oxazolidinone derivative **10a** by reacting with (*S*)-benzyloxazolidinone using a standard protocol.[14] It should be noted that conversion of acid **16** to an alkyl ester followed by enolate generation and treatment with an N-electrophile (e.g., $TrisN_3$) is expected to produce a diastereomer opposite to the required one.[15] A two-step approach through α-bromination followed by azidation was not desirable (*vide supra*).

Assignment of the Absolute Stereochemistry and a Second-Generation Route. In order to determine the absolute configuration of **16**, we decided to compare imide **10a** with its diastereomer prepared via a different route. To that end, acid **9** was converted to oxazolidinone derivative **17** in order to evaluate its hydrogenation products. Literature precedents of

(11) (a) Kimura, M.; Yamazaki, T.; Kitazume, T.; Kubota, T. *Org. Lett.* **2004**, *6*, 4651. (b) Eguchi, T.; Aoyama, T.; Kakinuma, K. *Tetrahedron Lett.* **1992**, *38*, 5545. (c) Pinna, G. A.; Cignarella, G.; Ruiu, S.; Loriga, G.; Murineddu, G.; Villa, S.; Grella, G. E.; Cossu, G.; Fratta, W. *Bioorg. Med. Chem.* **2003**, *11*, 4015. (d) Carceller, E.; Merlos, M.; Giral, M.; Almansa, C.; Bartoli, J.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.* **1993**, *36*, 2984. For a reported example of predominant formation of *Z*-isomer, see: (e) Ohno, N.; Fukamiya, N.; Okano, M.; Tagahara, K.; Lee, K.-H. *Bioorg. Med. Chem.* **1997**, *5*, 1489.

(12) Interestingly, examination of experimental details in various reports of HWE olefination of phenyl trifluoromethyl ketone in THF or toluene using NaH as a base might suggest an opposite hold-time/selectivity relationship.

(13) Walphos 8-1: (*R*)-1-[(*R*)-2-(2′-dicyclohexylphosphinophenyl-)ferrocenyl]ethyldi(bis-(3,5-trifluoromethyl)phenyl)phosphine, available from Solvias, SL-W008-1; nbd: norbornadiene.

(14) (a) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525. (b) Cage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.

(15) Anti-diastereomer formation with up to 80% de was reported for a similar substrate with electron-rich aryl substituent and BnBr as an electrophile; 62% de and low conversion was reported for N-electrophile. Tamura, K.; Yamazaki, T.; Kitazume, T.; Kubota, T. *J. Fluorine Chem.* **2005**, *126*, 918.

(16) (a) Sellstedt, J.; Cheal, G.; Noureldin, R.; Chan, A.W.-Y.; Raveendranath, P.; Caggiano, T. J. Production of Pure Chiral Amino Alcohol Intermediates, Derivatives Thereof, and Uses Thereof. U.S. Patent Publ. Appl. US 2007/249869, 2007; *Chem. Abstr.* **2007**, *147*, 486150. (b) Prashad, M.; Liu, Y.; Kim, H.-Y.; Repic, O.; Blacklock, T. J. *Tetrahedron: Asymmetry* **1999**, *10*, 3479.

(17) Once again, the (*R*)-enantiomer of benzyloxazolidinone chiral auxiliary needed for introduction of (*S*)-stereocenter at the β-position that way would not generate the required diastereomer after α-azidation.

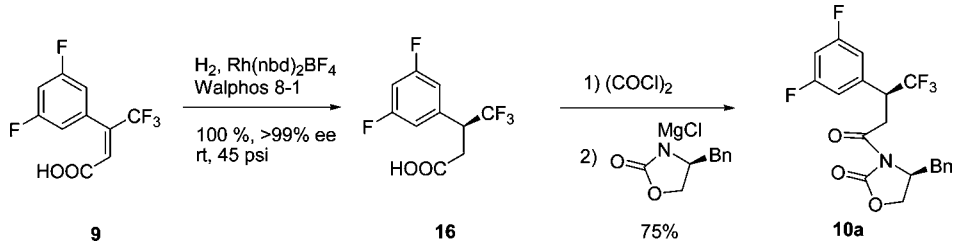
(18) Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271.

(19) In a typical run, 4−5 HPLC area % of **18** was formed, with 2.1% remaining after crystallization.

(20) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(21) For triisopropylsulfonyl azide stability data, see: Tuma, L. D. *Thermochim. Acta* **1994**, *243*, 161.

