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Organocatalytic Asymmetric Synthesis of Dihydrobenzoxazinones Bearing Trifluoromethylated Quaternary Stereocenters

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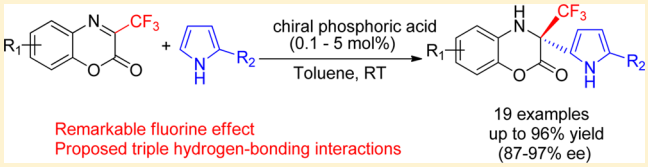
Supporting Information

ABSTRACT: Chiral phosphoric acid-catalyzed enantioselective aza-Friedel−Crafts reaction of trifluoromethyl benzoxazinones with pyrroles is reported. Under mild conditions, a range of enantioenriched dihydrobenzoxazinones bearing trifluoromethylated quaternary stereocenters could be obtained in good to excellent yield and ee. A remarkable fluorine effect is observed, and preliminary mechanistic studies combined with theory calculations suggest that triple-hydrogen-bonding interactions hold the transition structure rigidly and allow the bulky substituents of the catalyst to influence the enantioselectivity.



INTRODUCTION

Trifluoromethylated heterocycles have shown a large diversity of superior biological properties, mainly due to the incorporation of the trifluoromethyl group, which can improve chemical and metabolic stability, lipophilicity, and membrane permeability of the molecules.[1] In particular, some biologically active molecules that feature a heterocyclic segment with a C−CF_3 quaternary stereocenter have emerged in agricultural and medicinal chemistry,[2] such as HIV reverse transcriptase inhibitor (Efavirenz,[2a] DPC 961, DPC 963, DPC 083[2b]), NK-1 receptor antagonist (CJ-17493),[2c] and antimalarial agents (Fluoroartemisinin).[2d] Thus, asymmetric synthesis of enantioenriched trifluoromethylated heterocycles has been receiving great interest.[3] Early synthetic studies either focused on a diastereoselective strategy or used a stoichiometric amount of chiral reagents.[4] Recently, significant efforts have been devoted to the catalytic enantioselective approaches, including asymmetric transition-metal catalysis[5] or cooperative catalysis,[6] as well as organocatalysis.[7] Despite these impressive advances, further exploration of novel methods and strategies for the catalytic asymmetric construction of CF_3-containing quaternary stereocenters in heterocyclic systems remains highly desirable.

In the meantime, asymmetric phosphoric acid catalysis has proven to be very successful for a large number of important enantioselective transformations,[8] and some mechanism studies[9] have revealed that double-hydrogen-bonding interactions (A, Figure 1) and synergetic hydrogen-bonding and ion-pairing interactions (B, Figure 1) play a crucial functional role in activating the substrate and determining the stereoselectivity in these asymmetric reactions. Further exploration of a novel mode of activation remains highly desirable, though it presents a formidable challenge. We developed a novel class of chiral spirocyclic phosphoric acids (SPAs) that proved to be highly efficient in asymmetric catalysis.[10] Employing such chiral SPAs, we recently reported a triple-hydrogen-bond-directed enantioselective Pictet−Spengler reaction for construction of

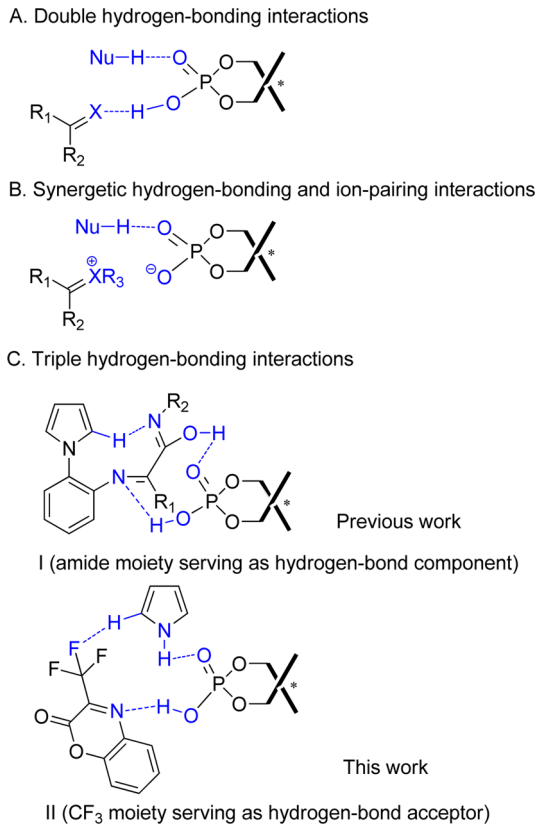


Figure 1. Asymmetric activation mode of phosphoric catalysis.

