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Palladium(II)-Catalyzed Enantioselective Synthesis of α-(Trifluoromethyl)arylmethylamines

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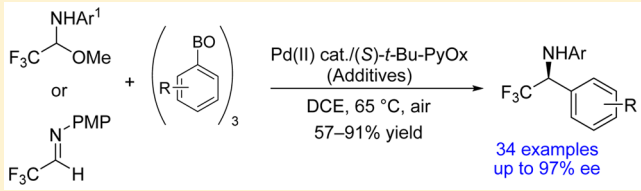
Supporting Information

ABSTRACT: We describe a method for the synthesis of α-(trifluoromethyl)arylmethylamines that consists of the palladium(II)-catalyzed addition of arylboroxines to imines derived from trifluoroacetaldehyde. Palladium acetate is used as a catalyst with electron-neutral or electron-rich arylboroxines, and it was found that addition of an ammonium or silver salt was crucial to promote the reaction of electron-poor boroxines. With (*S*)-*t*-Bu-PyOX as the chiral ligand, this method delivers a variety of α-trifluoromethylated amines in 57−91% yield and with greater than 92% ee in most cases.



INTRODUCTION

Chiral amines are structures commonly found in natural and synthetic biologically active compounds where their ability to form hydrogen bonds is one of their most desirable features.[1] As a subset of this class of compounds, α-(trifluoromethyl)-amines have attracted the interest of organic and medicinal chemists, more intensely so over the past two decades. The presence of the electron-withdrawing CF_3 group adjacent to the C−N bond decreases the basicity of the nitrogen lone pair while preserving the hydrogen bond donor ability of the amine, making them good amide bond isosteres.[2] The most prominent application of an α-(trifluoromethyl)amine in a biologically active compound is undoubtedly odanacatib, a late-stage drug candidate (cathepsin K inhibitor) for the treatment of osteoporosis.[3] This motif has also been featured in other potential medicines.[4] Previous reports on the enantioselective synthesis of α-(trifluoromethyl)amines are in the fields of catalytic hydrogenation (high pressure[5] or transfer hydrogenation[6]), nucleophilic addition to fluorinated imines,[7] trifluoromethylation of C═N bonds,[8] and the cinchona alkaloid-catalyzed isomerization of fluorinated imines.[9] Among these methods, those involving nucleophilic addition to fluorinated imines (or their *N*,*O*-acetals) have received the most attention, likely due to the variety of nucleophiles that can be used (Grignard,[7d,e,10] organolithium,[7a,e,11] organozinc,[7b,12] boronic acids[7c,13]) in racemic or asymmetric versions. In this area, palladium has emerged as a viable alternative to rhodium for the enantioselective addition of arylboron reagents to activated imines.[14] The functional group tolerance and the large number of commercially available boronic acids are particularly attractive features.

In 2013, we reported the palladium(II)-catalyzed enantioselective addition of arylboroxines to *N*,*O*-acetals of trifluoroacetaldehyde for the preparation of α-(trifluoromethyl)-arylmethylamines.[13] This operationally simple protocol (i.e., no rigorous exclusion of air and moisture, easily accessible chiral ligand) was, however, only applicable to electron-neutral and electron-rich arylboroxines. In order to overcome this limitation, we recognized that modifications would have to be made to the catalytic system to improve its activity. Herein, we describe the development of such a system, which ultimately enabled a broad scope of arylboroxines, including electron-poor ones, to participate in this palladium(II)-catalyzed reaction.

RESULTS AND DISCUSSION

The scope under our original reaction conditions is shown in Table 1.

Screening chiral nitrogen-based ligands of the BOX, PyBOX, and PyOx classes led to the identification of *t*-Bu-PyOX as the optimal ligand, which performed best with DCE as the solvent.[13] We initially studied the effect of the electronic character of the nitrogen-bound aryl ring on the *N*,*O*-acetal and found consistently good to high yields and high enantioselectivity (**2a**−**g**), with the exception of **2h**, bearing an *o*-methoxy group. The reactivity of arylboroxines was also examined, with substrate **1a** bearing a *p*-methoxyphenyl (PMP) group. We observed that electron-neutral and moderately electron-rich boroxines reacted to give the products **2i**−**k** in 80−87% yield and with 92−95% ee. More electron-rich boroxines delivered products **2l**−**n** with somewhat diminished enantioselectivity (76−84% ee) but still in high yield. A different result was observed when a substrate with a 3-Br-substituted nitrogen-bound aryl ring was used, delivering **2m** with 92% ee using (4-methoxyphenyl)boroxine. While (4-fluorophenyl)boroxine was reactive after a prolonged reaction time of 48 h, other electron-poor arylboroxines, such as those bearing a 3-Cl, 4-Cl, or 4-Ac substituents, as well as *ortho*-substituted ones, performed poorly. Cognizant of the lower rate of transmetalation of electron-poor boronic acids[15] and the

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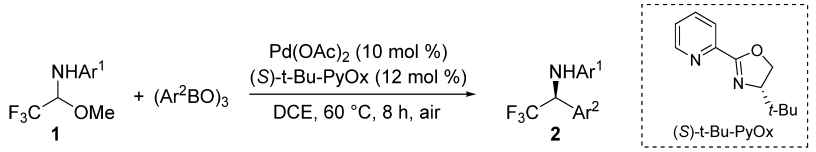
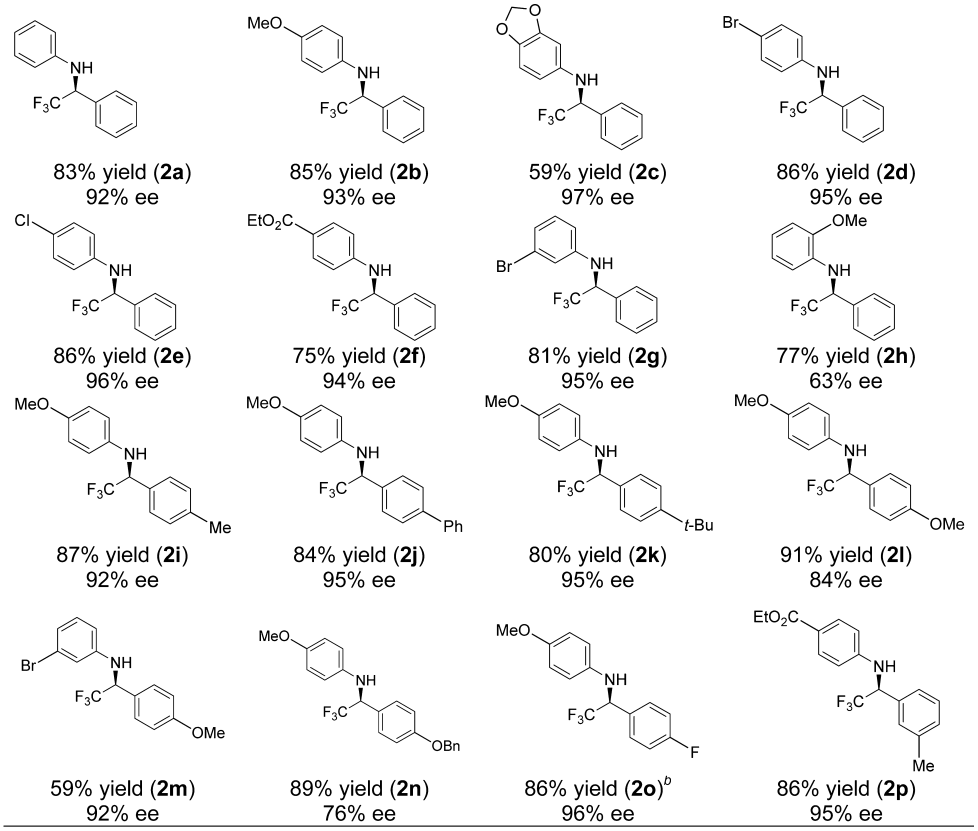
Table 1. Scope of the Pd(II)-Catalyzed Enantioselective Synthesis of α-(Trifluoromethyl)arylmethylamines with Electron-Neutral and Electron-Rich Boroxines[a]