Scheme 5. **Asymmetric hydrogenation and conversion to acyloxazolidinone**



hydrogenation of similar olefins indicate that, due to dipole−dipole interactions of the carbonyl groups, the hydrogenation of **17** would proceed through conformation **A** (Figure 1), yielding predominantly (*S*,*R*)-diastereomer **10b**.[16,17]

We reasoned that in the presence of a Lewis acid hydrogenation on Pd/C would proceed via chelation-controlled conformation **B**, resulting in reversal of the sense of stereoinduction and formation of the (*S*,*S*)-diastereomer **10a** predominantly. Correlation of spectral properties with imide **10a** produced from acid **16** would then allow us to assign its stereochemistry. We were also hopeful that a choice of an appropriate Lewis acid might yield a selectivity high enough to allow the preparation of diastereomer **10a** from olefin **17** directly, thus using the same chiral auxiliary to set both stereocenters and avoiding the need for the expensive chiral hydrogenation catalyst.

Gratifyingly, both assumptions proved to be true. Hydrogenation of olefin **17** at room temperature and 450 psig H_2 in the absence of a Lewis acid resulted in the formation of a 71:29 mixture of isomers **10b** and **10a**. The sense of stereoinduction was reversed when LiCl was added. Correlation of spectral data for the diastereomers allowed assignment of absolute stereochemistry of acid **16** as (*S*) to be confirmed. More importantly, hydrogenation was highly selective in the presence of $MgBr_2$, producing a 95:5 mixture of **10a** and **10b**, albeit initially with 79% conversion. Further optimization studies demonstrated that full conversion could be achieved in 4 h at 50 °C at useful H_2 pressures (50−65 psig). Use of dry catalyst (<3% water) was important for achieving high selectivity (up to 96.5:3.5).

This result presented a more practical alternative to asymmetric hydrogenation. Therefore, a second-generation route eliminating the need for the chiral ligand was used further. The procedure used for large-scale preparation of **10a** from acid **9** involved conversion to acryloxazolidinone derivative **17** by treating the mixture of **9**, (*S*)-benzyloxazolidinone, LiCl, and pivaloyl chloride with triethylamine at −20 °C,[18] followed by crystallization from heptane or IPA/water. Olefin **17** was then hydrogenated at 60−65 psig H_2 and 45−50 °C in THF in the presence of 1.2 equiv of $MgBr_2$ and Pd/C catalyst, followed by crystallization from IPA−water to afford **10a** typically in 70−76% yield and >98% de. It should be noted that an aqueous wash to remove $MgBr_2$ was necessary before the solvent switch to IPA. When a direct solvent replacement from THF to IPA via atmospheric pressure distillation was attempted, significant decomposition of **10a** occurred, generating impurity **18** and its derivative resulting from further loss of HBr (m/z = 369). In addition, prolonged reaction times led to increased formation of impurity **19** (Figure 2; structure assignments based on LC/MS data). Formation of this impurity is presumed to have occurred via $MgBr_2$-promoted oxazolidinone ring-opening of **10a** (or **17** followed by olefin hydrogenation) followed by decarboxylation to generate **18**, followed by further reduction to generate **19**.[19]

Completion of Synthesis. The oxazolidinone derivative **10a** was converted to azide **20** via enolization and reaction with triisopropylsulfonyl azide ($TrisN_3$).[20,21] The reaction could be run at −40 °C, with only a minor selectivity loss compared to typical lower-temperature conditions, and afforded intermediate

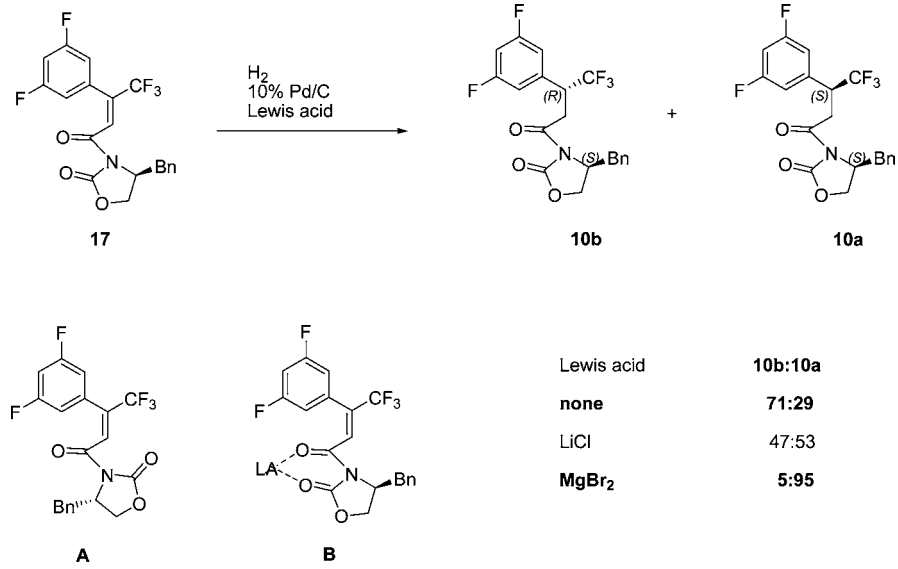


Figure 1. **Hydrogenation of olefin 17.**

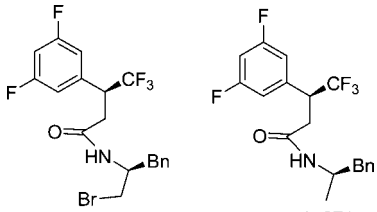


Figure 2. **Proposed structures for impurities generated during hydrogenation of 17 in the presence of $MgBr_2$.**

