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Synthesis of Enantiopure *trans*-2,5-Disubstituted Trifluoromethylpyrrolidines and (2*S*,5*R*)-5-Trifluoromethylproline

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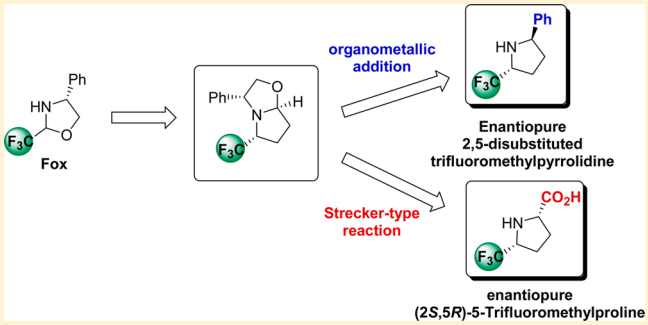
Supporting Information

ABSTRACT: Enantiopure *trans*-2,5-disubstituted trifluoromethylpyrrolidines were prepared on a several gram scale starting from a readily available chiral fluorinated oxazolidine (Fox). A pure oxazolopyrrolidine intermediate could be obtained after an efficient separation by selective diastereomer destruction. The addition of various Grignard reagents on this oxazolopyrrolidine provided disubstituted pyrrolidines with moderate to complete *trans* diastereoselectivity. The highly valuable compound (2*S*,5*R*)-5-trifluoromethylproline could be synthesized from the same oxazolopyrrolidine intermediate via a Strecker-type reaction.



INTRODUCTION

2,5-Disubstituted pyrrolidines constitute important motifs found in natural alkaloids,[1] and 5-substituted prolines are conformationally constrained unnatural amino acids.[2] Both can be considered as compounds with high biological interest.[3] They also have been used for asymmetric synthesis as chiral auxiliaries,[4,5] chiral ligands,[6] and organocatalysts.[7] The fluorinated fragments can deeply modify physicochemical properties of organic compounds and sometimes change their biological features significantly.[8−10] Among them, the powerful electron-withdrawing trifluoromethyl group has been used to modulate the pK_a of neighboring functions,[11] promote specific conformations,[12] and increase the lipophilicity[13] and the metabolic stability[14] of molecules of biological interest.

Several trifluoromethylpyrrolidines have already been synthesized in the literature, mostly in their racemic forms. Since the first example of pyrrolidine synthesis published by Burger et al.,[15] the [3 + 2] cycloaddition of an azomethine ylide and a dipolarophile has often been used to reach β-substituted[13,16] or α-substituted[17,18] trifluoromethylpyrrolidines. Highly functionalized trifluoromethylpyrrolidines can also be synthesized from a Michael-type addition/annulation sequence on a CF_3-substituted vinylsulfonium salt,[19] intramolecular cyclization of fluorinated homoallylamines, and one-pot intramolecular cyclization of aminoalkynes followed by nucleophilic addition of the Ruppert reagent.[20] However, very few methods giving an access to optically active compounds have been published. Fustero et al.[21] described a tandem cross-metathesis intramolecular aza-Michael reaction of an enantiomerically enriched aminoalkene, and Li et al.[22] obtained good enantioselectivities in their copper-catalyzed asymmetric 1,3-dipolar cycloaddition. Several racemic and stereoselective syntheses of trifluoromethylprolines are also found in the literature. Highly substituted 3-trifluoromethylprolines have been obtained through an enantioselective cycloaddition reaction.[23] Other syntheses of diversely substituted trifluoromethylprolines have also been published. Dipeptides incorporating racemic 2-trifluoromethylproline can be directly prepared using the Ugi reaction.[24] Our group reported the synthesis of both enantiomers of 2-trifluoromethylproline involving a chiral trifluoromethylated allylmorpholinone as the key intermediate.[25] Such a 2-trifluoromethylproline has recently been incorporated into a tripeptide that presents an interesting analgesic biological activity.[26] Haufe and co-workers[27] reported the addition of an isocyanoacetate on a trifluoromethyl alkoxyenone to obtain a trifluoromethylpyrrole. The catalytic hydrogenation of this pyrrole provided the first example of a racemic synthesis of *cis*-5-trifluoromethylproline. Recently, Meffre and co-workers[28] described the synthesis of *cis*-5-trifluoromethylproline starting from L-glutamic acid but reported racemization of the final compound. We report herein a stereoselective strategy for the synthesis of enantiopure (2*R*,5*R*)-5-trifluoromethylproline as well as enantiopure 2,5-disubstituted trifluoromethylpyrrolidines.

Over the past several years, we have developed efficient methods for the synthesis of enantiopure α-trifluoromethyl-substituted amino acids (α-Tfm-AAs),[29,30] amino alcohols,[31] and diamines[29] starting from readily available fluorinated oxazolidine (Fox) compounds.[32] Considering the very few examples of asymmetric syntheses of trifluoromethylated pyrrolidines reported in the literature, we turned our attention to the nonfluorinated series and were inspired by the early work of Husson[33] and, more recently, by Kadouri-Puchot's and Mangeney's synthesis of 2,5-disubstituted pyrrolidines and 5-substituted proline involving chiral oxazolidines.[34] We decided

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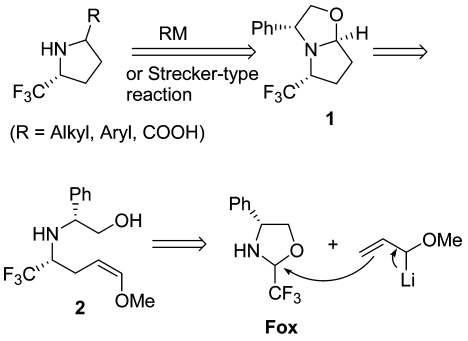
to investigate this strategy in the fluorinated series. Our target chiral pyrrolidines and proline should be obtained from a common trifluoromethylated oxazolopyrrolidine intermediate **1** via an organometallic addition or a Strecker-type reaction (Scheme 1). Compound **1** should be obtained by the intramolecular condensation under acidic conditions of the amino alcohol **2**, which in turn should be obtained from the addition of an aldehyde precursor lithium reagent on the fluorinated oxazolidine (**Fox**). This retrosynthetic pathway should provide an asymmetric, robust and scalable synthesis of trifluoromethylpyrrolidines (Scheme 1).

Scheme 1. Retrosynthetic Plan

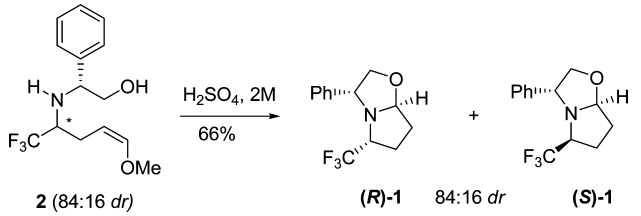


RESULTS AND DISCUSSION

Synthesis of Oxazolopyrrolidine 1. The condensation of fluoral with (*R*)-phenylglycinol gave the corresponding fluorinated oxazolidine (**Fox**) as a 68:32 mixture of two inseparable diastereomers.[32] The reaction of the allyllithium reagent with the mixture of oxazolidines proceeded mostly through γ-addition but was not completely diastereoselective and led to the major formation of the diastereomer (*R*)-**2** (84:16 *dr*). Considering that the same diastereoselectivity was obtained starting from pure *trans*-**Fox**, we propose an open-oxazolidine imine-type cyclic transition state involving chelation of the lithium metal by both the imine and the phenylglycinol residue (Scheme 2).[35]

Since the two diastereomers (*R*)-**2** and (*S*)-**2** were not easily separable, the aldehydes were generated from the mixture under aqueous acidic conditions, and the two corresponding oxazolopyrrolidines (*R*)-**1** and (*S*)-**1** were obtained in 66% yield with a similar diastereomeric ratio (84:16 *dr*) (Scheme 3).