[a]Reaction conditions: *N*,*O*-acetal (0.20 mmol, 1 equiv), boroxine (0.20 mmol, 1 equiv), $Pd(OAc)_2$ (0.020 mmol, 10 mol %), ligand (0.024 mmol, 12 mol %), solvent (1.1. mL), 60 °C, 8 h, under air. Yields of products isolated after purification by flash chromatography. Enantiomeric excess determined by HPLC on a chiral stationary phase. [b]Reaction time was 48 h.

tendency of Pd(II) catalysts to be deactivated by reduction to Pd(0), we sought to find a catalyst that would be longer-lived under the reaction conditions. Recently, Stoltz[16] and Hayashi[14c] reported the use of NH_4PF_6 and $AgBF_4$ as additives in Pd(II)-catalyzed additions of boronic acids to enones and cyclic sulfonimines, respectively. Each of these additives can generate cationic palladium, either by replacement of a TFA ligand from $Pd(TFA)_2$ or by chloride abstraction from $Pd(PyOX)Cl_2$ by Ag. Silver can also potentially oxidize Pd(0) to Pd(II).[17] We wondered if we could take advantage of these features in the present reaction. To test this idea, arylboroxines with electron-withdrawing substituents were employed with *N*,*O*-acetal **1a** as the model substrate under a variety of conditions (Table 2).

We were pleased to find that replacement of $Pd(OAc)_2$ by $Pd(TFA)_2$ and the addition of 30 mol % of NH_4PF_6 enabled the reaction of 4-chlorophenylboroxine (Table 2, entry 1) to give the product in 60% yield and with 95% ee. No reaction occurred in the absence of NH_4PF_6. Under the same conditions, [4-(trifluoromethyl)phenyl]boroxine gave similar results (Table 2, entry 2). Such was not the case for (4-bromophenyl)boroxine (Table 2, entry 3), indicating that further refinement of the reaction conditions was necessary. We prepared palladium complex **Pd-1** and postulated that in the presence of silver it would generate a cationic Pd species that would be more reactive toward transmetalation. Indeed, when (4-bromophenyl)boroxine was subjected to these modified conditions, an 85% yield of the desired product with 95% ee was obtained (Table 2, entry 4).[18] The same conditions applied to [4-(methoxycarbonyl)phenyl]boroxine gave the corresponding product in 72% yield and with 95% ee (Table 2, entry 5). Having achieved a marked increase in reactivity compared to our initial system (Table 1), it remained that some boroxines, such as (4-acetylphenyl)boroxine, did not react under either set of conditions outlined in Table 2. Since we observed the gradual conversion of *N*,*O*-acetal **1a** to its corresponding imine over the course of the reaction, it seemed logical to employ the analogous imine as the starting material to accelerate the reaction. A second screening of reaction conditions with imine **3** was thus undertaken (Table 3).

With (4-bromophenyl)boroxine, results similar to those observed when starting with *N*,*O*-acetal **1a** (Table 2, entry 5) were observed with imine **3** as the starting material (Table 3, entries 1 and 2). (4-Acetylphenyl)boroxine, which was unreactive under the previous conditions, was finally engaged,

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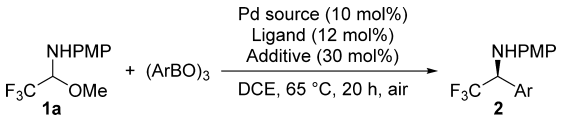
Table 2. Evaluation of Conditions for the Reaction of Electron-Poor Arylboroxines with *N,O*-Acetal 1a[a]



entry	Ar	Pd source	ligand	additive	yield[b] (%)	ee[c] (%)
1	4-ClC_6H_4	$Pd(TFA)_2$	(*S*)-*t*-Bu-PyOX	NH_4PF_6	60 (**2q**)	95
2	4-$CF_3C_6H_4$	$Pd(TFA)_2$	(*S*)-*t*-Bu-PyOX	NH_4PF_6	65 (**2r**)	97
3	4-BrC_6H_4	$Pd(TFA)_2$	(*S*)-*t*-Bu-PyOX	NH_4PF_6	<5 (**2s**)	
4	4-BrC_6H_4	**Pd-1**		$AgBF_4$[d]	85 (**2s**)	95
5	4-$MeO_2CC_6H_4$	**Pd-1**		$AgBF_4$[d]	72 (**2t**)	95
6	4-AcC_6H_4	$Pd(TFA)_2$	(*S*)-*t*-Bu-PyOX	NH_4PF_6	<5 (**2u**)	
7	4-AcC_6H_4	**Pd-1**		$AgBF_4$[d]	<5 (**2u**)	

[a]Reaction conditions: *N,O*-acetal (0.20 mmol, 1 equiv), boroxine (0.10 mmol, 0.50 equiv), Pd source (0.020 mmol, 10 mol %), ligand (0.024 mmol, 12 mol %), additive (0.06 mmol, 30 mol %), solvent (1.1. mL), 60 °C, 20 h, under air. [b]Yields of products isolated after purification by flash chromatography (yields <5% estimated by ^{19}F NMR of the crude reaction mixture). [c]Enantiomeric excess determined by HPLC on a chiral stationary phase. [d]50 mg of powdered 4 Å MS were added PMP = *p*-methoxyphenyl.