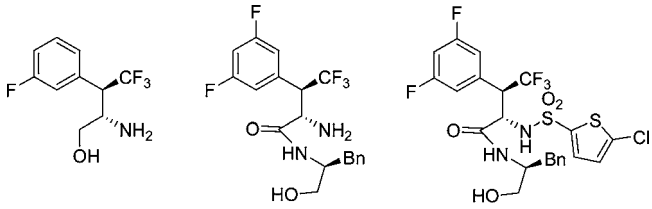


Figure 3. **Proposed structures for impurities generated during $LiBH_4$ reduction of 21, and fate of 24 in API.**

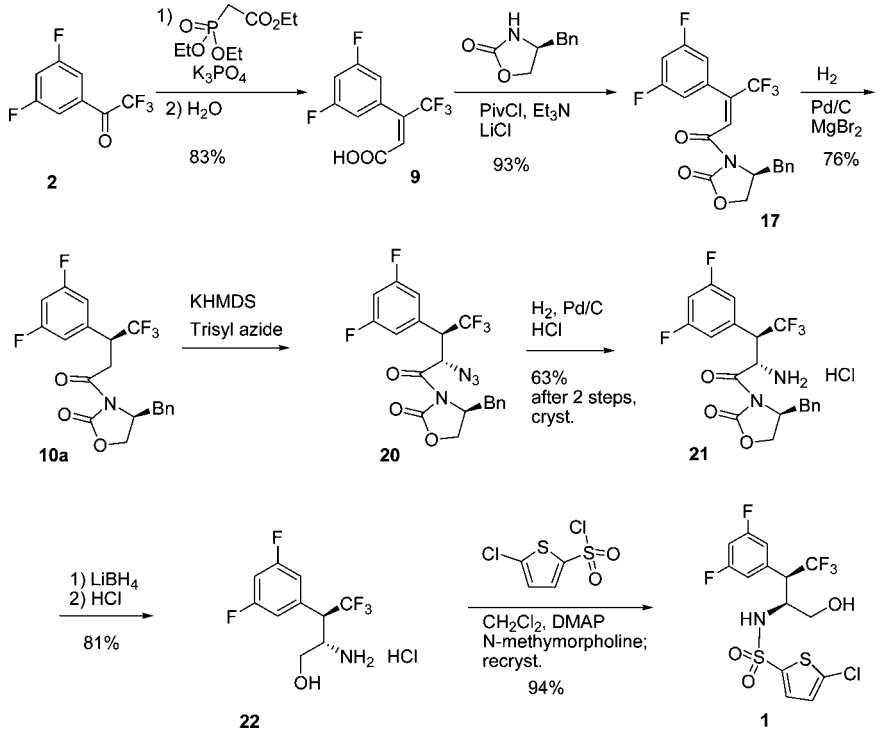
azide **20** with high selectivity (93:7 dr at −40 °C; 97:3 dr at −78 °C). Evidently, the directing effect of the oxazolidinone chiral auxiliary overrides any directing effect of the β-substituent. The use of other N-electrophiles ($RO_2CN{=}NCO_2R$, R = *t*-Bu, *i*-Pr, Bn) resulted in significantly lower diastereomer ratios even at −78 °C. The crude azide **20** was used without isolation. Hydrogenation after a solvent switch afforded amine **21**, which was crystallized as a hydrochloride salt of high purity and as a ~98.5:1.5 mixture of diastereomers.

The conversion of amine **21** to the target **1** through sulfonylation followed by reductive removal of the auxiliary would require chromatographic purification to remove the oxazolidinone byproduct. In addition, sulfonylation of **21** was found to be slow and was accompanied by the formation of ~15% of an impurity resulting from intramolecular attack of the amine on the oxazolidinone moiety. For those reasons imide **21** was first converted to aminoalcohol **22** which was isolated as its hydrochloride salt. It should be noted that direct conversion of crude azide **20** to aminoalcohol **22** was also possible, but it resulted in an inferior impurity profile and required extensive purification at the expense of the yield.