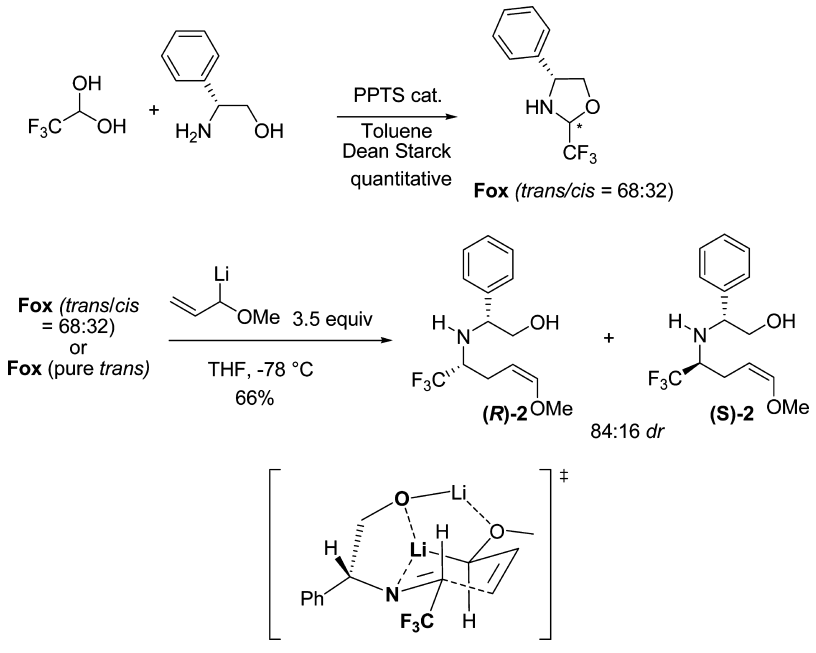
Scheme 3. Synthesis of Oxazolopyrrolidines (*R*)-1 and (*S*)-1



It should be noted that the cyclization is completely diastereoselective, giving only the *trans*-oxazolidine relative configuration. Unfortunately, the two diastereomers could not be separated either at this step.

In order to obtain 2,5-disubstituted pyrrolidines, addition of organometallic reagents on the diastereomeric mixture of oxazolopyrrolidines **1** was investigated. The addition of 2 equiv of phenyl Grignard reagent on the mixture of oxazolopyrrolidines **1** resulted in the formation of the two addition products (*R*,*R*)-**3** and (*S*)-**3** arising from (*R*)-**1** and (*S*)-**1** along with nonreacted oxazolopyrrolidine (*R*)-**1** (Scheme 4). Three important reaction features could be deduced from this result: (i) under these experimental conditions, oxazolopyrrolidine (*S*)-**1** reacted more rapidly than oxazolopyrrolidine (*R*)-**1**; (ii) the addition on (*R*)-**1** was completely selective, furnishing *trans*-pyrrolidine (*R*,*R*)-**3**; (iii) the addition on (*S*)-**1** was not selective, giving a mixture of undetermined *cis*- and *trans*-pyrrolidine (*S*)-**3**. Moreover, the nonreacted oxazolopyrrolidine

Scheme 2. Synthesis of Amino Alcohols (*R*)-2 and (*S*)-2



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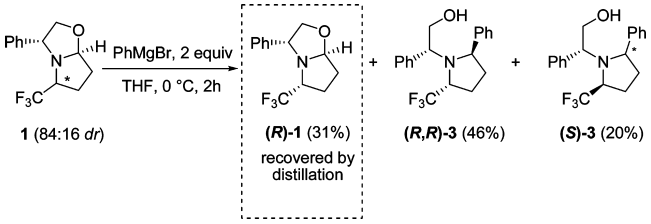
Scheme 4. Addition of Phenyl Grignard Reagent on Oxazolopyrrolidines 1



(*R*)-**1** could be recovered from the mixture by a simple distillation (Scheme 4).

Considering that the stereoselective synthesis of trifluoromethylpyrrolidines requires starting from pure oxazolopyrrolidine (*R*)-**1**, we intended to take advantage of the kinetic difference between the Grignard reagent addition reactions on (*R*)-**1** and (*S*)-**1** to perform a separation based on the selective consumption of the undesired diastereomer.

To test the feasibility of such a resolution, substoichiometric portions of phenyl Grignard reagent were sequentially added to the diastereomeric mixture of oxazolopyrrolidines (*R*)-**1** and (*S*)-**1**, and the reaction was monitored by fluorine NMR spectroscopy to track the total consumption of the more reactive diastereomer (*S*)-**1** (Figure 1). From this study, it appeared that the addition of 0.7 equiv of Grignard reagent was the best compromise to transform the entire amount of undesired compound (*S*)-**1** and preserve the maximum amount of oxazolopyrrolidine (*R*)-**1** in the mixture (Figure 1). At a preparative scale, the treatment of the oxazolopyrrolidine mixture **1** with 0.7 equiv of phenyl Grignard reagent allowed the isolation of pure oxazolopyrrolidine (*R*)-**1** by distillation in 69% yield. This resolution is scalable, and pure oxazolopyrrolidine (*R*)-**1** could be obtained on a scale of more than 9 g according to this procedure (Scheme 5).

Synthesis of 2,5-Trifluoromethylpyrrolidines. The addition of various Grignard and organolithium reagents was tested on pure isolated (*R*)-**1**. Good results were observed with hindered Grignard reagents such as PhMgBr and *i*-PrMgBr, since the addition reaction was completely diastereoselective to give only the *trans*-pyrrolidines (*R*,*R*)-**3** and (*R*,*R*)-**4**, respectively (Table 1, entries 1 and 2). The selectivity decreased for less hindered reagents such as *n*-butyl or methyl Grignard reagents (entries 3−6), and the reaction did not proceed at all with organolithium reagents (entries 7−9).

To rationalize this good *trans* stereoselectivity, we propose an iminium-based open transition state with the benzylic proton of the phenylglycinol moiety close to the trifluoromethyl group. The transition state leading to the *cis*-pyrrolidine would be higher in energy because of the sterically unfavorable proximity of the phenyl and trifluoromethyl groups (Figure 2). According to this transition state, the better diastereoselectivity observed for hindered Grignard reagents can be explained by the fact that their steric hindrance reinforces the repulsion between the CF_3 group and the phenyl group of the chiral auxiliary. Organolithium reagents are known to attack trifluoromethylated oxazolidines directly, mainly with retention of configuration.[32] The lower Lewis acidities of the organolithium reagents seem, in our case, to prevent the formation of the iminium. If this is true, then the absence of reactivity could be explained by the sterically hindered approach of the organolithium reagent to oxazolopyrrolidine (*R*)-**1** (Figure 2). All attempts to increase the reactivity of (*R*)-**1** toward organolithium reagents failed. No reaction occurred even upon increasing the number of equivalents of nucleophile, using organolithium in the presence of lithium bromide, increasing the temperature from 0 °C to room temperature, or preopening the oxazolopyrrolidine (*R*)-**1** by treatment with a Lewis acid ($BF_3{\cdot}OEt_2$).

The last step required for the synthesis of the target trifluoromethylated pyrrolidines consisted of the removal of the phenylethanol moiety. In the case of the phenyl-substituted pyrrolidine (*R*,*R*)-**3**, this cleavage could not be performed by hydrogenolysis because of an unselective cleavage of the two benzylic positions. However, the target pyrrolidine (*R*,*R*)-**9** could be obtained in enantiomerically pure form in 74% yield by oxidative cleavage of the phenylglycinol side chain promoted by cerium(IV) ammonium nitrate (CAN) (Scheme 6).

To demonstrate the efficiency of our strategy, a scaled-up procedure without any chromatographic purification was achieved starting from 10 g of **Fox** to give 1.93 g of pure pyrrolidine (*R*,*R*)-**9**. An overall yield of 21% was obtained for this procedure involving only two purification steps: distillation of oxazolopyrrolidine (*R*)-**1** and distillation of the final pyrrolidine (*R*,*R*)-**9**.