pyrrolobenzo-1,4-diazine skeletons with an amide-containing quaternary stereocenter, and the amide moiety as an enol tautomer served as an unexpected hydrogen-bond component

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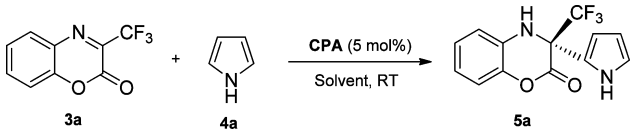
to form a C−H···N hydrogen bond (C−I, Figure 1).[11] Here, we report a highly enantioselective aza-Friedel−Crafts reaction[12] catalyzed by chiral SPAs for the synthesis of dihydrobenzoxazinones bearing trifluoromethylated quaternary stereocenters. Interestingly, a remarkable fluorine effect was observed. Preliminary mechanistic studies combined with theory calculations disclose that triple-hydrogen-bonding interactions are crucial in activating substrates and inducing chirality, and the CF_3 moiety serves as an attractive hydrogen-bond acceptor to form an attractive C−H···F hydrogen bond (C−II, Figure 1).

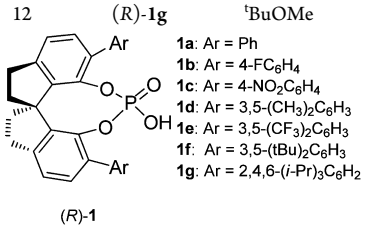
RESULTS AND DISCUSSION

In our initial study, we examined the reaction of trifluoromethyl benzoxazinone **3a** with pyrrole **4a** by chiral phosphoric acid catalysis. In the presence of 5 mol % (*R*)-**1a**, the reaction provided the desired product **5a** in 92% yield with 20% ee (Table 1, entry 1). Further evalutation of various chiral

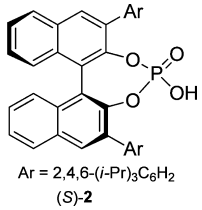
Table 1. Reaction Optimization[a]



entry	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	(*R*)-**1a**	toluene	92	20
2	(*R*)-**1b**	toluene	90	40
3	(*R*)-**1c**	toluene	94	40
4	(*R*)-**1d**	toluene	90	7
5	(*R*)-**1e**	toluene	96	40
6	(*R*)-**1f**	toluene	90	91
7	(*R*)-**1g**	toluene	96	91
8	(*S*)-**2**	toluene	97	87
9	(*R*)-**1g**	*m*-xylene	93	91
10	(*R*)-**1g**	CH_2Cl_2	96	90
11	(*R*)-**1g**	MeCN	85	87
12	(*R*)-**1g**	^{t}BuOMe	86	83



1a: Ar = Ph
1b: Ar = 4-FC_6H_4
1c: Ar = 4-$NO_2C_6H_4$
1d: Ar = 3,5-$(CH_3)_2C_6H_3$
1e: Ar = 3,5-$(CF_3)_2C_6H_3$
1f: Ar = 3,5-$(tBu)_2C_6H_3$
1g: Ar = 2,4,6-$(i\text{-}Pr)_3C_6H_2$



[a]Reactions were performed with **3a** (0.1 mmol), **4a** (0.12 mmol), and catalyst (5 mol %) in 1 mL of solvent at rt for 18 h. [b]Isolated yields. [c]Determined by chiral HPLC analysis.

phosphoric acid catalysts with different substituents and backbones indicated that all of the reactions proceeded smoothly to afford the desired trifluoromethylated dihydrobenzoxazinone **5a** in generally excellent yield with variable enantiocontrol (Table 1, entries 1−8). Among the catalysts screened, (*R*)-SPINOL-derived **1g** provided the best results in terms of yield and enantioselectivity (96% yield, 91% ee, Table 1, entry 7). Other reaction solvents such as *m*-xylene, CH_2Cl_2, MeCN, and ^{t}BuOMe were also effective but with either reduced yield or diminished enantioselectivity (Table 1, entries 9−12).