During the reduction of **21** to **22**, two impurities were identified, the structures of which were proposed on the basis of LC/MS data (Figure 3). Significant levels of the des-fluoro impurity **23** were formed when the substrate was added to a solution of lithium borohydride while attempting to increase the reaction throughput. Changing the order of addition easily controlled the level of **23** generated, and it was not detected in isolated **22**. Controlling the formation of **24** and limiting the amount of it in **22** proved more challenging and critical. Compound **24** reacted with the sulfonyl chloride used in the last step and generated a persistent impurity **25** that was difficult to purge from the API. Further experiments identified that the level of **24** in **22** had to be controlled at <1.0 HPLC area % in order to control the level of **25** below 0.5% in the API. To minimize the formation of **24**, the temperature was maintained between −10 and 0 °C during the addition of $LiBH_4$. Using these conditions, the level of **24** generated in-process was controlled at 2−3%. Filtration of the slurry of **22** at 35−40 °C assisted in controlling the level of **24** in **22** to the desired level.

Aminoalcohol **22** was then treated with 5-chlorothiophene-2-sulfonyl chloride to afford sulfonamide **1**. Use of *N*-methylmorpholine as the base and catalytic amounts of 4-dimethylaminopyridine (DMAP) in dichloromethane at 0−10 °C was found to be optimal, as it minimized the amount of O-

Scheme 6. **Large-scale synthesis of 1**



sulfonylation byproduct. Addition of *N*-methylpiperazine to the reaction mixture, when the reaction was deemed complete, scavenged residual 4-dimethylaminopyridinium-(5-chlorothiophene)-2-sulfonyl chloride, which otherwise tended to survive the acidic workup and react with the product. The crude product isolated from the reaction mixture was dissolved in IPA, polish-filtered, and precipitated by addition of water. Following this sequence, the target compound was isolated as a single stereoisomer as detected by chiral HPLC, in seven steps and 28% overall yield starting from ketone **2**. The absolute configuration of **1** was confirmed by single crystal X-ray analysis (see Supporting Information for details).

Conclusions

A practical enantioselective approach to a 3-aryl-3-trifluoromethyl-2-aminopropanol and its derivatives has been developed. The described method relies on a Lewis acid-mediated hydrogenation followed by Evans azidation. It is amenable to scale-up and was the basis for two campaigns that produced kilogram quantities of API. Although the approach relies on the stoichiometric use of a chiral auxiliary, it utilizes the auxiliary to set both stereocenters of the target compound and avoids the use of an expensive chiral ligand.

This method is complementary to the one relying on a hydrogenation directed by a chiral auxiliary in the absence of a Lewis acid, followed by enolate trapment with an electrophilic nitrogen.[16a] The latter method would produce a different diastereomer of the product when the same enantiomer of the chiral auxiliary is used. The combination of both methods potentially allows for selective, highly practical, and industrially applicable routes to any isomer of 3,3-disubstituted 2-aminopropanol or 3,3-disubstituted alanine derivative by starting from a single isomer of a 3,3-disubstituted acrylic acid and choosing an appropriate chiral auxiliary. This approach is an alternative to the one relying on asymmetric conjugate addition of organocuprates to acryloxazolidinone derivatives followed by Evans azidation (Route II, Scheme 2). The described synthesis also demonstrates a case where the developed methodology offered an advantage over the conjugate addition approach.

Experimental Section

General. HPLC analysis of the intermediates and reaction monitoring was carried out on an Agilent 1100 liquid chromatograph equipped with a Phenomenex Prodigy ODS3 4.6 mm × 50 mm column. LC/MS data were obtained on an Agilent 1100 LC system with an Agilent 1100 LC/MS detector equipped with a 4.6 mm × 50 mm Chromolith SpeedROD column.

Chiral HPLC conditions for **16**: column type: Chiralpak AS-H 250 mm × 4.6 mm; mobile phase: 98% heptane/TFA/2% isopropanol isocratic; flow rate: 1.0 mL/min; column temperature: room temperature; injection solvent: methanol; wavelength: 254 nm; retention times: enantiomer 1: 10.0 min; enantiomer 2: 11.3 min. Chiral HPLC conditions for **1**: column type: Chiralcel AD 250 mm × 4.6 mm; mobile phase:15% isopropanol in hexane isocratic; flow rate: 1.0 mL/min; column temperature: room temperature; injection solvent: ethanol; wavelength: 254 nm; Retention times: isomer 1: 4.66 min; isomer 2: 4.79 min; isomer 3 (isomer of interest): 5.54 min; isomer 4: 7.51 min.