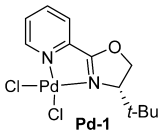
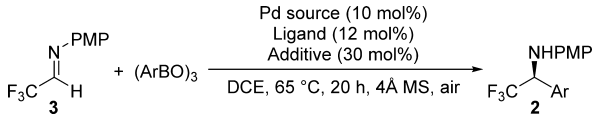


Table 3. Evaluation of Conditions for the Reaction of Electron-Poor Arylboroxines with Imine 3[a]



entry	Ar	Pd source	ligand	additive	yield[b] (%)	ee[c] (%)
1	4-Br C_6H_4	$Pd(TFA)_2$	(*S*)-*t*-BuPyOX	NH_4PF_6	86 (**2s**)	96
2	4-Br C_6H_4	**Pd-1**		$AgBF_4$	91 (**2s**)	91
3	4-Ac C_6H_4	$Pd(TFA)_2$	(*S*)-*t*-BuPyOX	NH_4PF_6	<5 (**2u**)	
4	4-Ac C_6H_4	$Pd(TFA)_2$	(*S*)-*t*-BuPyOX	NH_4BF_4	<5 (**2u**)	
5	4-Ac C_6H_4	**Pd-1**		$AgBF_4$	62 (**2u**)	95

[a]Reaction conditions: *N,O*-acetal (0.20 mmol, 1 equiv), boroxine (0.10 mmol, 0.50 equiv), Pd source (0.020 mmol, 10 mol %), ligand (0.024 mmol, 12 mol %), additive (0.06 mmol, 30 mol %), solvent (1.1. mL), powdered 4 Å molecular sieves (50 mg), 65 °C, 20 h, under air. [b]Yields of products isolated after purification by flash chromatography (yields <5% estimated by ^{19}F NMR of the crude reaction mixture). [c]Enantiomeric excess determined by HPLC on a chiral stationary phase. PMP = *p*-methoxyphenyl.

delivering amine **2u** in 62% yield and with 95% ee (Table 3, entry 5). It was ultimately found that addition of 4 Å molecular sieves was beneficial, preventing partial hydrolysis of the starting imine. In all cases, reactions proceeded to full conversion in 20 h, and the desired amine **2** is the only fluorinated product observed by ^{19}F NMR.

From the results in Tables 2 and 3, it appeared that the **Pd-1**/$AgBF_4$ couple would allow the largest number of boroxines to react, and for that reason, it was selected to study the scope of the reaction (Table 4).

As noted previously, arylboroxines with electron-withdrawing substituents at the *para* position gave the desired products in good to high yield and with greater than 90% ee (Table 4, **2q**–**u**). The synthesis of **2q** was also carried out on a 1 mmol scale, using 4 mol % of **Pd-1** and 25 mol % of $AgBF_4$ in 81% yield and with 93% ee. Various functional groups (e.g., halogen, −OMe, −Ac, and $-CO_2Me$) could be introduced at the *meta* position of the boroxine, giving products **2v**–**ab** in 64–88% yield and with greater than 93% ee. A few electron-rich boroxines were also employed. Products with an aryl ring bearing a 3-Me (**2ac**), 4-$NHCOCF_3$ (**2ad**), and methylenedioxy (**2ae**) substituents were prepared in 57–83% yield and with 93% to 96% ee. When an *ortho*-substituent is introduced, as in the 2-Me (**2af**) and 1-naphthyl (**2ag**) cases, a drop in ee to 72–74% is observed.[19] Finally, amine **2ah** bearing a 2-naphthyl group was prepared in 75% yield and with 90% ee. The absolute configuration of **2b** was previously established[13] by comparing the value of the optical rotation of the corresponding primary amine HCl salt to that of the known compound. Assuming a uniform reaction mechanism, the same configuration is assigned to the other products. As noted in our previous communication,[13] boroxines were used instead of boronic acids because the latter fail to react in our reaction.[20] This situation is not without precedent[14a,21] and may be due to the lower transmetalation rate of boronic acids, although a definitive explanation has not been put forth. Boroxines can be obtained by heating boronic acids (which already contain variable amounts of boroxine) under vacuum or in toluene solution in a Dean–Stark apparatus. We were unfortunately not able to obtain furan-, thiophene-, or pyridine-containing boroxines due to their apparent instability.[22] A distinguishing feature of our method is the absence of a strongly electron-withdrawing group (e.g., SO_2R) on nitrogen, which is usually necessary to activate the substrate in Pd- or Rh-catalyzed addition to imines. In our

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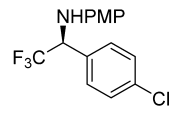
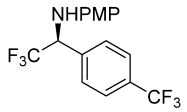
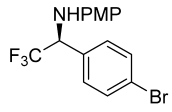
Table 4. Scope of the Pd(II)-Catalyzed Enantioselective Synthesis of α-(trifluoromethyl)arylmethylamines with Catalyst Pd-1[a]



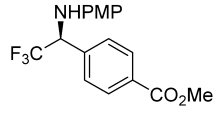
73% yield (**2q**)
94% ee



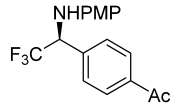
90% yield (**2r**)
96% ee



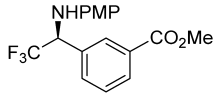
91% yield (**2s**)
91% ee



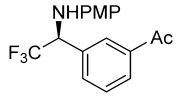
77% yield (**2t**)
95% ee



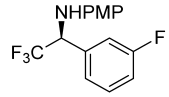
62% yield (**2u**)
95% ee



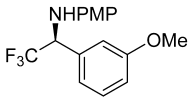
72% yield (**2v**)
95% ee



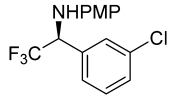
88% yield (**2w**)
96% ee



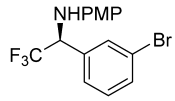
69% yield (**2x**)
95% ee



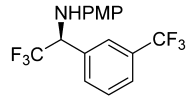
71% yield (**2y**)
93% ee



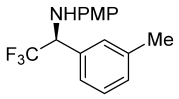
71% yield (**2z**)
95% ee



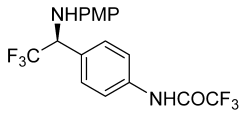
78% yield (**2aa**)
96% ee



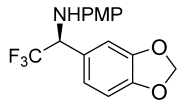
64% yield (**2ab**)
94% ee



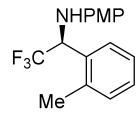
83% yield (**2ac**)
96% ee



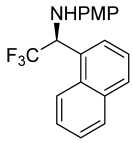
57% yield (**2ad**)
93% ee



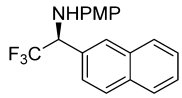
69% yield (**2ae**)
93% ee



58% yield (**2af**)
74% ee



60% yield (**2ag**)[b]
72% ee



75% yield (**2ah**)
90% ee

[a]Reaction conditions: imine (0.20 mmol, 1 equiv), boroxine (0.10 mmol, 0.5 equiv), **Pd-1** (0.020 mmol, 10 mol %), $AgBF_4$ (0.06 mmol, 30 mol %), powdered 4 Å molecular sieves (50 mg), 65 °C, 20 h, under air. Yields of products isolated after purification by flash chromatography. Enantiomeric excess determined by HPLC on a chiral stationary phase. [b]With $AgSbF_6$ instead of $AgBF_4$, 48 h reaction time.

reaction, the CF_3 group plays that role[23] in the presence of the electron-*donating* (and easily cleavable) PMP group on nitrogen.

With the scope of the reaction now delineated, it was applied to the synthesis of trifluoromethylated analogues of cinacalcet, a calcimimetic drug (Scheme 1). The synthesis of (trifluoromethyl)amines **2ag** and **2ah** was accomplished on a 1−2 mmol scale using a reduced palladium loading with outcomes nearly identical to those seen on a smaller scale (Table 4). Following oxidative removal of the PMP group, the primary amine was combined with aldehyde **4** via reductive amination to obtain the desired analogs **5** and **6** in 40 and 49% overall yield, respectively. To the best of our knowledge, these compounds related to cinacalcet have not previously been reported.