Synthesis of 5-Trifluoromethylproline (*R*,*S*)-13. A straightforward synthesis of 5-trifluoromethylproline (*R*,*S*)-**13**

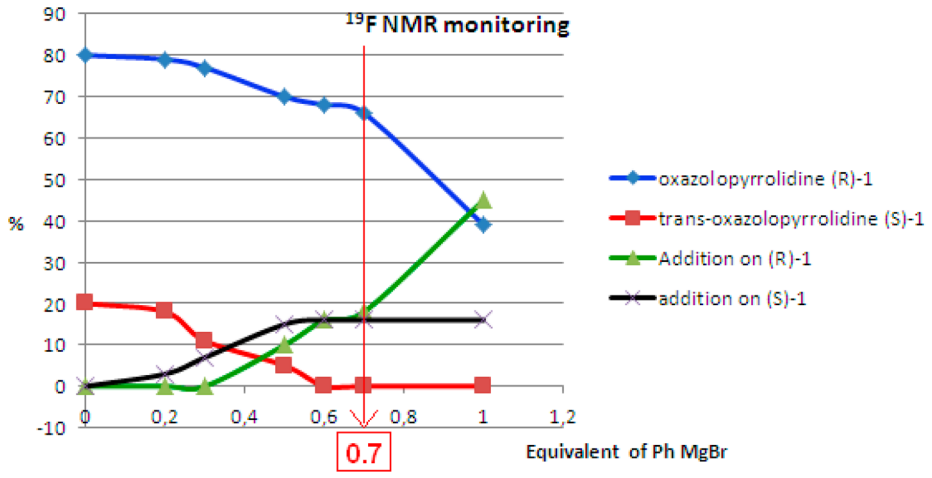


Figure 1. Monitoring of the addition reaction by ^{19}F NMR spectroscopy.

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Scheme 5. Separation of (*R*)-1 from (*S*)-1 by Selective Diastereomer Destruction

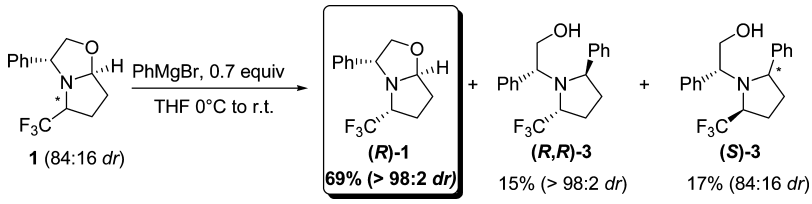
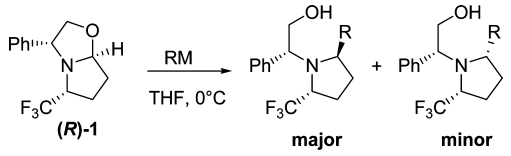


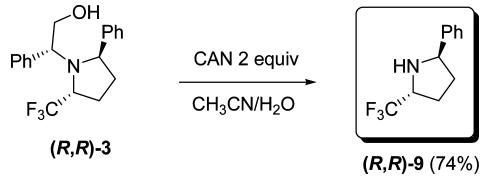
Table 1. Addition of Organometallics on (*R*)-1



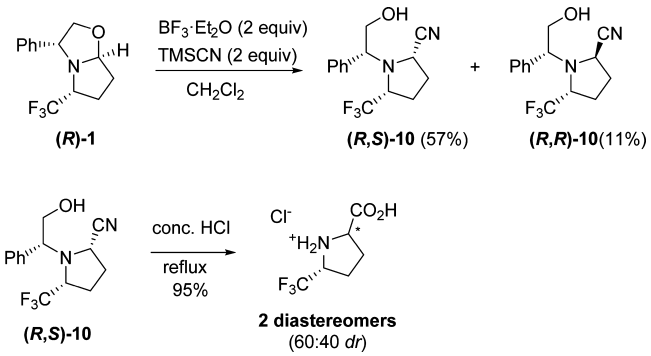
entry	RM	equiv	yield (%)	*de* (%)[a]	product
1	PhMgBr	2	97	>98	(*R*,*R*)-**3**
2	*i*-PrMgBr	4	61	>98	(*R*,*R*)-**4**
3	allyl-MgBr	4	73	84[b]	**5**
4	MeMgBr	3.3	95	70	**6**
5	vinyl-MgBr	4	52	68	**7**
6	*n*-BuMgBr	12	66	52	**8**
7	MeLi	2	0		
8	*n*-BuLi	2	0		
9	PhLi	2	0		

[a]Determined by ^{1}H and ^{19}F NMR analysis of the crude mixture. [b]>98% *de* after silica gel purification.

Scheme 6. Synthesis of Pyrrolidine (*R*,*R*)-9



Scheme 7. Strecker-Type Reaction on (*R*)-1



was envisioned through a three-step procedure involving a Strecker-type reaction on oxazolopyrrolidine (*R*)-**1** followed by hydrolysis of the corresponding aminonitrile and removal of the phenylglycinol side chain. This strategy has already been successfully employed for the preparation of several Tfm-amino acids.[29,30] The Strecker-type addition reaction on (*R*)-**1** was performed using trimethylsilyl cyanide as the cyanide donor in the presence of boron trifluoride diethyl etherate to promote the formation of the iminium intermediate (Scheme 7). Under these conditions, a diastereomeric mixture of amino nitriles **10** (70% *de*) was obtained in fairly good yield. In this case, a nonchelate transition state should lead to the major formation of the *cis* adduct (*R*,*S*)-**10**. Fortunately the two diastereomers were easily separated by silica gel chromatography to give the major amino nitrile (*R*,*S*)-**10** in 57% isolated yield and the minor isomer (*R*,*R*)-**10** in 11% yield. One-pot hydrolysis of the cyano group/removal of the phenylethanol moiety was tested on the enantiopure amino nitrile (*R*,*S*)-**10** in strongly acidic aqueous solution, but this resulted in partial epimerization of the target 5-trifluoromethylproline (Scheme 7).

To achieve the synthesis of the target enantiopure 5-trifluoromethylproline, the cyano group of amino nitrile (*R*,*S*)-**10** was converted into methyl ester (*R*,*S*)-**11** in 74% yield under acidic conditions without any epimerization (Scheme 8). In opposition to the results obtained in the nonfluorinated series,[34] we did not observe any formation of a bicyclic lactone. After saponification of the ester in the presence of LiOH and hydrogenolysis of the phenylethanol moiety, the expected (2*S*,5*R*)-5-trifluoromethylproline (*R*,*S*)-**13** was obtained in

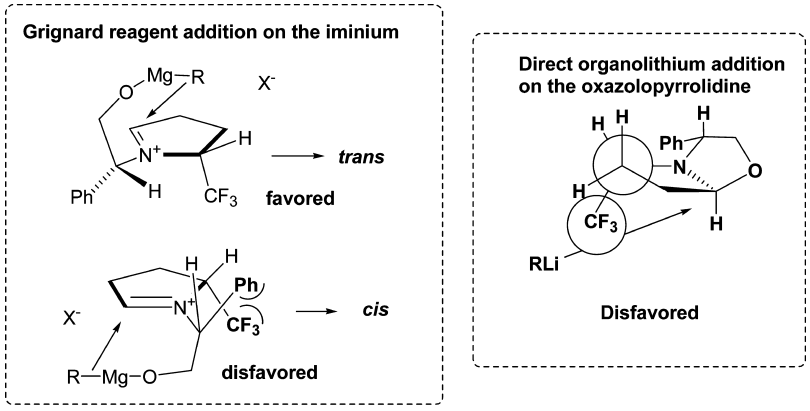


Figure 2. Proposed transition state.