(*E*)-3-(3,5-Difluorophenyl)-4,4,4-trifluorobut-2-enoic acid (9). *Method A.* A mixture of 1-(3,5-difluorophenyl)-2,2,2-trifluoroethanone **2** (114.59 g, 0.545 mol), NaOAc (89.48 g, 1.091 mol, 2 equiv), and acetic anhydride (773 mL, 8.18 mol, 15 equiv) was stirred at 100 °C for 5 h. The reaction mixture was cooled to 4 °C, and 1.375 L of water was added over 30 min at 4−12 °C. The mixture was allowed to warm up to room temperature and stirred for 2 h (completion of hydrolysis was monitored by HPLC). MTBE (1 L) was added, followed by 1.145 L of water. Phases were separated. The aqueous phase was extracted with 2 × 0.5 L of MTBE. The combined organic fractions were concentrated in vacuum. Toluene was added, and the mixture was concentrated in vacuum. Crude product, 138.83 g, was obtained as a yellow solid (96:4 mixture of *E/Z* isomers based on ^{1}H and ^{19}F NMR). The solids were dissolved in 2.7 L of 4:1 heptane−toluene mixture at 70 °C. The solution was allowed to cool to room temperature and then stirred at 2−4 °C for 6 h. Precipitated solids were filtered, washed with 3 × 150 mL of heptane, and dried in vacuum at room temperature for 24 h to afford 117.5 g of the title product as a white solid (85% yield; single isomer as judged by ^{1}H, ^{19}F NMR, and HPLC; >99.9% pure by HPLC). Mp: 129−130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95−6.78 (m, 3 H), 6.64 (br. q, J = 1.2 Hz, 1 H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.18 (s, 3 F), −109.14 (s, 2 F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168, 162.63 (dd, J = 250, 12 Hz), 142.51 (q, J = 31 Hz), 133.01 (dd, J = 10, 10 Hz), 124.44 (q, J = 5.4 Hz), 121.71 (q, J = 274 Hz), 112.03 (dd, J = 19, 8 Hz), 105.31 (dd, J = 25, 25 Hz). HRMS (for M − H): calcd: 251.0137; found: 251.0135.

Method B. A solution of **2** (11.5 kg, 54.74 mol) in triethyl phosphonoacetate (12.3 kg, 54.86 mol) was added to a mixture of K_3PO_4 (29.1 kg, 137.09 mol, 2.5 equiv) and anhydrous ethanol (40.2 kg) over 1 h at ≤30 °C After the addition the temperature was adjusted to 23−28 °C, and the mixture was stirred for 20 h. Water (80.5 kg) was added to the mixture. Ethanol was distilled off at atmospheric pressure (pot temperature 95−96 °C). The batch was cooled to 12 °C, and 6 N HCl solution (46 L) was added over 45 min. The temperature was adjusted to 20−25 °C, and the mixture was stirred for 1.5 h. The solids were filtered. The cake was washed with water (11.5 kg). The wet cake was reslurried in water (115 kg) at 50 °C for 30 min. The slurry was filtered. The cake was washed with water (2 × 11.5 kg) and dried in vacuum at 40−50 °C to afford 12.7 kg of the title product (92% yield; 90.6% strength, 83% yield adjusted to strength).

(*S*)-3-(3,5-Difluorophenyl)-4,4,4-trifluorobutanoic acid (16). $Rh(nbd)_2BF_4$ (0.501 g, 0.00134 mol, 0.005 equiv) and Walphos 8-1 (1.262 g, 0.00134 mol, 0.005 equiv) were placed in a 2.5-L Parr bottle. MeOH (1 L; deoxygenated by purging with N_2) was added. The mixture was kept at room temperature for 30 min to allow solids to dissolve. Acid **9** (67.37 g, 0.267 mol) was added. The resultant solution was hydrogenated in a Parr shaker at 45 psig H_2 at room temperature for 23 h. Solvent was distilled off in vacuum to afford 69.17 g of the title product as a gray solid (99.3% pure by HPLC). A single enantiomer was observed by chiral HPLC. The product was used without

further purification. Mp: 73−75 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92−6.76 (m, 3H), 3.94−3.78 (m, 1 H), 3.08 (dd, J = 17, 4.6 Hz, 1H), 2.89 (dd, J = 17, 10 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.72 (s, 3 F), −108.94 (s, 2 F). MS (*m*/*z*, negative ESI, for M − H): 253. $[\alpha]^{25}_D$ +28 (c = 1, MeOH).