With the optimized reaction conditions in hand (Table 1, entry 7), we next explored the reaction scope. The results are summarized in Table 2. First, the effect of the substituents on the trifluoromethyl benzoxazinones **3** was investigated by examining their reaction with pyrrole **4a**. A range of trifluoromethyl benzoxazinones (**3a−g**) all smoothly participated in the asymmetric reaction to provide the corresponding products in excellent yields and enantioselectivities (**5a−g**, 86−96% yield, 87−93% ee; Table 2). Next, the reactions of trifluoromethyl benzoxazinones **3** with 2-phenylpyrrole **4b** were also tested. In all cases, high yields and excellent enantioselectivities were achieved (**5h−l**, 87−91% yield, 90−94% ee; Table 2). In addition, 2-arylpyrroles bearing either an electron-donating or an electron-withdrawing substituent on the aryl group were also well tolerated, and the desired products were generated smoothly with satisfactory efficiency and enantioselectivity (**5m−s**, 85−96% yield, 91−97% ee; Table 2). It is noteworthy that the absolute configuration (*R*) of the quaternary stereogenic center in **5a** was determined by X-ray crystallographic analysis (Figure 2).

To further demonstrate that this protocol is readily practical, we next carried out scale-up experiments with low catalyst loading. These results are summarized in Scheme 1. When the catalyst loading was decreased to 1 and 0.5 mol %, the reaction of **3a** with pyrrole proceeded smoothly with comparable yield and slightly improved enantioselectivity (91% yield, 94% ee and 85% yield, 93% ee, respectively). However, a further decrease of the catalyst loading to 0.1 mol % led to a drop in yield after extending the reaction time to 72 h but did not compromise the enantioselectivity (70% yield, 91% ee).

To understand the mechanism and the origin of the enantioselectivity, we performed computational studies for the transition-state structure leading to the major product (*R*)-**5a** (see the Supporting Information). The results of the theory calculations and the transition states are represented in Figure 3. In support of the experimental observations, the *re* face attack **R-TS-CF$_3$** is predicted to be favored over the *si* face attack **S-TS-CF$_3$** by 5.4 kcal mol^{-1} after adding the solvent free energy.[13] In addition, the chiral phosphoric acid catalyst concurrently activates both the nucleophilic group and the electrophilic group through the usual double-hydrogen-bonding interactions, and an unexpected attractive C−H···F hydrogen bond (2.21 Å) is observed in the calculated transition state. In the most favorable transition state **R-TS-CF$_3$**, a benzoxazinone fragment of substrate **3a** is almost parallel to the aryl plane of the catalyst substituent to avoid steric congestion. This is not the case for the transition state **S-TS-CF$_3$**, which has a perpendicular orientation that leads to steric repulsion between the pyrrole and one of the triisopropylphenyl groups of the catalyst. This likely causes the large relative energy (5.4 kcal mol^{-1}) between the two transition states. Thus, the triple-hydrogen-bonding interactions hold the transition structure rigidly and allow the bulky substituents of the catalyst to influence the enantioselectivity.

To gain further mechanistic insight into this asymmetric aza-Friedel−Crafts reaction, we attempted to use *N*-benzylpyrrole as a nucleophile to react with trifluoromethyl benzoxazinone **3a** with the standard protocol; however, the desired adduct was not detected, even under reflux with an extended reaction time (24 h). Hence, this result suggests that the pyrrole NH moiety provides a hydrogen-bonding interaction with the phosphoryl oxygen atom of the catalyst. Furthermore, we treated benzoxazinones **3h−k** with pyrrole to form the corresponding products **5t−w** with only moderate yields and poor to moderate enantioselectivities under standard reaction con-