CONCLUSION

We have developed a palladium(II)-catalyzed enantioselective synthesis of α-(trifluoromethyl)arylmethylamines involving 1,2-addition of arylboroxines to α-(trifluoromethyl)acetaldimines or their corresponding *N*,*O*-acetals. With electron-neutral or electron-rich boroxines, a simple combination of $Pd(OAc)_2$ and (*S*)-*t*-Bu-PyOx is used as catalyst. The reaction of electron-poor and *ortho*-substituted boroxines was enabled after modification of the catalytic system by changing the palladium source and adding an ammonium or silver salt. While each of them was effective in several cases, it was ultimately found that a $Pd(PyOx)Cl_2$ catalyst with $AgBF_4$ was the most versatile system. Under these sets of conditions, we prepared 34 α-(trifluoromethyl)arylmethylamines in 57−91% yield and in most cases with greater than 92% ee.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed without taking any precautions to exclude air or moisture except for the addition of molecular sieves, when stated. Analytical thin-layer chromatography (TLC) was performed with normal-phase silica plates (60 Å pore diameter, F254 indicator). Visualization was accomplished under UV light (254 nm) followed by immersion in a $KMnO_4$ solution and heating with a heat gun. Purification of reaction products was done by flash chromatography with 230−400 mesh silica gel. DCE was

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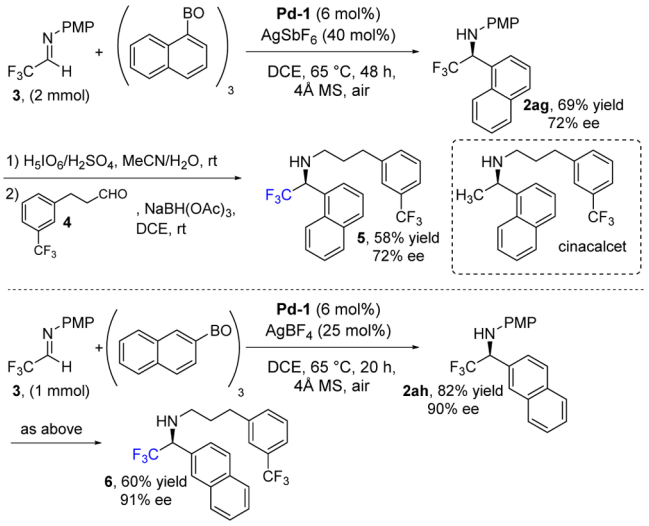
Scheme 1. Synthesis of Trifluoromethylated Analogues of Cinacalcet



distilled under nitrogen from CaH_2 before use. Arylboroxines were prepared by heating the corresponding boronic acid at 120 °C (oil bath) under high-vacuum (approximately 0.1 mbar) for 8−16 h. Conversion can be monitored by ^{1}H NMR in anhydrous DMSO-d_6; up to 10% boronic acid sometimes remains. ^{1}H, ^{19}F, and ^{13}C NMR spectra were acquired on a 300 or 400 MHz spectrometer. Shifts for proton spectra are reported in parts per million and are referenced to residual $CHCl_3$ (δ= 7.26 ppm). Chemical shifts for fluorine spectra are reported in parts per million (δ scale) and referenced to external $CFCl_3$ (δ = 0 ppm). Chemical shifts for carbon resonances are reported in parts per million and are referenced to the carbon resonance of the solvent (δ = 77.16 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (J, Hz), and integration. High-resolution mass spectra were obtained in positive ESI mode with a triple quadrupole detector or in DART mode with a time-of-flight (TOF) detector. Enantiomeric excesses (ee) were determined by normal-phase HPLC analysis with a chiral stationary phase using a mixture of hexanes−2-propanol as eluent and with the UV detector set at 254 nm. HPLC conditions for all compounds are reported below.

N,O-Acetals **1**,[13] imine **3**,[24] aldehyde **4**,[25] **Pd-1**,[26] and (*S*)-*t*-Bu-PyOX[16] were synthesized as previously described. Products **2a**−**p** were prepared according to our original report and have been fully characterized.[13]

General Procedure for the Synthesis of α-(Trifluoromethyl)-arylmethylamines from *N,O*-Acetals in Table 2. Palladium complex **Pd-1** (0.020 mmol, 10 mol %) or $Pd(TFA)_2$ (0.020 mmol, 10 mol %) and (*S*)-*t*-Bu-PyOX (0.024 mmol, 12 mol %), the additive (0.030 mmol, 15 mol %), arylboroxine (0.10 mmol, 0.50 equiv), and 1 mL of DCE were introduced in a 2-dram vial. In a separate 2-dram vial, *N,O*-acetal **1a** (0.20 mmol, 1 equiv) and the additive (0.030 mmol, 15 mol %) were dissolved in 1 mL of DCE. After both solutions were stirred for 15 min at room temperature, the starting material solution was added to the catalyst solution. The vial was capped and placed in a preheated 65 °C oil bath. After the indicated amount of time, the reaction was diluted with ethyl acetate and filtered through a short plug of silica, washing with ethyl acetate. The solvent was evaporated, and the crude mixture was purified by flash chromatography, eluting with a mixture of hexanes and ethyl acetate.

General Procedure for the Synthesis of α-(Trifluoromethyl)-arylmethylamines in Table 4. Palladium complex **Pd-1** (0.020 mmol, 10 mol %), $AgBF_4$ (0.030 mmol, 15 mol %), the arylboroxine (0.10 mmol, 0.50 equiv), powdered 4 Å molecular sieves (50 mg), and 1 mL of DCE were introduced in a 2-dram vial. In a separate 2-dram vial, imine **3** (0.20 mmol, 1 equiv) and $AgBF_4$ (0.030 mmol, 15 mol %) were dissolved in 1 mL of DCE, giving a purple solution. After both solutions were stirred for 15 min at room temperature, the starting material solution was added to the catalyst solution. The vial was capped and placed in a preheated 65 °C oil bath. After the indicated amount of time, the reaction was diluted with ethyl acetate and filtered through a short plug of silica, washing with ethyl acetate. The solvent was evaporated, and the crude mixture was purified by flash chromatography, eluting with a mixture of hexanes and ethyl acetate. Racemic products were synthesized according to the same protocol, but with bipy or (*rac*)-*t*-Bu-PyOx as the ligand.

*(S)-N-(1-(4-Chlorophenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline (**2q**).*[6b] Colorless oil. 46 mg, 73% yield, 94% ee. Eluent: hexanes/EtOAc 25:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.36 (m, 4H), 6.76−6.74 (m, 2H), 6.59−6.57 (m, 2H), 4.82−4.79 (brm, 1H), 4.08−4.06 (br, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 139.2, 135.2, 132.9, 129.5, 129.3, 125.0 (q, J(C−F) = 282 Hz), 115.9, 115.0, 61.3 (q, J(C−F) = 30 Hz), 55.8. ^{19}F NMR ($CDCl_3$): −74.2 (d, J = 7.6 Hz). IR (ATR, cm^{-1}): 3378, 2835, 1597, 1513, 1492, 1236, 1173, 1124. $[\alpha]_D^{20}$: +45.5 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 1.0 mL/min, 9.0 min (major), 11.0 min (minor).