(*S*, *E*)-4-Benzyl-3-(3-(3,5-difluorophenyl)-4,4,4-trifluorobut-2-enoyl)oxazolidin-2-one (17). Acid **9** (11 kg, 43.63 mol), (*S*)-(−)-4-benzyl-2-oxazolidinone (8.5 kg, 47.97 mol, 1.1 equiv) and LiCl (3.7 kg, 87.28 mol, 2 equiv) were added to THF (95.7 kg) cooled to −15 °C. The temperature was adjusted to 20 °C, the mixture was stirred for 30 min and then cooled to −21 °C. Trimethyl acetyl chloride (13.1 kg, 108.54 mol, 2.5 equiv) was added over 30 min at −21 °C. Triethylamine (11.5 kg, 113.64 mol, 2.6 equiv) was added over 4.5 h at −22 to −20 °C. The mixture was stirred at −23 °C for 30 min. The reaction completion was confirmed by HPLC (no residual acid **9** was detected). The mixture was warmed to 15 °C over 30 min. A 12.5% ammonium chloride solution (37.7 kg) was added over 10 min. Phases were separated. The aqueous phase was extracted with THF (53.6 kg). The combined THF solutions were distilled at atmospheric pressure to a final volume of 35 L. Isopropanol (80.1 kg) was added. The mixture was concentrated by atmospheric pressure distillation to a volume of 55 L. An in-process GC showed the presence of 3.2% residual THF. Water (55 kg) was added over ∼30 min at 60−70 °C. The resulting slurry was cooled to 0 °C over 75 min and stirred for 30 min. The slurry was filtered and washed with water (2 × 44 kg). The solid was dried on the filter for 19 h and then in a vacuum oven at 43−48 °C to afford 16.68 kg of the title product (93% yield; 96.6% HPLC strength). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (q, J = 1.5 Hz, 1 H), 7.36−7.23 (m, 3H), 7.15−7.1 (m, 2 H), 6.94−6.85 (m, 3 H), 4.64−4.54 (m, 1 H), 4.28−4.16 (m, 2 H), 3.18 (dd, J = 13.5, 3 Hz, 1 H), 2.67 (dd, J = 13.5, 9.5 Hz, 1 H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.68 (s, 3 F), −108.91 (s, 2 F). MS (*m*/*z*, positive ESI, for M + H): 412.

(*S*)-4-Benzyl-3-((*S*)-3-(3,5-difluorophenyl)-4,4,4-trifluorobutanoyl)oxazolidin-2-one (10a). *Method A.* $MgBr_2$ (0.58 kg, 3.15 mol, 1.2 equiv), 10% Pd/C (0.109 kg, anhydrous) and **17** (1.08 kg, 2.63 mol) were charged to a pressure reactor. The reactor was sealed, and THF (19.1 kg) was added. The reactor contents were stirred, and hydrogen was introduced into the reactor at a pressure of 60−65 psig. The reaction mixture was stirred at 45−50 °C while maintaining hydrogen pressure at 50−65 psig for 4 h. The hydrogen was vented, and the reactor was flushed with nitrogen. The reaction mixture was filtered through a sparkler filter that was precoated with Celite (0.6 kg), and the cake was rinsed with MTBE (9.7 kg). The combined filtrate was washed three times with a brine solution (∼1 kg NaCl + 5.5 kg water for each wash), and the organic layer was concentrated to 8−10 L in vacuum (25−30 °C batch temperature). Isopropyl alcohol (6 L) was added, and the mixture was concentrated at 70 °C to a volume of about 4 L. Water (4 L) was added, and the slurry was cooled to 25 °C. The solid was filtered and dried in vacuum at 60 °C to afford 0.825 kg of the title product (76% yield; 94.2% pure by HPLC; single largest impurity: 2.1%). Mp: 127−128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 3 H), 7.21−7.14 (m, 2 H), 6.94 (app. d, J = 6 Hz, 2 H), 6.85−6.75 (m, 1 H), 4.63−4.53 (m, 1 H), 4.18 (d, J = 5 Hz, 2 H), 4.17−4.03 (m, 1 H), 3.67 (dd, J = 18.5, 9.5 Hz, 1 H), 3.56 (dd, J = 18.5, 4.5 Hz, 1 H), 3.26 (dd, J = 13, 3.5 Hz, 1 H), 2.74 (dd, J = 13, 9.5 Hz, 1 H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.17 (s, 3 F), −109.14 (s, 2 F). MS (*m*/*z*, positive ESI, for M + H): 414. $[\alpha]^{25}_D$ +96.2 (c = 1, MeOH).

Method B. To a solution of acid **16** (1.06 g, 4.2 mmol) in toluene (15 mL), oxalyl chloride (0.63 g, 0.445 mL, 5 mmol, 1.2 equiv; 98% pure) was added at room temperature, followed by DMF (0.01 mL). The mixture was stirred at room temperature for 1 h. NMR of an aliquot indicated consumption of the acid and acid chloride formation. Solvent and excess oxalyl chloride were distilled off in vacuum. The residue was dissolved in THF (12 mL).