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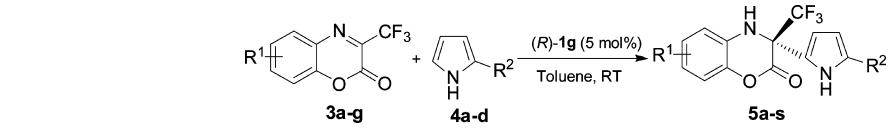
Table 2. Substrate Scope[a]



5a
96% yield, 91% ee

5b
95% yield, 91% ee

5c
96% yield, 92% ee

5d
90% yield, 93% ee

5e
86% yield, 90% ee

5f
92% yield, 88% ee

5g[b]
88% yield, 87% ee

5h
87% yield, 93% ee

5i
90% yield, 94% ee

5j[c]
90% yield, 90% ee

5k[c]
87% yield, 92% ee

5l
91% yield, 90% ee

5m(Ar= p-ClC_6H_4)
85% yield, 92% ee

5n[c](Ar=*p*-ClC_6H_4)
96% yield, 94% ee

5o[c](Ar=*p*-ClC_6H_4)
86% yield, 92% ee

5p[c](Ar=*p*-ClC_6H_4)
89% yield, 97% ee

5q (Ar=*p*-MeC_6H_4)
92% yield, 94% ee

5r (Ar=*p*-MeC_6H_4)
96% yield, 91% ee

5s(Ar=*p*-MeC_6H_4)
86% yield, 93% ee

[a]Reactions were performed with **3** (0.1 mmol), **4** (0.12 mmol), and (*R*)-**1g** (5 mol %) in 1 mL of toluene at rt for 18 h. Yields are of isolated product. Enantioselectivity was determined by chiral HPLC. [b]Under reflux. [c]With (*S*)-**2** (5 mol %) as the catalyst.

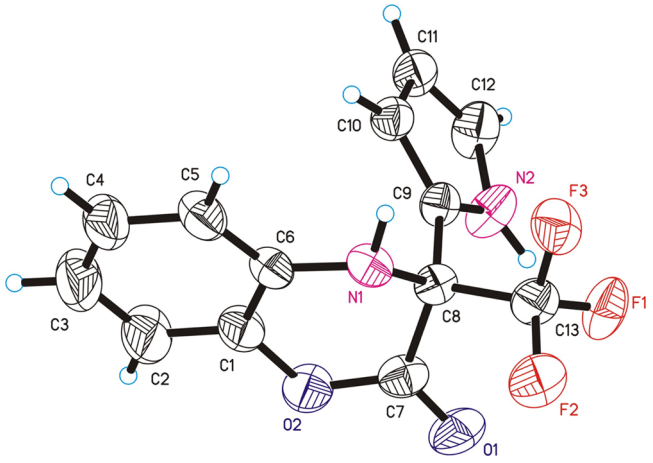
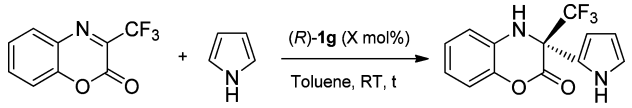


Figure 2. X-ray crystal structure of (*R*)-**5a** (ellipsoids are drawn at the 50% probability level).

Scheme 1. Scalable Preparation with Low Catalyst Loading



3a
0.43 g
2 mmol

4a
0.16 g
2.4 mmol

5a
X=1, t= 24h: 91% yield, 94% *ee*
X=0.5, t= 60h: 85% yield, 93% *ee*
X=0.1, t= 72h: 70% yield, 91% *ee*

ditions (Scheme 2). These results clearly indicate a remarkable fluorine effect[14] of the CF_3-bearing substrate on the activation and stereoinduction, and this is consistent with the theory calculations.