*(S)-4-Methoxy-N-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)-ethyl)aniline (**2r**).*[6b] Colorless oil. 63 mg, 90% yield, 96% ee. Eluent: hexanes/EtOAc 25:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67−7.65 (m, 2H), 7.61−7.58 (m, 2H), 6.76−6.73 (m, 2H), 6.58−6.56 (m, 2H), 4.91−4.87 (brm, 1H), 4.12−4.10 (br, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 139.0, 138.4, 131.5 (q, J(C−F) = 32 Hz), 128.6, 126.0 (q, J(C−F) = 3.8 Hz), 124.9 (q, J(C−F) = 282 Hz), 124.0 (q, J(C−F) = 272 Hz), 115.9, 115.1, 61.6 (q, J(C−F) = 30 Hz), 55.8. ^{19}F NMR ($CDCl_3$): −62.8 (s), −74.0 (d, J = 7.6 Hz). IR (ATR, cm^{-1}): 3391, 2837, 1621, 1514, 1325, 1236, 1168, 1123, 1068, 820. $[\alpha]_D^{20}$: +28.8 (c 1.0, $CHCl_3$). HPLC: IA column, hexanes−2-propanol (90:10), flow rate: 0.7 mL/min, 9.2 min (minor), 9.7 min (major).

*(S)-N-(1-(4-Bromophenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline (**2s**).*[6b] White amorphous solid. 65 mg, 91% yield, 91% ee. Eluent: hexanes/EtOAc 25:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.51 (m, 2H), 7.35−7.32 (m, 2H), 6.76−6.73 (m, 2H), 6.58−6.56 (m, 2H), 4.82−4.75 (brm, 1H), 4.07−4.05 (br, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 139.2, 133.4, 132.2, 129.8, 124.9 (q, J(C−F) = 282 Hz), 123.4, 115.9, 115.0, 61.4 (q, J(C−F) = 30 Hz), 55.8. ^{19}F NMR ($CDCl_3$): −74.2 (d, J = 7.6 Hz). IR (ATR, cm^{-1}): 3378, 2835, 1593, 1512, 1489, 1234, 1171, 1122, 1035, 1011, 818. $[\alpha]_D^{20}$: +46.8 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 1.0 mL/min, 9.6 min (major), 11.2 min (minor).

*(S)-Methyl 4-(2,2,2-Trifluoro-1-((4-methoxyphenyl)amino)ethyl)-benzoate (**2t**).* White amorphous solid. 52 mg, 77% yield, 95% ee. Eluent: hexanes/EtOAc 5:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07−8.05 (m, 2H), 7.55−7.52 (m, 2H), 6.74−6.72 (m, 2H), 6.59−6.56 (m, 2H), 4.90−4.86 (brm, 1H), 4.14−4.12 (br, 1H), 3.91 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 153.6, 139.3, 139.1, 131.1, 130.2, 128.2, 125.0 (q, J(C−F) = 282 Hz), 115.9, 115.0, 61.7 (q, J(C−F) = 30 Hz), 55.8, 52.4. ^{19}F NMR ($CDCl_3$): −74.2 (d, J = 7.6 Hz). IR (film, NaCl): 3375, 2840, 1720, 1514, 1437, 1268, 1236, 1178, 1119, 1035, 820. HRMS (DART): m/z calcd for $C_{17}H_{17}F_3NO_3$ [M + H] 340.11605, found 340.11561. $[\alpha]_D^{20}$: +63.8 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 0.7 mL/min, 31.2 min (minor), 33.0 min (major).

*(S)-1-(4-(2,2,2-Trifluoro-1-((4-methoxyphenyl)amino)ethyl)-phenyl)ethanone (**2u**).* Clear oil. 42 mg, 62% yield, 95% ee. Eluent: hexanes/EtOAc 5:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98−7.96 (m, 2H), 7.57−7.55 (m, 2H), 6.74−6.72 (m, 2H), 6.59−6.57 (m, 2H), 4.91−4.88 (brm, 1H), 4.19−4.18 (br, 1H), 3.71 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 153.6, 139.4, 139.1, 137.8, 128.9, 128.4, 124.9 (q, J(C−F) = 282 Hz), 115.9, 115.0, 61.6 (q, J(C−F) = 30 Hz), 55.7, 26.7. ^{19}F NMR ($CDCl_3$): −73.8 (d, J = 7.2 Hz). IR (film, NaCl): 1720, 1683, 1514, 1359, 1267, 1236, 1175, 1124, 817. HRMS (DART): m/z calcd for $C_{17}H_{17}F_3NO_2$ [M + H] 324.12114, found 324.12079. $[\alpha]_D^{20}$: +75.3 (c 1.0, $CHCl_3$). HPLC: AD-H

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column, hexanes−2-propanol (80:20), flow rate: 1.0 mL/min, 16.0 min (major), 20.3 min (minor).

*(S)-Methyl 3-(2,2,2-Trifluoro-1-((4-methoxyphenyl)amino)ethyl)-benzoate (**2v**).* Colorless oil. 49 mg, 72% yield, 95% ee. Eluent: hexanes/EtOAc 5:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15−8.14 (m, 1H), 8.06−8.03 (m, 1H), 7.66−7.64 (m, 1H), 7.49−7.45 (m, 1H), 6.74−6.72 (m, 2H), 6.60−6.58 (m, 2H), 4.90−4.86 (brm, 1H), 4.16−4.14 (br, 1H), 3.93 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 153.6, 139.2, 135.0, 132.5, 131.0, 130.4, 129.3, 129.2, 125.0 (q, J(C−F) = 282 Hz), 115.9, 115.0, 61.6 (q, J(C−F) = 30 Hz), 55.8, 52.4. ^{19}F NMR ($CDCl_3$): −74.1 (d, J = 7.1 Hz). IR (film, NaCl): 3369, 2955, 1712, 1514, 1449, 1435, 1292, 1241, 1201, 1175, 1124, 1082, 821. HRMS (ESI): m/z calcd for $C_{17}H_{17}F_3NO_3$ [M + H] 340.1165, found 340.1155. $[\alpha]_D^{20}$: +35.0 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (85:15), flow rate: 1.0 mL/min, 9.6 min (minor), 10.5 min (major).

*(S)-1-(3-(2,2,2-Trifluoro-1-((4-methoxyphenyl)amino)ethyl)-phenyl)ethanone (**2w**).* Yellow oil. 57 mg, 88% yield, 96% ee. Eluent: hexanes/EtOAc 5:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07−8.06 (m, 1H), 7.96−7.93 (m, 1H), 7.68−7.66 (m, 1H), 7.52−7.48 (m, 1H), 6.74−6.72 (m, 2H), 6.60−6.58 (m, 2H), 4.92−4.88 (brm, 1H), 4.18−4.17 (bm, 1H), 3.70 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 153.6, 139.2, 137.8, 135.2, 132.6, 129.4, 129.3, 127.9, 125.0 (q, J(C−F) = 282 Hz), 115.9, 115.0, 61.6 (q, J(C−F) = 30 Hz), 55.8, 26.8. ^{19}F NMR ($CDCl_3$): −74.1 (d, J = 7.2 Hz). IR (film, NaCl): 3362, 2933, 1720, 1683, 1514, 1464, 1359, 1236, 1169, 1124, 1036, 822. HRMS (DART): m/z calcd for $C_{17}H_{17}F_3NO_2$ [M + H] 324.12104, found 324.12114. $[\alpha]_D^{20}$: +30.0 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (97:3), flow rate: 0.7 mL/min, 36.2 min (minor), 43.5 min (major).