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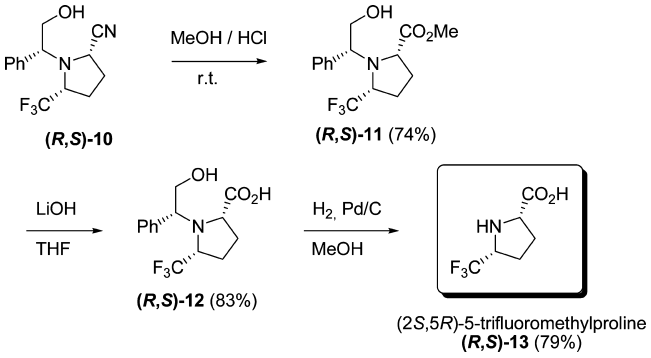
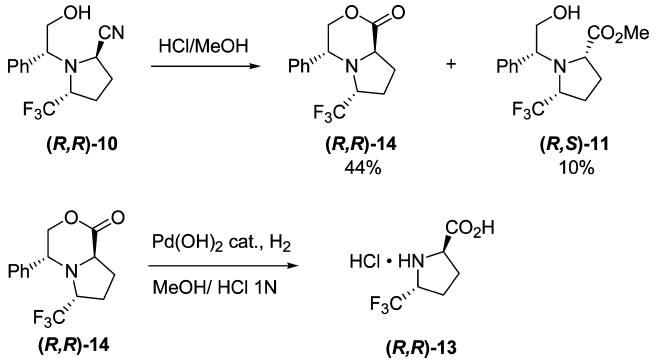
Scheme 8. Synthesis of (2*S*,5*R*)-5-Trifluoromethylproline (*R*,*S*)-13



Scheme 9. Synthesis of (2*R*,5*R*)-5-Trifluoromethylproline (*R*,*R*)-13



enantiopure form in 79% yield (Scheme 8). The *cis* relative configuration of (*R*,*S*)-**13** was deduced from the NMR data of the corresponding hydrochloride, which were rigorously identical to those recently reported by others in the racemic series.[27,28]

Determination of Absolute and Relative Configurations. As none of the new compounds synthesized were solids, X-ray crystallography could not be used to assign the absolute configurations of the trifluoromethylpyrrolidines. The absolute configuration of oxazolopyrrolidine (*R*)-**1** and pyrrolidine (*R*,*R*)-**9** could be assigned by NOE difference NMR experiments. For oxazolopyrrolidine (*R*)-**1**, the strong correlation between the proton at the α position of the phenyl group (H_3) and the proton at the α position of the trifluoromethyl group (H_5) clearly indicated the (*R*) configuration of the corresponding carbon (C_5). A similar correlation between the proton of the ring junction (H_8) and the pro-*S* proton of the phenylglycinol methylene ($H_{2'}$) allowed us to assign the (*S*) configuration to the ring junction. Using the same methodology on pyrrolidine (*R*,*R*)-**9**, we observed correlations between two sets of three protons corresponding to the two faces of the five-membered ring, confirming the *trans* configuration of the phenyl and trifluoromethyl groups (Figure 3).

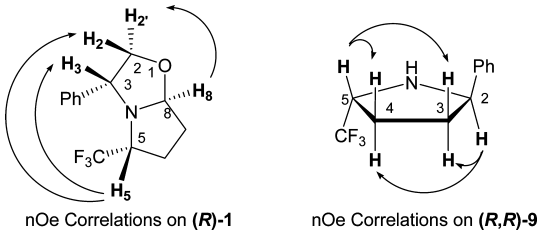


Figure 3. NOE experiments on (*R*)-**1** and (*R*,*R*)-**9**.

The configurations of pyrrolidines **4**−**11** were determined by comparison with ^{1}H NMR data for (*R*,*R*)-**3** according to the coupling constants and the chemical shifts of the cyclic protons. Further confirmation of the *cis* configuration of the major amino nitrile (*R*,*S*)-**10** and the final 5-trifluoromethylproline (*R*,*S*)-**13** was given indirectly by the synthesis of an analytical sample of (2*R*,5*R*)-5-trifluoromethylproline (*R*,*R*)-**13** and comparison of its NMR data with those for (*R*,*S*)-**13**. When the minor amino nitrile (*R*,*R*)-**10** was treated with an acidic methanol solution, *trans*-bicyclic lactone (*R*,*R*)-**14** was formed together with amino ester (*R*,*S*)-**11** (Scheme 9). The structure of *trans*-bicyclic lactone (*R*,*R*)-**14** was unambiguously determined by X-ray crystallography (cf. the Supporting Information). The palladium-catalyzed hydrogenolysis of a small quantity of lactone (*R*,*R*)-**14** afforded an analytical quantity of (*R*,*R*)-**13** hydrochloride presenting a *trans* configuration (Scheme 9).[36]

CONCLUSIONS

We have shown that the chiral fluorinated oxazolopyrrolidine (*R*)-**1** could be readily synthesized on a multigram scale starting from a fluorinated oxazolidine (Fox) using an organometallic-addition-based kinetic resolution. The addition of the Grignard reagent on (*R*)-**1** was diastereoselective, with hindered reagents leading to the *trans* adduct as the major product. Surprisingly, no addition reaction could be performed with organolithium reagents. The synthetic potential of this methodology was demonstrated by the scalable synthesis of enantiopure (2*R*,5*R*)-2-phenyl-5-trifluoromethylpyrrolidine (*R*,*R*)-**9**. Similarly, highly valuable enantiopure (2*S*,5*R*)-5-trifluoromethylproline (*R*,*S*)-**13** was synthesized in a few steps from the same oxazolopyrrolidine (*R*)-**1** via a Strecker-type reaction.

EXPERIMENTAL SECTION

(*R*)-2-[(1*R*)-(*Z*)-1-Trifluoromethyl-4-methoxybut-3-enylamino]-2-phenylethanol (2). To a solution of allyl methyl ether (20.2 g, 280.5 mmol, 3.0 equiv) in THF (220 mL) under an argon atmosphere at −78 °C was added dropwise a solution of *s*-BuLi (251.7 mL, 1.3 M in hexanes, 327.2 mmol, 3.5 equiv). The reaction mixture was stirred at −78 °C for 45 min. A solution of the diastereomeric Fox mixture (20.3 g, 93.5 mmol, 1.0 equiv) in THF (220 mL) was then added dropwise over a period of 30 min, and the reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched at −78 °C with a saturated NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product (33.9 g) as yellow oil. The desired amino alcohol **2** was obtained as a mixture of two diastereomers (84:16 *dr*). The crude mixture was employed in the next step without any purification. For characterization purposes, the reaction was performed starting from a small quantity of oxazolidine (0.434 g, 2 mmol) to give after purification by silica gel chromatography (cyclohexane/ethyl acetate 90:10 to 95:5) a diastereomeric mixture of (*R*)-**2** and (*S*)-**2** (0.383 g, 66%). A pure analytical sample of the major diastereomer (*R*)-**2** could be obtained. $[\alpha]_D$ −52.2 (*c* = 1.0, $CHCl_3$); IR 3341, 2935, 1665, 1454, 1397, 1264, 1224, 1129, 1105, 1025, 931, 758, 700 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.16 (bs, 2H, NH), 2.26−2.34 (ddd, 1H, *J* = 14.1, 13.5, 6.6 Hz), 2.59 (ddd, 1H, *J* = 14.1, 8.5, 5.3 Hz), 3.04 (ddq, 1H, *J* = 13.5, 5.3 Hz, J_{H-F} = 8.0 Hz), 3.55 (dd, 1H, *J* = 10.9, 8.1 Hz), 3.63 (s, 3H), 3.70 (dd, 1H, *J* = 10.9, 4.4 Hz), 4.03 (dd, 1H, *J* = 8.1, 4.4 Hz), 4.44 (ddd, 1H, *J* = 8.5, 6.6, 6.2 Hz), 6.09 (d, 1H, *J* = 6.2 Hz), 7.22−7.39 (m, 5H); ^{13}C NMR (100.5 MHz) δ

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23.0, 56.6 (q, J_{C-F} = 27.8 Hz), 59.8, 62.5, 67.4, 100.4, 126.5 (q, J_{C-F} = 282.1 Hz), 127.8, 127.9, 128.7, 140.1, 149.4; ^{19}F NMR (376.2 MHz) δ −77.7 (d, 3F, J_{H-F} = 8.0 Hz); HRMS (EI+, direct inlet probe) m/z [M$^+$] calcd for $C_{14}H_{18}F_3NO_2$ 289.1290, found 289.1290.