We also computationally investigated the low yield and enantioselectivity of the reaction of methyl benzoxazinone **3i** with pyrrole under standard reaction conditions (see the Supporting Information). The optimized transition states (**S-TS-CH$_3$** and **R-TS-CH$_3$**) and their relative stabilities are represented in Figure 4. Interestingly, the *si* face attack **S-TS-**

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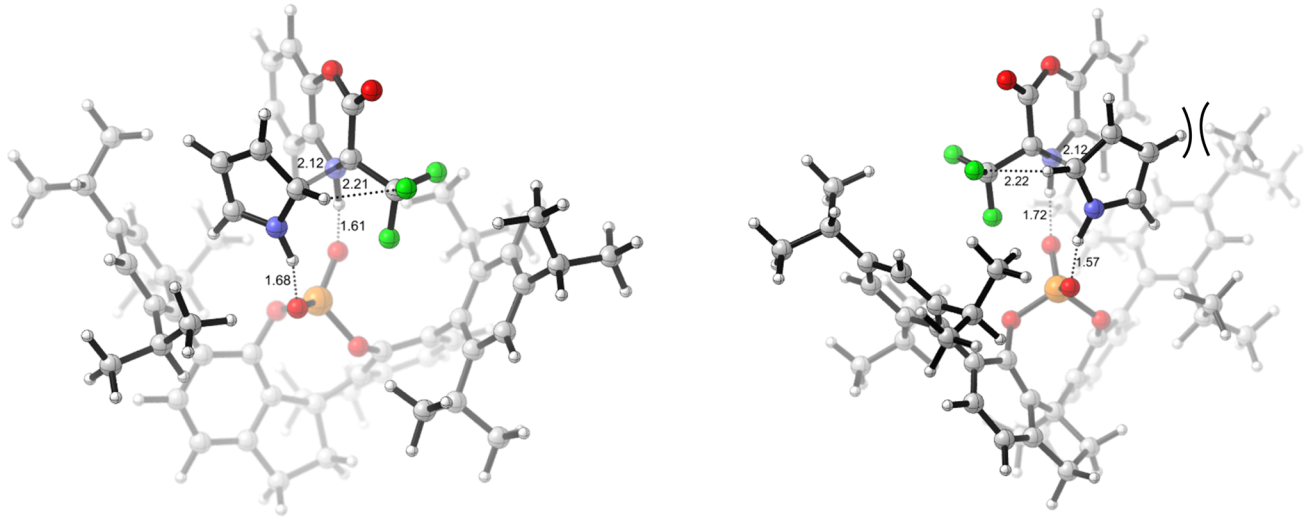
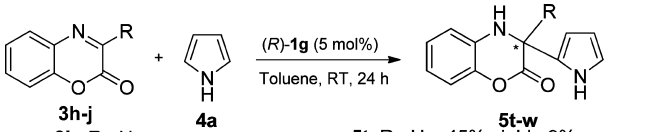


R-TS-CF_3 *Re* face
$\Delta\Delta G$ = 0.0 kcal mol^{-1}

S-TS-CF_3 *Si* face
$\Delta\Delta G$ = 5.4 kcal mol^{-1}

Figure 3. Optimized transition states of (*R*)-**1g**-catalyzed reaction between **3a** and pyrrole. Relative energies are in kcal mol^{-1}, and distances are in Å.