*(S)-4-methoxy-N-(2,2,2-trifluoro-1-(3-fluorophenyl)ethyl)aniline (**2x**).* Colorless oil. 41 mg, 69% yield, 95% ee. Eluent: hexanes/EtOAc 25:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.34 (m, 1H), 7.25−7.23 (m, 1H), 7.20−7.17 (m, 1H), 7.09−7.04 (m, 1H), 6.76−6.74 (m, 2H), 6.60−6.58 (m, 2H), 4.83−4.80 (brm, 1H), 4.08−4.06 (br, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1 (d, J = 247 Hz), 153.6, 139.2, 136.9 (d, J = 7 Hz), 130.6 (d, J = 8 Hz), 125.0 (q, J = 282 Hz), 123.9 (d, J = 3 Hz), 116.3 (d, J = 21 Hz), 115.9, 115.2 (d, J = 23 Hz), 115.0, 61.5 (q, J(C−F) = 30 Hz), 55.8. ^{19}F NMR ($CDCl_3$): −74.1 (d, J = 7.1 Hz), −112.5 (m). IR (ATR): 3383, 2837, 1615, 1594, 1511, 1489, 1450, 1232, 1179, 1148, 1118, 1034, 819. HRMS (ESI): m/z calcd for $C_{15}H_{14}F_4NO$ [M + H] 300.1017, found 300.1006. $[\alpha]_D^{20}$: +39.6 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 1.0 mL/min, 6.5 min (minor), 7.2 min (minor).

*(S)-4-Methoxy-N-(2,2,2-trifluoro-1-(3-methoxyphenyl)ethyl)-aniline (**2y**).*[6b] Colorless oil. 44 mg, 71% yield, 93% ee. Eluent: hexanes/EtOAc 25:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.29 (m, 1H), 7.05−7.04 (m, 1H), 6.99−6.98 (m, 1H), 6.92−6.89 (m, 1H), 6.76−6.73 (m, 2H), 6.62−6.60 (m, 2H), 4.81−4.74 (brm, 1H), 4.07−4.05 (br, 1H), 3.81 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 153.5, 139.7, 136.0, 130.1, 125.2 (q, J(C−F) = 282 Hz), 120.4, 115.8, 115.0, 114.3, 114.1, 61.9 (q, J(C−F) = 30 Hz), 55.8, 55.4. ^{19}F NMR ($CDCl_3$): −74.0 (d, J = 7.6 Hz). IR (ATR): 3378, 2940, 2837, 1603, 1588, 1513, 1492, 1235, 1161, 1120, 1037, 821. $[\alpha]_D^{20}$: +47.5 (c 1.0, $CHCl_3$). HPLC: OD-H column, hexanes−2-propanol (96:4), flow rate: 1.0 mL/min, 11.4 min (major), 12.7 min (minor).

*(S)-N-(1-(3-Chlorophenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline (**2z**).*[6c] Yellow oil. 45 mg, 71% yield, 95% ee. Eluent: hexanes/EtOAc 25:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.45 (m, 1H), 7.36−7.34 (m, 3H), 6.76−6.74 (m, 1H), 6.59−6.57 (m, 2H), 4.83−4.75 (brm, 1H), 4.08−4.06 (d, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 139.2, 136.5, 135.0, 130.3, 129.5, 128.3, 126.3, 124.9 (q, J(C−F) = 282 Hz), 115.9, 115.0, 61.5 (q, J(C−F) = 30 Hz), 55.8. ^{19}F NMR ($CDCl_3$): −74.0 (d, J = 7.0 Hz). IR (ATR): 3410, 2835, 1513, 1235, 1175, 1123, 1035, 820. $[\alpha]_D^{20}$: +43.0 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 0.7 mL/min, 10.4 min (major), 11.0 min (minor).

*(S)-N-(1-(3-Bromophenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline (**2aa**).* Yellow oil. 56 mg, 78% yield, 96% ee. Eluent: hexanes/EtOAc 25:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62−7.61 (m, 1H), 7.52−7.49 (m, 1H), 7.40−7.38 (m, 1H), 7.28−7.24 (m, 1H), 6.77−6.74 (m, 2H), 6.60−6.57 (m, 2H), 4.81−4.75 (brm, 1H), 4.07 (s, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 139.1, 136.7, 132.4, 131.2, 130.6, 126.8, 124.9 (q, J(C−F) = 282 Hz), 123.1, 115.9, 115.0, 61.4 (q, J(C−F) = 30 Hz), 55.8. ^{19}F NMR ($CDCl_3$): −74.0 (d, J = 7.1 Hz). IR (film, NaCl): 3415, 1514, 1476, 1348, 1236, 1176, 1125, 1036, 820. HRMS (DART): m/z calcd for $C_{15}H_{14}BrF_3NO$ [M + H] 360.02045, found 360.02109. $[\alpha]_D^{20}$: +43.3 (c 1.0, $CHCl_3$). HPLC: IA column, hexanes−2-propanol (96:4), flow rate: 0.5 mL/min, 11.4 min (major), 12.7 min (minor).

*(S)-4-methoxy-N-(2,2,2-trifluoro-1-(3-(trifluoromethyl)phenyl)-ethyl)aniline (**2ab**).* Colorless oil. 45 mg. 64% yield, 94% ee. Eluent: hexanes/EtOAc 25:1.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.67−7.63 (m, 2H), 7.55−7.51 (m, 1H), 6.76−6.74 (m, 2H), 6.59−6.57 (m, 2H), 4.92−4.85 (brm, 1H), 4.12−4.10 (br, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 139.1, 135.6, 131.53 (q, J(C−F) = 32 Hz), 131.49, 129.6, 126.20 (q, J(C−F) = 4 Hz), 125.0 (q, J(C−F) = 4 Hz), 124.9 (q, J(C−F) = 282 Hz), 123.9 (q, J(C−F) = 271 Hz), 115.9, 115.1, 61.6 (q, J(C−F) = 30 Hz), 55.8. ^{19}F NMR ($CDCl_3$): −62.7 (d, J = 8.0 Hz), −74.1 (d, J = 7.0 Hz). IR (film, NaCl): 3405, 1514, 1329, 1236, 1166, 1124, 1076, 821. HRMS (ESI): m/z calcd for $C_{16}H_{14}F_6NO$ [M + H] 350.0984, found 350.0974. $[\alpha]_D^{20}$: +28.3 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 0.7 mL/min, 7.8 min (minor), 8.2 min (major).