(3*R*,5*R*,7a*S*)-3-Phenyl-5-(trifluoromethyl)hexahydropyrrolo-[2,1-*b*]oxazole ((*R*)-1). To a solution of crude amino alcohol **3** (13.3 g, 46.04 mmol, 1.0 equiv) in diethyl ether (175 mL) was slowly added a sulfuric acid aqueous solution over 15 min (172.65 mL, 2 M, 345.3 mmol, 7.5 equiv). After 2 min of vigorous stirring, the aqueous layer was extracted with diethyl ether (3 × 75 mL). The organic layers were combined, washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the desired bicyclic oxazolidines **1** as a mixture of two diastereomers (84:16 *dr*). Purification by silica gel chromatography afforded the pure bicyclic oxazolidines (7.8 g, 30.4 mmol, 66%) as an inseparable mixture of two diastereoisomers (*R*)-**1** and (*S*)-**1** (84:16 *dr*). To the mixture of bicyclic oxazolidines **1** (7.8 g, 30.3 mmol, 1.0 equiv) in THF (150 mL) under an argon atmosphere at 0 °C was added dropwise a solution of PhMgCl over 5 min (3.2 mL, 25% in THF, 6.1 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature for 16 h. Aliquots were taken at regular intervals and worked up, and the evolution of the reaction was monitored by ^{19}F NMR spectroscopy. After 16 h of stirring, an additional amount of PhMgCl solution (8.0 mL, 25% in THF, 15.2 mmol, 0.5 equiv) was added to allow the completion of the reaction after 3 h of stirring. The reaction was quenched at 0 °C with a saturated NH_4Cl solution (75 mL). The aqueous layer was extracted with DCM (3 × 100 mL). The organic layers were combined, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 90:10) to provide the diastereomerically pure bicyclic oxazolidine (*R*)-**1** as a colorless oil (5.348 g, 20.79 mmol, 69%, >98% *de*). Alternatively, the crude reaction mixture could also be purified by distillation under vacuum to give (*R*)-**1** as a colorless oil (bp 110 °C, 1 mbar). $[\alpha]_D$ −52.2 (c = 1.0, $CHCl_3$); IR 2872, 1497, 1451, 1396, 1376, 1282, 1183, 1153, 1123, 1024, 986, 890, 755, 698 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.96−2.13 (m, 2H), 2.17−2.32 (m, 2H), 3.42 (ddq, 1H, J = 8.0, 3.7 Hz, J_{H-F} = 7.6 Hz), 3.59 (dd, 1H, J = 8.2, 6.6 Hz), 4.28−4.37 (m, 2H), 4.96 (d, 1H, J = 4.1 Hz), 7.23−7.27 (m, 1H), 7.31−7.39 (m, 4H); ^{13}C NMR (100.5 MHz) δ 24.0, 29.9, 68.2 (q, J_{C-F} = 29.7 Hz), 70.6, 73.3, 98.9, 126.3, 126.4 (q, J_{C-F} = 278.9 Hz), 127.3, 128.6, 141.5; ^{19}F NMR (376.2 MHz) δ −79.7 (d, 3F, J_{H-F} = 7.6 Hz); HRMS (EI+, direct inlet probe) m/z [M$^+$] calcd for $C_{13}H_{14}F_3NO$ 257.1027, found 257.1025.

General Procedure for the Synthesis of Trifluoromethylated Pyrrolidines 3−8. To a solution of bicyclic oxazolidine (*R*)-**1** (1.0 equiv) in THF under argon at 0 °C was added dropwise a solution of the Grignard reagent over 5 min. The reaction mixture was stirred at room temperature for 2 h, and the evolution of the reaction was monitored by ^{19}F NMR spectroscopy. If necessary, a second portion of the organometallic reagent, identical to the first one, was added. After 8 h of stirring at room temperature, the reaction was quenched with a saturated NH_4Cl solution. The aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography to provide the pure pyrrolidine.

(R)-2-Phenyl-2-[(2R,5R)-5-trifluoromethyl-2-phenylpyrrolidin-1-yl]ethanol ((R,R)-3). Obtained from (*R*)-**1** (3.9 g, 15.0 mmol, 1.0 equiv) in THF (75 mL) following the general procedure using PhMgCl (15.8 mL, 25% in THF, 30.0 mmol, 2.0 equiv). The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 75:25) to provide the pure pyrrolidine (*R*,*R*)-**3** (4.9 g, 14.5 mmol, 97%, >98% *de*) as a colorless oil. $[\alpha]_D$ −48.9 (c = 1.15, $CHCl_3$); IR 3374, 2888, 1493, 1452, 1380, 1269, 1129, 1108, 1077, 1022, 869, 797, 759, 698 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.66−1.72 (m, 1H), 1.95−2.05 (m, 2H), 2.17 (tt, 1H, J = 11.0, 8.5 Hz), 2.34 (tt, 1H, J = 13.2, 8.5 Hz), 3.67 (dd, 1H, J = 11.0, 7.3 Hz), 3.80−3.88 (m, 2H), 4.20 (t, 1H, J = 7.3 Hz), 4.42 (dd, 1H, J = 8.0, 3.4 Hz), 7.01−7.06 (m, 2H), 7.17−7.37 (m, 8H); ^{13}C NMR (100.5 MHz) δ 25.5, 32.5, 60.3 (q, J_{C-F} = 29.7 Hz), 61.4, 63.0, 65.8, 127.5 (q, J_{C-F} = 286.6 Hz), 127.6, 127.8, 127.8, 128.5, 128.7, 129.2, 137.6, 144.5; ^{19}F NMR (376.2 MHz) δ −76.2 (d, 3F, J_{H-F} = 7.8 Hz); HRMS (EI+, direct inlet probe) m/z [M$^+$] calcd for $C_{19}H_{20}F_3NO$ 335.1497, found 335.1497.

(R)-2-[(2R,5R)-2-Isopropyl-5-trifluoromethylpyrrolidin-1-yl]-2-phenylethanol ((R,R)-4). Obtained from (*R*)-**1** (1.5 g, 5.8 mmol, 1.0 equiv) in THF (15 mL) following the general procedure using two additions of *i*-PrMgBr (2 × 3.9 mL, 3.0 M in THF, 2 × 11.7 mmol, 4.0 equiv). The crude material was purified by silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 75:25) to provide the pure pyrrolidine (*R*,*R*)-**4** (1.1 g, 3.5 mmol, 61%, >98% *de*) as a colorless oil. $[\alpha]_D$ −20.2 (c = 1.0, $CHCl_3$); IR 3416, 2960, 2875, 1471, 1451, 1389, 1370, 1270, 1162, 1129, 1091, 1035, 945, 762, 701 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.91 (d, 3H, J = 6.6 Hz), 1.05 (d, 3H, J = 6.4 Hz), 1.13−1.20 (m, 1H), 1.44−1.54 (m, 1H), 1.67 (ddd, 1H, J = 8.6, 5.7, 2.9 Hz), 1.70−1.78 (m, 1H), 2.16 (dqq, 1H, ^3J = 7.3, 6.6, 6.4 Hz), 2.70 (bs, 1H), 3.02 (q, 1H, J = 7.3 Hz), 3.76 (dd, 1H, J = 11.0, 5.9 Hz), 3.77 (quint d, 1H, J = 8.8, 2.5 Hz), 3.93 (dd, 1H, J = 11.0, 9.3 Hz), 4.34 (dd, 1H, J = 9.3, 5.9 Hz), 7.23−7.37 (m, 5H); ^{13}C NMR (100.5 MHz) δ 19.0, 21.0, 24.9, 27.5, 28.8, 59.6, 59.7 (q, J_{C-F} = 28.8 Hz), 62.6, 69.0, 124.8 (q, J_{C-F} = 291.4 Hz), 127.9, 128.7, 128.9, 138.5; ^{19}F NMR (376.2 MHz) δ −76.8 (bs, 3F); HRMS (EI+, direct inlet probe) m/z [M$^+$] calcd for $C_{16}H_{22}F_3NO$ 301.1653, found 301.1644.