Scheme 2. Experiments for Mechanistic Studies



3h-j
3h: R= H
3i: R= Me
3j: R= Ph
3k: R= CHF_2

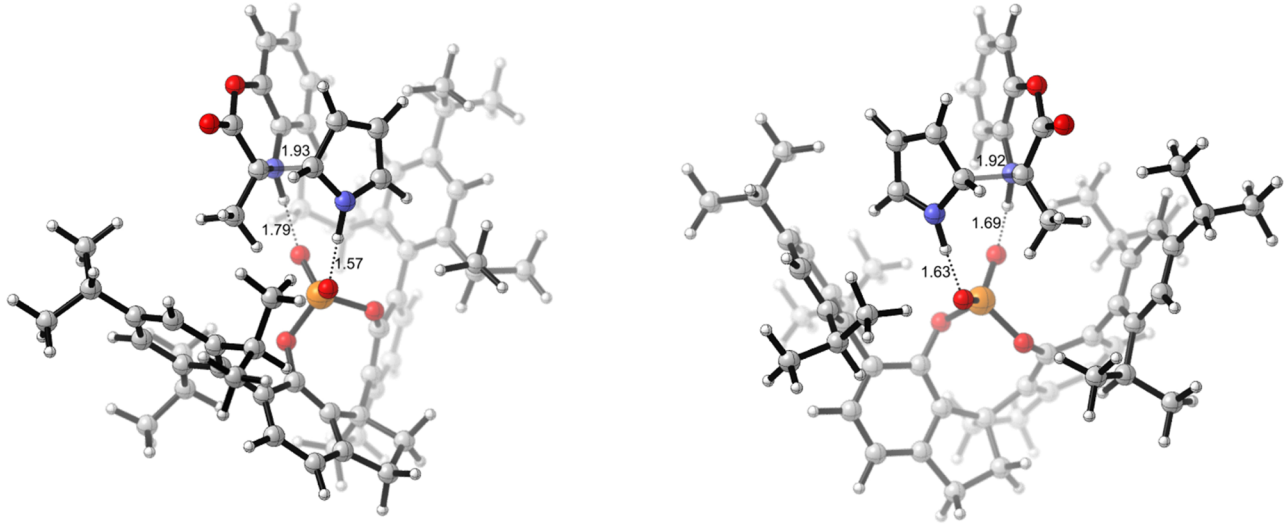
4a

5t-w
5t: R= H, 45% yield, 9% *ee*
5u: R= Me, 41% yield, 20% *ee*
5v: R= Ph, 47% yield, 66% *ee*
5w: R= CHF_2, 80% yield, 70% *ee*

CH_3 is predicted to be more favored than the *re* face attack **R-TS-CH_3** by 0.4 kcal mol^{-1} after adding the solvent free energy. Only usual double-hydrogen-bonding interactions are identified to activate the substrate, which may lead to a low reaction rate and yield and the generation of the opposite enantiomer via *si* face attack. The calculated enantioselectivity of **3i** ($\Delta\Delta G$ = 0.4 kcal mol^{-1}) is much lower when compared to that of trifluoromethyl benzoxazinone **3a** ($\Delta\Delta G$ = 5.4 kcal mol^{-1}), and the calculations are in agreement with the experiments (20% ee vs 91% ee). This is likely caused by the different relative steric clash between the bulky substituent groups of the catalyst and substrate during different hydrogen-bonding interactions.

CONCLUSION

In summary, a highly enantioselective chiral phosphoric acid-catalyzed aza-Friedel–Crafts reaction of trifluoromethyl benzoxazinones with pyrroles has been developed.[15] This



S-TS-CH_3 *Si* face
$\Delta\Delta G$ = -0.4 kcal mol^{-1}

R-TS-CH_3 *Re* face
$\Delta\Delta G$ = 0.0 kcal mol^{-1}

Figure 4. Optimized transition states of the (*R*)-**1g**-catalyzed reaction between **3i** and pyrrole. Relative energies are in kcal mol^{-1}, and distances are in Å.

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protocol provides facile and highly efficient access to functionalized dihydrobenzoxazinones bearing trifluoromethylated quaternary stereocenters in excellent yields and enantioselectivities and involves a simple scalable experimental procedure with low catalyst loading under mild conditions. A remarkable fluorine effect is observed, and preliminary mechanistic studies combined with theory calculations suggest that triple-hydrogen-bond interactions hold the transition structure rigidly to activate substrates and induce chirality in asymmetric phosphoric acid catalysis with the CF_3 moiety serving as an attractive hydrogen-bond acceptor.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were measured on 400, 100, and 376 MHz spectrometers, respectively. The chemical shifts were reported relative to internal standard TMS (0) in $CDCl_3$. Infrared spectra were recorded on an ATR-FTIR spectrometer. HRMS data were obtained using EI ionization. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at 20 °C. Enantiomeric excesses (ee) were determined by chiral high-performance liquid chromatography. Analytical-grade solvents for column chromatography and commercially available reagents were used as received. The chiral spirocyclic phosphoric acid catalysts were prepared according to the literature procedures.[10b,d] The syntheses of 2-arylpyrroles and substituted benzoxazinone derivatives were accomplished following the literature procedures.[16,17]

General Procedure for Asymmetric Synthesis of Dihydrobenzoxazinones (5). To a solution of benzoxazinone **3** (0.1 mmol) and pyrrole **4** (0.12 mmol) in toluene (1 mL) was added either catalyst (*R*)-**1g** (0.005 mmol) or catalyst (*S*)-**2** (0.005 mmol). The resulting mixture was stirred for the indicated time at room temperature under a nitrogen atmosphere. After the reaction was complete, the reaction mixture was subjected to a silica gel column (petroleum ether/ethyl acetate) to afford the desired product **5**. All of the products were fully characterized, and their characterization data are listed below.