In a separate flask, *i*-PrMgCl (4 mmol, 2 mL of 2 M THF solution) was added to a solution of (*S*)-(−)-4-benzyl-2-oxazolidinone (0.675 g, 3.81 mmol) in THF (12 mL) at −30 °C. The mixture was stirred at −30 °C for 1.5 h, then a THF solution of acid chloride prepared as described above was added over 15 min. The reaction mixture was allowed to warm up to room temperature and was stirred for 18 h. Water (10 mL) was added. THF was distilled off in vacuum. MTBE and sodium citrate solution were added. Phases were separated, and the aqueous phase was extracted with MTBE. The combined organic fractions were washed with $NaHCO_3$ solution and then brine, and were dried over $MgSO_4$, filtered through a pad of silica gel, and concentrated to afford 1.6 g of crude product. Recrystallization from MTBE−heptane afforded 1.3 g of the title product as a white solid (75% yield based on acid **16**).

(*S*)-3-((2*S*,3*R*)-2-Amino-3-(3,5-difluorophenyl)-4,4,4-trifluorobutanoyl)-4-benzyloxazolidin-2-one hydrochloride (21). To a solution of **10a** (5.18 kg, 12.53 mol) in THF (11.2 kg) was added KHMDS (20% THF solution, 13.5 kg, 13.54 mol, 1.08 equiv) at −48 to −42 °C over 75 min. The solution was stirred at −49 °C for 30 min. A solution of 2,4,6-triisopropylbenzensulfonyl azide (3.77 kg, 12.18 mol, 0.97 equiv) in toluene (8.8 kg) was added over 75 min at −49 to −40 °C. The mixture was held at −46 °C for 30 min. A solution of acetic acid (3.4 kg, 56.6 mol, 4.5 equiv) in water (3.4 kg) was added over 5 min. The temperature was adjusted to 20 °C, and the mixture was stirred for 20 min. Heptanes (8.65 kg) were added. Phases were separated. The organic phase was heated to 34 °C, washed at that temperature with 28 kg of 0.5 M K_3PO_4 solution, 2 × 28 kg of 0.25 M K_3PO_4 solution, 31.6 kg of 20% NaCl solution, and concentrated in vacuum to a volume of ∼26 L. Solvent exchange to ethanol was performed by adding 41.1 kg of ethanol and concentrating in vacuum to a volume of 25 L. (Residual solvents: toluene, 2.7%; heptane, not detected.) The concentrated solution was filtered and split into two equal portions for hydrogenation.

Half of the solution was acidified with 6 N hydrogen chloride (2.2 kg). A hydrogenation reactor was charged with 10% Pd/C (50% wet, 0.258 kg). The acidified solution described above was added, chasing with 7.4 kg of ethanol. The mixture was hydrogenated at 50 psig H_2 at 24−28 °C for 5 h. Methanol (4.97 kg) was added. The mixture was filtered through Celite

(0.65 kg). The Celite pad was washed with methanol (3.0 kg), and the wash was combined with the filtrate. The hydrogenation was repeated with the second half of the solution of intermediate **20**.

The solutions containing hydrogenation products were combined and distilled in vacuum to a volume of 25 L. Heptanes (13.8 kg) were added over 30 min. The mixture was stirred at 22 °C for 30 min then at −9 °C for 15 min. The resulting slurry was filtered, washed with a mixture of heptanes/ethanol (6.9 kg/2.02 kg) and dried on the filter under a stream of nitrogen to afford 3.65 kg of the title product as a white solid (63% yield; 99.5% HPLC strength). Mp: 151−153 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 7.37−7.04 (m, 8 H), 5.9 (d, J = 9 Hz, 1 H), 4.52 (p, J = 9 Hz, 1 H), 4.4−4.3 (m, 1 H), 4.21 (dd, J = 9, 2 Hz, 1 H), 3.9 (dd, J = 9, 7.5 Hz, 1 H), 3.23 (dd, J = 13.5, 3 Hz, 1 H), 2.85 (dd, J = 13.5, 9 Hz, 1 H).^{19}F NMR (282 MHz, CD_3OD) δ −65.79 (s, 3 F), −109.23 (s, 2 F). MS (*m*/*z*, positive ESI, for M + H): 429.

(2*S*,3*R*)-2-Amino-3-(3,5-difluorophenyl)-4,4,4-trifluorobutan-1-ol hydrochloride (22). To a solution of **21** (11 kg, 23.67 mol) in THF (59.6 kg), $LiBH_4$ (5% solution in THF, 24.1 kg, 55.33 mol, 2.3 equiv) was added at −7 to −10 °C over 2 h. The mixture was warmed up to 21 °C and stirred for 15 min. HPLC analysis confirmed the completion of conversion (1% of **21** remaining). The mixture was cooled to 9 °C. Methanol (15.1 kg) was added over 30 min at <25 °C. 37% HCl solution (22.9 kg) was added over 30 min at <25 °C. The mixture was cooled to 10 °C, and water (56.1 kg) was added over 10 min. The mixture was allowed to warm to 17 °C and stirred for 30 min. HPLC analysis confirmed decomposition of borane complexes (<2.5% of borane complex remaining). The mixture was concentrated in vacuum at 25−30 °C to a volume of 66 L, diluted with water (56.1 kg) and washed with dichloromethane (2 × 74.4 kg). Toluene (68.1 kg) was added. A 50% NaOH solution (26.7 kg) was added over 75 min at 7−18 °C. Phases were separated. The aqueous phase was extracted with toluene (68.1 kg). The combined toluene solution was washed with water (2 × 45 kg).