(R)-2-[(2R,5R)-2-Allyl-5-trifluoromethylpyrrolidin-1-yl]-2-phenylethanol (5). Obtained from (*R*)-**1** (0.26 g, 1.0 mmol, 1.0 equiv) in THF (3 mL) following the general procedure using two additions of allyl-MgBr (2 × 2.0 mL, 1.0 M in diethyl ether, 2 × 2.0 mmol, 4.0 equiv). The crude product (0.3 g, 84% *de*) was purified by silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 95:5) to provide the pure major pyrrolidine **5** (0.22 g, 0.73 mmol, 73%, >98% *de*) as a colorless oil. The minor diastereoisomer could not be isolated. $[\alpha]_D$ −93.0 (c = 1.28, $CHCl_3$); IR 3423, 2980, 2903, 1640, 1495, 1451, 1379, 1281, 1156, 1131, 1073, 1055, 1026, 914, 848, 763 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.17 (ddt, 1H, J = 13.5, 12.4, 8.4 Hz), 1.59 (dddd, 1H, J = 12.8, 12.6, 8.4, 6.9 Hz), 1.78 (dd, 1H, J = 13.5, 6.9 Hz), 1.82 (dd, 1H, J = 12.8, 6.9 Hz), 2.20 (dt, 1H, J = 14.7, 7.4 Hz), 2.57 (dddd, 1H, J = 14.7, 6.9, 5.0, 1.4 Hz), 2.72 (bs, 1H), 3.35 (ddt, 1H, ^3J = 8.4, 7.4, 5.0 Hz), 3.47 (dq, 1H, J_{H-F} = 8.6 Hz, J = 8.4 Hz), 3.71 (dd, 1H, J = 10.2, 3.2 Hz), 3.96 (dd, 1H, J = 10.8, 10.2 Hz), 4.01 (dd, 1H, J = 10.2, 3.9 Hz), 5.08 (dt, 1H, J = 10.2, 0.9 Hz), 5.14 (ddd, 1H, J = 17.3, 1.4, 0.9 Hz), 5.84 (dddd, 1H, ^3J = 17.3, 10.2, 7.4, 6.9 Hz), 7.21−7.40 (m, 5H); ^{13}C NMR (100.5 MHz) δ 26.4, 29.9, 40.2, 59.1 (q, $^2J_{C-F}$ = 29.7 Hz), 62.4, 65.0, 65.9, 117.3, 126.9 (q, $^1J_{C-F}$ = 280.8 Hz), 128.5, 128.7, 128.9, 135.3, 136.3; ^{19}F NMR (376.2 MHz) δ −78.2 (d, 3F, J_{H-F} = 8.6 Hz); HRMS (EI+, direct inlet probe) m/z [M$^+$] calcd for $C_{16}H_{20}F_3NO$ 299.1497, found 299.1494.

(R)-2-[(2S,5R)-2-Methyl-5-trifluoromethylpyrrolidin-1-yl]-2-phenylethanol (6). Obtained from (*R*)-**1** (0.26 g, 1.0 mmol, 1.0 equiv) in THF (3 mL) following the general procedure using two additions of MeMgBr (0.34 mL + 0.7 mL, 3.2 M in MeTHF, 1.1 + 2.2 mmol, 1.1 + 2.2 equiv). The crude material (0.26 g, 0.95 mmol, 95%, 70% *de*) was purified by silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 95:5) to provide the pyrrolidines **9** as a mixture of two diastereomers (0.17 g, 0.64 mmol, 6%, 70% *de*) as a colorless oil. Separation of the two diastereoisomers could not be achieved by silica gel chromatography. The NMR data for the major *trans* diastereoisomer **6** were determined from the mixture. IR 3390, 2964, 2897, 1496, 1451, 1380, 1280, 1186, 1127, 1072, 1031, 942, 899, 852, 762, 699 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.28 (d, 1H, ^3J = 6.6 Hz), 1.24−1.35 (m, 1H), 1.71−1.86 (m, 2H), 1.96−2.05 (m, 1H), 3.52 (qd, 1H, J_{H-F} = 8.0 Hz, J = 3.0 Hz), 3.60 (sext, 1H, J = 6.6 Hz), 3.75 (dd, 1H, J = 10.8, 5.8 Hz), 3.94 (dd, 1H, J = 10.8, 9.4 Hz), 4.33 (dd, 1H, J = 9.4, 5.8 Hz), 7.22−7.43 (m, 5H); ^{13}C NMR (100.5 MHz) δ 19.2, 24.9, 32.2, 58.8 (q, $^2J_{C-F}$ = 29.7 Hz), 59.2, 60.8, 63.3, 127.2 (q, $^1J_{C-F}$ = 283 Hz), 127.9, 128.2, 128.8, 128.9, 137.9; ^{19}F NMR (376.2 MHz) δ −78.85 (d, 3F, J_{H-F} = 8.0 Hz); HRMS (EI+, direct inlet probe) m/z [M$^+$] calcd for $C_{14}H_{18}F_3NO$ 273.1340, found 273.1341.

(R)-2-Phenyl-2-[(2R,5R)-2-trifluoromethyl-5-vinylpyrrolidin-1-yl]-ethanol (7). Obtained from (*R*)-**1** (1.5 g, 5.9 mmol, 1.0 equiv) in THF (10 mL) following the general procedure using two equal additions of vinyl-MgBr (2 × 16.7 mL, 0.7 M in THF, 2 × 11.7 mmol, 4.0 equiv). The crude product (1.3 g) was purified by silica gel chromatography

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(cyclohexane/ethyl acetate 100:0 to 90:10) to provide an inseparable mixture of pyrrolidines **7** (0.9 g, 3.0 mmol, 52%, 68% *de*) as a yellow oil. IR 3368, 2873, 1714, 1700, 1455, 1403, 1373, 1267, 1131, 1083, 1028, 877, 737, 723, 701 cm^{-1}; ^1H NMR (400 MHz) δ 1.28−1.35 (m, 1H), 1.45−1.69 (m, 1H), 1.80−1.91 (m, 1H), 2.00−2.27 (m, 1H), 2.89−3.28 (m, 1H), 3.31−3.62 (m, 1H), 3.62−4.07 (m, 2H), 4.17−4.44 (m, 1H), 4.79−5.40 (m, 2H), 5.42−5.71 (m, 0.16H), 5.83 (ddd, 0.8H, J = 16.5, 10.3, 9.4), 7.26−7.36 (m, 5H); ^{13}C NMR (100.5 MHz) δ 25.0, 29.7 (minor), 30.4, 52.3 (minor), 58.2 (q, $^2J_{C-F}$ = 29.7 Hz), 61.4, 62.3 (minor), 63.0, 66.7 (minor), 67.6, 98.6 (minor), 117.4, 126.8 (q, $^1J_{C-F}$ = 282.7 Hz), 127.7, 128.2, 128.5, 129.0, 137.2, 139.9; ^{19}F NMR (376.2 MHz) δ −78.03 (d, 2.52F, J_{H-F} = 7.8), −79.70 (d, 0.48F, J_{H-F} = 7.8 Hz); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{19}F_3NO$ 286.1419, found 286.1420.