*(R)-3-(1H-Pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5a**).* Twenty-seven milligrams, 96% yield; yellow solid; mp 104.1−105.2 °C; 91% ee; HPLC analysis (Chiralpak OD-H hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 10.978 min, t_R (major) 16.172 min; $[\alpha]_D^{20}$ = −190.1 (*c* = 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.15−7.04 (m, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.94 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.91−6.84 (m, 2H), 6.28 (m, 1H), 6.16 (dd, *J* = 6.1, 2.8 Hz, 1H), 4.74 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −69.59 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 139.3, 128.8, 125.9, 122.9 (q, *J* = 285 Hz), 121.3, 121.1, 120.9, 116.8, 114.9, 109.5, 108.9, 63.1 (q, *J* = 29 Hz); IR (film) 3406, 3058, 2926, 2855, 1620, 1596, 1560, 1495, 1474, 1459, 1058, 958, 746 cm^{-1}; HRMS (EI-TOF) calcd for $C_{13}H_9F_3N_2O_2$ 282.0616, found 282.0613.

*(R)-6-Fluoro-3-(1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5b**).* Twenty-nine milligrams, 95% yield; white solid; mp 122.5−124.7 °C; 91% ee; HPLC analysis (Chiralpak OD-H hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 13.745 min, t_R (major) 18.205 min; $[\alpha]_D^{20}$ = −127.1 (*c* = 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 6.97−6.91 (m, 1H), 6.91−6.87 (m, 1H), 6.72−6.64 (m, 1H), 6.62−6.51 (m, 1H), 6.33−6.26 (m, 1H), 6.21−6.14 (m, 1H), 4.87 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.64 to −80.10 (m, 3F), −109.85 to −120.57 (m, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (d, *J* = 243 Hz), 159.6, 135.4 (d, *J* = 3 Hz), 129.9 (*J* = 11 Hz), 122.8 (q, *J* = 285 Hz), 121.6, 120.5, 117.9 (d, *J* = 10 Hz), 110.0, 109.0, 107.4 (d, *J* = 24 Hz), 102.1 (d, *J* = 28 Hz), 62.5 (q, *J* = 29 Hz); IR (film) 3395, 1755, 1636, 1514, 1409, 1332, 1280, 1196, 1104, 1040, 992, 843, 733 cm^{-1}; HRMS (EI-TOF) calcd for $C_{13}H_8F_4N_2O_2$ 300.0522, found 300.0523.

*(R)-6-Chloro-3-(1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5c**).* Thirty milligrams, 96% yield; brown solid; mp 131.1−133.5 °C; 92% ee; HPLC analysis (Chiralpak OD-H hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 14.620 min, t_R (major) 29.410 min; $[\alpha]_D^{20}$ = −173.8 (*c* = 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 6.95 (d, *J* = 4 Hz, 1H), 6.94−6.88 (m, 2H), 6.88−6.82 (m, 1H), 6.32−6.26 (m, 1H), 6.23−6.15 (m, 1H), 4.82 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.41 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 137.8, 131.0, 129.8, 122.8 (q, *J* = 285 Hz), 121.6, 120.9, 120.4, 117.9, 114.8, 110.1, 109.0, 62.5 (q, *J* = 296 Hz); IR (film) 3373, 1763, 1498, 1392, 1311, 1282, 1201, 1119, 1098, 990, 929, 849, 803, 733 cm^{-1}; HRMS (EI-TOF) calcd for $C_{13}H_8ClF_3N_2O_2$ 316.0226, found 316.0227.