*(S)-4-Methoxy-N-(2,2,2-trifluoro-1-(m-tolyl)ethyl)aniline (**2ac**).*[5] Colorless oil. 49 mg, 83% yield, 96% ee. Eluent: hexanes/EtOAc 25:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.26 (m, 1H), 7.25−7.23 (m, 2H), 7.20−7.17 (m, 1H), 6.76−6.74 (m, 2H), 6.63−6.61 (m, 2H), 4.81−4.73 (brm, 1H), 4.07−4.05 (br, 1H), 3.72 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 139.8, 138.8, 134.4, 130.0, 128.9, 128.7, 125.3 (q, J(C−F) = 282 Hz), 125.1, 115.8, 115.0, 61.9 (q, J(C−F) = 30 Hz), 55.8, 21.6. ^{19}F NMR ($CDCl_3$): −74.0 (d, J = 7.1 Hz). IR (film, NaCl): 3410, 2835, 1593, 1514, 1489, 1452, 1240, 1182, 1165, 1124, 1035, 822. $[\alpha]_D^{20}$: +28.3 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 0.5 mL/min, 13.0 min (major), 13.7 min (minor).

*(S)-2,2,2-Trifluoro-N-(4-(2,2,2-trifluoro-1-((4-methoxyphenyl)-amino)ethyl)phenyl)acetamide (**2ad**).* Amorphous white solid. 45 mg, 57% yield, 93% ee. Eluent: hexanes/EtOAc 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.61−7.59 (m, 2H), 7.49−7.47 (m, 2H), 6.75−6.72 (m, 2H), 6.58−6.56 (m, 2H), 4.84−4.80 (brm, 1H), 4.10−4.09 (br, 1H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.03 (q, J(C−F) = 38 Hz), 153.6, 139.2, 135.9, 132.5, 126.4, 123.6, 120.9, 115.9, 115.7 (q, J(C−F) = 291 Hz), 115.0, 61.3 (q, J(C−F) = 30 Hz), 55.8. ^{19}F NMR ($CDCl_3$): −74.2 (d, J = 7.4 Hz), −75.8(m). IR (film, NaCl): 1709, 1514, 1294, 1240, 1167, 1124, 1036, 822. HRMS (DART): m/z calcd for $C_{17}H_{15}F_6N_2O_2$ [M + H] 393.10445, found 393.10377. $[\alpha]_D^{20}$: +45.6 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 1.0 mL/min, 26.7 min (major), 28.4 min (minor).

*(S)-N-(1-(Benzo[d][1,3]dioxol-5-yl)-2,2,2-trifluoroethyl)-4-methoxyaniline (**2ae**).* Clear oil. 45 mg, 69% yield, 93% ee. Eluent: hexanes/EtOAc 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93−6.90 (m, 2H), 6.81−6.79 (m, 1H), 6.76−6.73 (m, 2H), 6.60−6.58 (m, 2H), 5.97−5.96 (m, 2H), 4.72−4.70 (brm, 1H), 4.03 (s, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 148.4, 148.3, 139.5, 128.1, 125.2 (q, J(C−F) = 282 Hz), 122.0, 115.9, 115.0, 108.6, 108.1, 101.5, 61.6 (q, J(C−F) = 30 Hz), 55.8. ^{19}F NMR ($CDCl_3$): −74.4 (d, J = 7.6 Hz). IR (film, NaCl): 3381, 2940, 1514, 1491, 1445, 1241 1176, 1123, 1037, 932, 820. HRMS (DART): m/z calcd for $C_{16}H_{15}F_3NO_3$ [M + H] 326.09994, found 326.10040. $[\alpha]_D^{20}$: +57.0 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 1.0 mL/min, 12.4 min (major), 15.7 min (minor).

*(S)-4-Methoxy-N-(2,2,2-trifluoro-1-(o-tolyl)ethyl)aniline (**2af**).*[5] Colorless oil. 34 mg, 58% yield, 74% ee. Eluent: hexanes/EtOAc 25:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.48 (s, 1H), 7.26−7.23 (m, 3H), 6.76−6.74 (m, 2H), 6.60−6.58 (m, 2H), 5.16−5.09 (brm, 1H), 4.05 (s, 1H), 3.72 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (100 MHz,

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$CDCl_3$): δ 153.4, 139.9, 137.0, 133.1, 131.0, 128.9, 126.8, 126.6, 125.7 (q, J(C−F) = 282 Hz), 115.5, 115.0, 57.4 (q, J(C−F) = 30 Hz), 55.8, 19.9. ^{19}F NMR ($CDCl_3$): −73.6 (d, J = 7.4 Hz). $[\alpha]_D^{20}$: +30.8 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 0.7 mL/min, 8.3 min (major), 11.0 min (minor)

*(S)-4-Methoxy-N-(2,2,2-trifluoro-1-(naphthalen-1-yl)ethyl)aniline (**2ag**).* Colorless oil. 40 mg, 60% yield, 72% ee. Eluent: hexanes/EtOAc 25:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.4 Hz, 1H), 7.94−7.87 (m, 2H), 7.77 (d, J = 7.3 Hz, 1H), 7.62−7.48 (m, 3H), 6.72−6.70 (m, 2H), 6.60−6.58 (m, 2H), 5.77−5.71 (brm, 1H), 4.26−4.24 (bm, 1H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 139.7, 134.1, 131.8, 130.3, 129.8, 129.4, 127.1, 126.1, 125.7 (q, J(C−F) = 282 Hz), 125.5, 125.4, 122.5, 115.4, 115.0, 56.7 (q, J = 30 Hz), 55.8. ^{19}F NMR ($CDCl_3$): −72.8 (d, J(C−F) = 7.0 Hz). IR (film, NaCl): 3401, 2957, 2926, 2835, 1514, 1462, 1240, 1165, 1120, 1036, 820, 800. HRMS (DART): m/z calcd for $C_{19}H_{17}F_3NO$ [M + H] 332.12595, found 332.12622. $[\alpha]_D^{20}$: −45.8 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 0.7 mL/min, 12.8 min (minor), 15.2 min (major).

*(S)-4-Methoxy-N-(2,2,2-trifluoro-1-(naphthalen-2-yl)ethyl)aniline (**2ah**).*[6b] Colorless oil. 50 mg, 75% yield, 90% ee. Eluent: hexanes/EtOAc 25:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.90−7.85 (m, 3H), 7.57−7.51 (m, 3H), 6.75−6.73 (m, 2H), 6.66−6.64 (m, 2H), 5.01−4.98 (brm, 1H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 139.6, 133.7, 133.3, 131.8, 129.0, 128.3, 127.9, 126.8, 126.7, 125.4 (q, J(C−F) = 282 Hz), 125.1, 115.9, 115.0, 62.1 (q, J = 30 Hz), 55.8. ^{19}F NMR ($CDCl_3$): −73.6 (d, J = 7.6 Hz). IR (ATR): 3385, 3060, 2935, 2834, 1512, 1235, 1164, 1120, 1035, 817. $[\alpha]_D^{20}$: +42.0 (c 1.0, $CHCl_3$). HPLC: AD-H column, hexanes−2-propanol (90:10), flow rate: 1.0 mL/min, 12.2 min (major), 15.7 min (minor)