*(R)-2-[(5R)-2-Butyl-5-trifluoromethylpyrrolidin-1-yl]-2-phenylethanol (**8**).* Obtained from (**R**)-**1** (0.26 g, 1.0 mmol, 1.0 equiv) in THF (3 mL) following the general procedure using two additions of *n*-BuMgCl (1.2 + 5.9 mL, 20% in THF and toluene, 2.0 + 10 mmol, 2 + 10 equiv). The crude product (0.32 g) was purified by silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 96:4) to provide an inseparable mixture of pyrrolidines **8** (0.2 g, 0.7 mmol, 66%, 52% *de*) as a colorless oil. ^1H NMR (400 MHz) δ 0.94 (t, 3H, J = 7.1 Hz), 1.19−1.50 (m, 6H), 1.58−1.67 (m, 1H), 1.70−1.79 (m, 1H), 1.82−1.96 (m, 2H), 2.69 (bs, 1H), 3.20−3.27 (m, 0.2H) (minor), 3.28−3.36 (m, 0.8H) (major), 3.43 (p, 0.2H, J = 8.9 Hz) (minor), 3.55−3.63 (m, 0.8H) (major), 3.68−3.77 (m, 1H), 3.89−4.0 (m, 1.2H), 4.32 (dd, 0.8H, J = 9.6, 5.5 Hz) (major), 7.20−7.39 (m, 5H); ^{13}C NMR (100.5 MHz) δ 14.1, 22.9, 24.5, 26.4 (minor), 26.9 (major), 28.8 (minor), 29.6, 30.0, 32.0 (major), 35.7 (minor), 58.7 (q, J = 28.7 Hz) (minor), 58.9 (q, J = 28.7 Hz) (major), 60.1, 62.1 (minor), 62.9 (major), 64.1, 65.5, 126.7 (q, J = 280.8 Hz) (minor), 127.1 (q, J = 270.3 Hz) (major), 127.8 (major), 128.2 (minor), 128.6 (2C), 128.7 (2C), 136.1 (minor), 138.2 (major); ^{19}F NMR (376.2 MHz) δ −77.6 (d, 3F, J = 8.6 Hz) (major), −78.4 (d, 3F, J = 8.6 Hz) (minor); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{25}F_3NO$ 316.1888, found 316.1888.

(2*R*,5*R*)-2-Phenyl-5-trifluoromethylpyrrolidine ((*R*,*R*)-9). To a solution of pyrrolidine (**R**,**R**)-**3** (4.1 g, 12.1 mmol, 1.0 equiv) in a 1:1 mixture of acetonitrile and water (120 mL) at room temperature was added CAN (14.6 g, 26.7 mmol, 2.2 equiv). The reaction mixture became black and was stirred at room temperature for 3 min. K_2CO_3 was added, and the reaction mixture was stirred for 10 min at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 25 mL), and the organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture (3.511 g) was distilled under reduced pressure (75 °C, 2 × 10^{-1} mbar), and the desired pyrrolidine (**R**,**R**)-**9** (1.9 g, 9.0 mmol, 74%) was obtained as a colorless liquid. $[\alpha]_D$ +34.9 (c = 1.0, $CHCl_3$); IR 3365, 3030, 2971, 1603, 1493, 1452, 1373, 1273, 1145, 1109, 1028, 943, 877, 757, 698 cm^{-1}; ^1H NMR (400 MHz) δ 1.76 (dq, 1H, J = 12.2, 8.2 Hz), 2.00 (dddd, 1H, J = 13.3, 8.2, 6.2, 5.7 Hz), 2.10 (bs, 1H), 2.20 (dtd, 1H, J = 13.3, 8.2, 5.0 Hz), 2.31 (dq, 1H, J = 12.2, 6.2 Hz), 3.93 (qdd, 1H, $^3J_{H-F}$ = 8.2 Hz, J = 8.2, 5.7 Hz), 4.37 (dd, 1H, J = 8.2, 6.2 Hz), 7.23−7.36 (m, 5H); ^{13}C NMR (100.5 MHz) δ 25.5, 34.3, 59.0 (q, $^2J_{C-F}$ = 29.7 Hz), 62.2, 126.3, 127.2 (q, $^1J_{C-F}$ = 281.8 Hz), 124.4, 128.7, 143.9; ^{19}F NMR (376.2 MHz) δ −80.04 (d, 3F, $^3J_{H-F}$ = 8.2 Hz); HRMS (EI+, direct inlet probe) m/z $[M^+]$ calcd for $C_{11}H_{12}F_3N$ 215.0922, found 215.0929.

(2*S*,5*R*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-2-cyano-5-trifluoromethylpyrrolidine ((*R*,*S*)-10) and (2*R*,5*R*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-2-cyano-5-trifluoromethylpyrrolidine ((*R*,*R*)-10). To a solution of pure (**R**)-**1** (3.9 g, 15.0 mmol, 1.0 equiv) in DCM (45 mL) under an argon atmosphere at 0 °C was slowly added boron trifluoride etherate (3.8 mL, 30 mmol, 2.0 equiv). The reaction mixture was stirred at 0 °C for 15 min, and then TMSCN (4.0 mL, 30 mmol, 2.0 equiv) was added dropwise over 5 min. The reaction mixture was slowly allowed to warm to room temperature and stirred overnight. The reaction was quenched at 0 °C with a saturated solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with DCM (3 × 50 mL). The organic layers were combined, washed with 2 M NaOH and water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude product (3.7 g, 70% *de*) by silica gel chromatography (cyclohexane/ethyl acetate 100/0 to 60/40) afforded the pure pyrrolidines (**R**,**S**)-**10** (2.4 g, 57%, >98% *de*) and (**R**,**R**)-**10** (0.5 g, 11%) as yellow oils. (**R**,**S**)-**10**: $[\alpha]_D$ −82.5 (c = 2.9, $CHCl_3$); IR 3459, 2887, 1495, 1452, 1381, 1278, 1154, 1117, 1146, 942, 882, 829, 763, 735, 700, 654 cm^{-1}; ^1H NMR (400 MHz) δ 1.74 (dq, 1H, J = 13.5, 8.9 Hz), 2.00−2.06 (m, 1H), 2.21 (dd, 2H, J = 14.0, 7.5 Hz), 2.67 (bs, 1H), 3.82 (quint d, 1H, J = 8.0, 2.6 Hz), 3.95 (dd, 1H, J = 11.5, 5.3 Hz), 4.07 (dd, 1H, J = 11.5, 8.6 Hz), 4.12 (t, 1H, J = 7.5 Hz), 4.19 (dd, 1H, J = 8.6, 5.3 Hz), 7.29−7.40 (m, 5H). ^{13}C NMR (100.5 MHz) δ 26.0, 30.1, 52.0, 61.4 (q, J_{C-F} = 29.7 Hz), 62.0, 66.0, 120.2, 126.2 (q, $^1J_{C-F}$ = 280.8 Hz), 128.1, 128.5, 128.9, 136.5; ^{19}F NMR (376.2 MHz) δ −78.6 (d, 3F, J_{H-F} = 8.0 Hz); HRMS (EI+, direct inlet probe) m/z $[M^+]$ calcd for $C_{14}H_{15}F_3N_2O$ 284.1136, found 284.1133. (**R**,**R**)-**10**: $[\alpha]_D$ +0.1 (c = 2.7, $CHCl_3$); IR 3459, 2887, 1495, 1452, 1381, 1278, 1154, 1117, 1146, 942, 882, 829, 763, 735, 700, 654 cm^{-1}; ^1H NMR (400 MHz) δ 2.03−2.33 (m, 5H, OH), 3.83 (quint d, 1H, J = 7.4, 1.0 Hz), 4.02 (d, 1H, J = 6.6 Hz), 4.13 (dd, 1H, J = 11.0, 5.9 Hz), 4.43 (dd, 1H, J = 11.0, 8.9 Hz), 4.59 (dd, 1H, J = 8.9, 5.9 Hz), 7.27−7.41 (m, 5H); ^{13}C NMR (100.5 MHz) δ 26.1, 30.0, 52.0, 59.3 (q, J_{C-F} = 29.7 Hz), 62.3, 62.8, 121.7, 126.4 (q, J_{C-F} = 282.8 Hz), 128.4, 128.5, 129.1, 136.5; ^{19}F NMR (376.2 MHz) δ −78.5 (d, 3F, J_{H-F} = 7.4 Hz); HRMS (EI+, direct inlet probe) m/z $[M^+]$ calcd for $C_{14}H_{15}F_3N_2O$ 284.1136, found 284.1150.