HCl (6 N solution in IPA, 8.5 kg) was added over 30 min. The solution was concentrated in vacuum to a volume of 88 L. The resultant suspension was heated to 70 °C, stirred for 1 h, cooled to 35 °C over 2 h, and filtered. The filter cake was washed with CH_2Cl_2 (20 kg) and toluene (19 kg), and dried in vacuum at 50−55 °C to afford 5.59 kg of the title product as a white solid (81% yield; 98.8% pure by HPLC). Mp: 231−233 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 7.15−7.05 (m, 3 H), 4.14−3.96 (m, 2 H), 3.64 (dd, J = 12, 2 Hz, 1 H), 3.25 (dd, J = 12, 3.5 Hz, 1 H). ^{19}F NMR (282 MHz, CD_3OD) δ −67.62 (s, 3 F), −110.9 (s, 2 F). MS (*m*/*z*, positive ESI, for M + H): 256. $[\alpha]^{25}_D$ +40.4 (c = 1, MeOH).

5-Chloro-*N*-((2*S*,3*R*)-3-(3,5-difluorophenyl)-4,4,4-trifluoro-1-hydroxybutan-2-yl)thiophene-2-sulfonamide (1). To a mixture of dichloromethane (59.4 kg), 4-dimethylaminopyridine (0.116 kg, 0.95 mol, 0.05 equiv) and **22** (5.57 kg, 19.09 mol), N-methylmorpholine (4.12 kg, 40.73 mol, 2.1 equiv) was added over ∼15 min at 0−3 °C, chasing with dichloromethane (5.6 kg). A solution of 5-chlorothiophene-2-sulfonyl chloride (4.39 kg, 20.22 mol, 1.06 eqiuv) in dichloromethane (4.9 kg) was added over 30 min at 1−4 °C. The mixture was stirred at 6 °C for ∼21 h. The completion of conversion was monitored by HPLC (<4% of **22** remaining). *N*-Methylpiperazine (0.172 kg, 1.48 mol) was added at 0−6 °C. A solution of concentrated hydrochloric acid (1.9 kg) and water (28 kg) was added, maintaining the temperature at 25−30 °C. Phases were separated. The organic layer was washed at 25−30 °C with a solution of concentrated hydrochloric acid (1.9 kg) and water (28 kg), then water (28 kg), and was then concentrated at atmospheric pressure to a volume of 38−40 L. Heptane (30.7 kg) was added over 55 min at 33−39 °C. The mixture was cooled to 2 °C and stirred for 1 h. The solids were filtered, washed with a heptane−dichloromethane mixture (15.3 kg/7.4 kg), and dried in vacuum.

The crude product was dissolved in isopropanol (24.7 kg) at 21 °C. The solution was filtered and heated to 42 °C. Water (23.7 kg) was added at 40−45 °C. The mixture was cooled to ∼21 °C over 30 min, then to 10 °C over 50 min. Water (55.2 kg) was added. The solids were filtered, washed with a cold isopropanol - water mixture (3.1 kg/35.5 kg), dried in vacuum at 50−55 °C and micronized (to 90% particle size <10 μm) to afford 7.4 kg of the title product (94% yield). Mp 125−126 °C. HPLC purity: 99.98%. Chiral purity: >99.9% as detected by chiral HPLC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 4 Hz, 1 H), 6.94 (d, J = 4 Hz, 1 H), 6.88−6.78 (m, 3 H), 5.25 (d, J = 8 Hz, 1 H), 3.96−3.64 (m, 3 H), 3.3 (ddd, J = 11, 4.6, 3.8 Hz, 1 H), 1.74 (t, J = 4.6 Hz, 1 H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.91 (s, 3 F), −108.07 (s, 2 F). Anal. Calc. for $C_{14}H_{11}ClF_5NO_3S_2$: C 38.58%, H 2.54%, N 3.21%; found: C 38.69%, H 2.7%, N 3.16%. HRMS (for M + H) calcd: 435.98618; found: 435.98728. $[\alpha]^{25}_D$ +33.6 (c = 1, MeOH).

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Supporting Information Available

Single crystal X-ray data and ORTEP diagram for compound **1**; experimental and spectral data for compounds **3a**, **3b**, **11**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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