Procedures for Compounds in Scheme 1. *(S)-N-(2,2,2-Trifluoro-1-(naphthalen-1-yl)ethyl)-3-(3-(trifluoromethyl)phenyl)-propan-1-amine (**5**).* (S)-4-Methoxy-N-(2,2,2-trifluoro-1-(naphthalen-1-yl)ethyl)aniline (**2ag**) (455 mg, 1.37 mmol, 1 equiv) was prepared according to the general procedure with 6 mol % of **Pd-1** and 40 mol % of $AgSbF_6$ on a 2 mmol scale (10 mL of DCE in a 10-dram vial). It was dissolved in 10 mL of MeCN and 10 mL of H_2O. Periodic acid (624 mg, 2.74 mmol, 2 equiv) was added followed by 5 drops of concentrated H_2SO_4. The mixture was stirred overnight and diluted with 40 mL of DCM and 40 mL of saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes/EtOAc 5:1) yielding the primary amine as an orange oil (244 mg, 1.08 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11−8.09 (m, 1H), 7.92−7.88 (m, 2H), 7.80−7.77 (m, 1H), 7.61−7.51 (m, 3H), 5.34 (q, J = 7.2 Hz, 1H), 1.92 (s, 2H). ^{19}F NMR ($CDCl_3$): −75.3 (d, J = 7.1 Hz). $[\alpha]_D^{20}$: +3.1 (c 2.5, $CHCl_3$). The primary amine (50 mg, 0.22 mmol, 1.1 equiv) and aldehyde **4** (40 mg, 0.20 mmol, 1 equiv) were dissolved in 2 mL of DCE. Sodium triacetoxyborohydride (59 mg, 0.28 mmol, 1.4 equiv) was added in one portion, and the mixture was stirred for 1 h at room temperature. Twenty milliliters of EtOAc and 20 mL of a saturated aqueous solution of $NaHCO_3$ were added, and the organic layer was separated. The aqueous layer was extracted three times with 10 mL EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes/EtOAc 30:1) yielding the product as a clear oil (61 mg, 0.15 mmol, 74% yield, 72% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.4 Hz, 1H), 7.93−7.89 (m, 2H), 7.75 (d, J = 7.2 Hz, 1H), 7.61−7.52 (m, 3H), 7.45−7.28 (m, 4H), 5.10−5.04 (m, 1H), 2.74−2.63 (m, 4H), 1.86−1.76 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 134.0, 132.3, 131.9 (q, J(C−F) = 1.5 Hz), 130.81, 130.80, 130.78 (q, J(C−F) = 32 Hz), 129.6, 129.2, 128.9, 126.8, 125.9 (q, J(C−F) = 282 Hz), 125.8, 125.5, 125.2 (q, J(C−F) = 4 Hz), 124.4 (q, J(C−F) = 271 Hz), 122.9 (q, J(C−F) = 4 Hz), 122.8, 47.3, 33.1, 31.7. Note: $\underline{C}(CF_3)$(1-naphthyl) (NHR) is visible only in the baseline ^{19}F NMR ($CDCl_3$): −62.6 (s), −72.9 (d, J = 6.5 Hz). IR (film, NaCl): 2933, 2862, 1450, 1330, 1263, 1163, 1121, 1074, 798, 779. HRMS (DART): m/z calcd for $C_{22}H_{20}F_6N$ [M + H] 412.14999, found 412.14989. $[\alpha]_D^{20}$: −5.3 (c 2.7, $CHCl_3$). HPLC: OD-H column, hexanes−2-propanol (90:10), flow rate: 0.7 mL/min, 7.6 min (minor), 9.0 min (major)

*(S)-N-(2,2,2-Trifluoro-1-(naphthalen-2-yl)ethyl)-3-(3-(trifluoromethyl)phenyl)propan-1-amine (**6**).* (S)-4-Methoxy-N-(2,2,2-trifluoro-1-(naphthalen-2-yl)ethyl)aniline (**2ah**) (272 mg, 0.82 mmol, 1 equiv) was prepared according to the general procedure with 6 mol % of **Pd-1** and 25 mol % of $AgBF_4$ on a 1 mmol scale (5 mL of DCE in a 6-dram vial). It was dissolved in 5 mL of MeCN and 5 mL of H_2O. Periodic acid (374 mg, 1.64 mmol, 2 equiv) was added, followed by 3 drops of concentrated H_2SO_4. The mixture was stirred overnight and diluted with 40 mL of DCM and 40 mL saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes/EtOAc 5:1) yielding the primary amine as an orange oil (142 mg, 0.63 mmol, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.89−7.85 (m, 3H), 7.56−7.52 (m, 3H), 4.57 (q, J = 7.4 Hz, 1H), 1.92 (s, 2H). ^{19}F NMR ($CDCl_3$): −76.4 (d, J = 7.5 Hz). $[\alpha]_D^{20}$: +20.8 (c 1.2, $CHCl_3$). The primary amine (50 mg, 0.22 mmol, 1.1 equiv) and aldehyde **4** (40 mg, 0.20 mmol, 1 equiv) were dissolved in 2 mL of DCE. Sodium triacetoxyborohydride (59 mg, 0.28 mmol, 1.4 equiv) was added in one portion, and the mixture was stirred for 1 h at room temperature. Twenty milliliters of EtOAc and 20 mL of a saturated aqueous solution of $NaHCO_3$ were added, and the organic layer was separated. The aqueous layer was extracted three times with 10 mL of EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexanes/EtOAc 30:1) yielding the product as a clear oil (64 mg, 0.16 mmol, 78% yield, 91% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90−7.85 (m, 4H), 7.55−7.51 (m, 3H), 7.45−7.41 (m, 2H), 7.37−7.30 (m, 2H), 4.28 (q, J = 7.5 Hz, 1H), 2.77−2.60 (m, 4H), 1.90−1.77 (m, 2H), 1.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 133.7, 133.2, 132.1, 131.91 (q, J(C−F) = 1.3 Hz), 130.80 (q, J(C−F) = 32 Hz), 128.9, 128.8, 128.5, 128.2, 127.9, 126.8, 126.6, 125.4, 125.30 (q, J(C−F) = 282 Hz), 125.18 (q, J(C−F) = 3.8 Hz), 124.37 (q, J(C−F) = 271 Hz), 122.91 (q, J(C−F) = 3.8 Hz), 65.1 (q, J(C−F) = 30 Hz), 47.0, 33.1, 31.5. ^{19}F NMR ($CDCl_3$): −62.6 (s), −73.8 (d, J = 7.5 Hz). IR (film, NaCl): 2933, 2862, 1450, 1330, 1263, 1163, 1121, 1074, 798, 779. HRMS (DART): m/z calcd for $C_{22}H_{20}F_6N$ [M + H] 412.14999, found 412.14999. $[\alpha]_D^{20}$: +29.8 (c 4.0, $CHCl_3$). HPLC: OD-H column, hexanes−2-propanol (90:10), flow rate: 0.7 mL/min, 7.7 min (major), 8.5 min (minor).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00657.

^{1}H and ^{13}C NMR spectra and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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