(2*S*,5*R*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-2-methoxycarbonyl-5-trifluoromethylpyrrolidine ((*R*,*S*)-11). Amino nitrile (**R**,**S**)-**10** (1.3 g, 4.7 mmol, 1.0 equiv) was dissolved in methanol saturated with gaseous hydrogen chloride (25 mL) and stirred overnight at room temperature. The reaction was quenched by careful addition of a saturated solution of $NaHCO_3$ (50 mL), and the mixture was extracted with DCM (3 × 50 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product (1.4 g) by silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 70:30) afforded the pure methyl ester (**R**,**S**)-**11** (1.1 g, 74%, >98% *de*) as a colorless oil. $[\alpha]_D$ −107.8 (c = 1.1, $CHCl_3$); IR 3435, 2954, 1734, 1282, 1154, 1116, 1044, 763, 701 cm^{-1}; ^1H NMR (400 MHz) δ 1.30−1.45 (m, 1H), 1.73 (bs, 1H), 1.88 (dd, 1H, J = 13.3, 6.9 Hz), 2.01 (ddd, 1H, J = 14.6, 8.2, 6.9 Hz), 2.18 (dt, 1H, J = 14.6, 8.0 Hz), 3.44 (quint, 1H, J = 8.2 Hz), 3.71−3.83 (m, 1H), 3.78 (s, 3H), 3.97 (bd, 1H, J = 9.6 Hz), 4.04 (dd, 1H, J = 12.3, 9.6 Hz), 4.12 (dd, 1H, J = 8.2, 8.0 Hz), 7.20−7.29 (m, 2H), 7.31−7.45 (m, 3H); ^{13}C NMR (100.5 MHz) δ 26.8, 28.5, 52.4, 59.2 (J_{C-F} = 30.7 Hz), 62.4, 67.3, 67.8, 126.3 (J_{C-F} = 281.8 Hz), 128.1 (2C), 128.5, 128.9 (2C), 135.9, 174.6; ^{19}F NMR (376.2 MHz) δ −78.2 (d, 3F, J_{H-F} = 7.9 Hz); HRMS (EI+, direct inlet probe) m/z $[M^+]$ calcd for $C_{15}H_{18}F_3NO_3$ 317.1239, found 317.1249.

(2*S*,5*R*)-1-[(*R*)-2-Hydroxy-1-phenylethyl]-5-trifluoromethylpyrrolidine-2-carboxylic Acid ((*R*,*S*)-12). (**R**,**S**)-**11** (1.0 g, 3.2 mmol, 1 equiv) was dissolved in THF (17 mL), and a solution of LiOH (3.5 mL, 1 M in H_2O, 1.1 equiv) was added dropwise at 0 °C. The resulting yellow solution was stirred overnight at room temperature, diluted with water (10 mL), acidified with 1 N HCl solution (pH ≈ 1), and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure, and the crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate 100:0 to 90:10) to give (**R**,**S**)-**12** (0.8 g, 83%, >98% *de*) as a white solid. Mp = 126−127 °C; $[\alpha]_D$ −93.1 (c = 0.61, $CHCl_3$); IR 2976, 2161, 2030, 1588, 1365, 1292, 1165, 1089, 1052, 820, 778, 702, 663 cm^{-1}; ^1H NMR (400 MHz) δ 1.41−1.54 (m, 1H), 1.86−1.95 (m, 1H), 2.02−2.13 (m, 1H), 2.24−2.33 (m, 1H), 3.52−3.62 (m, 1H), 3.88−3.94 (m, 1H), 4.08−4.22 (m, 3H), 7.20−7.25 (m, 2H), 7.34−7.42 (m, 3H); ^{13}C NMR (100.5 MHz) δ 27.0, 28.7, 60.1 (q, J_{C-F} = 29.7 Hz), 62.2, 67.2, 67.5, 125.9 (q, J_{C-F} = 206.1 Hz), 128.0 (2C), 128.8, 129.1 (2C), 135.3, 176.2; ^{19}F NMR (376.2 MHz) δ −77.9 (d, 3F, J_{H-F} = 7.6 Hz); HRMS (EI+, direct inlet probe) m/z $[M^+]$ calcd for $C_{14}H_{16}F_3NO_3$ 303.1082, found 303.1074.

(2*S*,5*R*)-5-Trifluoromethylproline ((*R*,*S*)-13). (**R**,**S**)-**12** (0.7 g, 2.2 mmol, 1 equiv) was dissolved in MeOH (22 mL), and a catalytic amount of palladium stabilized over charcoal (0.2 g, 10 wt %, 0.2

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mmol, 0.1 equiv) was carefully added. The heterogeneous mixture was stirred for 1 h under a H_2 atmosphere (gas balloon), filtered over Celite, and concentrated under reduced pressure. The crude product was crystallized in a minimum (2 mL) of a 1:1 pentane/Et_2O mixture to give (*R*,*S*)-**13** (0.315 g, 79%) as a white solid. Mp 80−81 °C; $[\alpha]_D$ −63.2 (*c* = 1.0, $CHCl_3$); IR 2976, 2161, 2030, 1588, 1365, 1292, 1165, 1089, 1052, 820, 778, 702, 663 cm^{-1}; ^1H NMR (400 MHz) δ 1.96 (dtd, 1H, *J* = 13.3, 7.3, 5.9 Hz), 2.15 (dq, 1H, *J* = 13.3, 7.3 Hz), 2.19−2.33 (m, 1H), 3.90 (sext, 1H, *J* = 7.3 Hz), 4.01−4.09 (m, 1H), 7.37 (bs, 2H); ^{13}C NMR (100.5 MHz) δ 25.7, 29.6, 59.8 (q, 3F, J_{C-F} = 30.7 Hz), 60.2, 125.8 (q, J_{C-F} = 277.9 Hz), 177.4; ^{19}F NMR (376.2 MHz) δ −79.2 (d, 3F, J_{H-F} = 7.3 Hz); HRMS (EI+, direct inlet probe) *m*/*z* [M^+] calcd for $C_6H_8F_3NO_2$ 183.0507, found 183.0507.

(4*R*,6*R*,8a*R*)-4-Phenyl-6-(trifluoromethyl)hexahydropyrrolo-[2,1-*c*][1,4]oxazin-1-one ((*R*,*R*)-14). A solution of (*R*,*R*)-**10** (0.4 g, 1.4 mmol, 1 equiv) was dissolved in methanol saturated with gaseous hydrogen chloride (7 mL), and the solution was stirred at room temperature until completion of the reaction (48 h). The reaction was quenched with $NaHCO_3$ (5 mL), and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (cyclohexane/ethyl acetate 100/0 to 70/30). The *trans*-lactone (*R*,*R*)-**14** (0.2 g, 0.6 mmol, 74%) was obtained as a white solid. Mp 104−105 °C; $[\alpha]_D$ +33.8 (*c* = 1.0, $CHCl_3$); IR 2161, 2030, 1750, 1281, 1156, 1113, 1025, 763, 701 cm^{-1}; ^1H NMR (400 MHz) δ 1.97−2.03 (m, 1H), 2.07−2.13 (m, 1H), 2.21−2.29 (m, 1H), 2.54−2.60 (m, 1H), 3.31−3.39 (m, 1H), 4.02−4.07 (m, 1H), 4.22−4.29 (m, 3H), 7.30−7.39 (m, 5H); ^{13}C NMR (100.5 MHz) δ 24.3, 26.4, 60.5, 64.4, 66.7 (q, $^2J_{C-F}$ = 30.7 Hz), 70.9, 125.8 (q, $^1J_{C-F}$ = 280.8 Hz), 127.4, 128.5, 128.7, 138.0, 171.4; ^{19}F NMR (376.2 MHz) δ −78.40 (d, 3F, $^3J_{H-F}$ = 7.9 Hz); HRMS (EI+, direct inlet probe) *m*/*z* [M^+] calcd for $C_{14}H_{14}F_3NO_2$ 285.0977, found 285.0977.

The methyl ester (*R*,*S*)-**11** (0.05 g, 0.14 mmol, 10%) resulting from the epimerization was also recovered.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General information, NMR spectra of all new compounds, and ORTEP/X-ray and CIF data for single-crystal X-ray analyses of compound (*R*,*R*)-**14** (CCDC 1046816). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This article is dedicated to Professor Iwao Ojima (State University of New York at Stony Brook) on the occasion of his 70th birthday.

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