*(R)-7-Bromo-3-(1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5d**).* Thirty-two milligrams, 90% yield; brown solid; mp 126.7−128 °C; 93% ee; HPLC analysis (Chiralpak OD-H hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 14.443 min, t_R (major) 26.229 min; $[\alpha]_D^{20}$ = −39.1 (*c* = 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.24−7.18 (m, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 6.93−6.87 (m, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.29−6.23 (m, 1H), 6.21−6.13 (m, 1H), 4.74 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.43 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 139.7, 128.8, 128.1, 122.7 (q, *J* = 285 Hz), 121.6, 120.4, 120.0, 116.1, 112.4, 110.1, 109.0, 62.7 (q, *J* = 28.9 Hz); IR (film) 3583, 3371, 1766, 1597, 1496, 1404, 1303, 1201, 1128, 1098, 1068, 992, 891, 808, 742 cm^{-1}; HRMS (EI-TOF) calcd for $C_{13}H_8BrF_3N_2O_2$ 359.9721, found 359.9722.

*(R)-6-Methyl-3-(1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5e**).* Twenty-six milligrams, 86% yield; brown solid; mp 113.8−115.5 °C; 90% ee; HPLC analysis (Chiralpak OD-H hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 14.512 min, t_R (major) 31.633 min; $[\alpha]_D^{20}$ = −100.8 (*c* = 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 6.90−6.83 (m, 2H), 6.74 (d, *J* = 1.2 Hz, 1H), 6.70−6.64 (m, 1H), 6.33−6.25 (m, 1H), 6.19−6.12 (m, 1H), 4.66 (s, 1H), 2.30 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.43 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 137.3, 135.9, 128.4, 122.9 (q, *J* = 285 Hz), 121.6, 121.2, 121.0, 116.5, 115.3, 109.9, 108.9, 62.8 (q, *J* = 29 Hz), 21.0; IR (film) 3368, 2923, 1754, 1624, 1517, 1487, 1321, 1204, 1122, 1098, 1040, 992, 804, 733 cm^{-1}; HRMS (EI-TOF) calcd for $C_{14}H_{11}F_3N_2O_2$ 296.0773, found 296.0777.

*(R)-7-Methyl-3-(1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5f**).* Twenty-seven milligrams, 92% yield; white solid; mp 131.5−133 °C; 88% ee; HPLC analysis (Chiralpak OD-H hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 9.975 min, t_R (major) 20.409 min; $[\alpha]_D^{20}$ = −43.1 (*c* = 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 6.93−6.77 (m, 4H), 6.31−6.24 (m, 1H), 6.21−6.11 (m, 1H), 4.59 (s, 1H), 2.26 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.38 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 139.3, 131.2, 126.4, 126.2, 122.9 (q, *J* = 285 Hz), 121.2, 120.9, 117.2, 114.9, 109.9, 108.9, 62.9 (q, *J* = 29.3 Hz), 20.5; IR (film) 3376, 3319, 1745, 1601, 1521, 1418, 1306, 1187, 1116, 1097, 1041, 1014, 985, 818, 748, 731 cm^{-1}; HRMS (EI-TOF) calcd for $C_{14}H_{11}F_3N_2O_2$ 296.0773, found 296.0770.

*(R)-5-Methyl-3-(1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5g**).* Twenty-six milligrams, 88% yield; brown solid; mp 97.3−99.6 °C; 87% ee; HPLC analysis (Chiralpak OD-H hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 7.925 min, t_R (major) 10.305 min; $[\alpha]_D^{20}$ = −29 (*c* = 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 6.96 (d, *J* = 8 Hz, 1H), 6.91−6.84 (m, 2H), 6.83−6.76 (m, 1H), 6.22−6.17 (m, 1H), 6.18−6.13 (m, 1H), 4.52 (s, 1H), 2.35 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.51 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 139.3, 126.1 (q, *J* = 248 Hz), 127.1, 126.9, 123.0, 121.4, 121.0, 120.5, 114.7, 109.4, 108.9, 62.9 (q, *J* = 291 Hz), 16.4; IR (film) 3401, 1764, 1484, 1303, 1246, 1197, 1119, 1098, 1044, 989, 769, 736 cm^{-1}; HRMS (EI-TOF) calcd for $C_{14}H_{11}F_3N_2O_2$ 296.0773, found 296.0775.

*(R)-3-(5-Phenyl-1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5h**).* Thirty-one milligrams, 87% yield; purple solid; mp 110.5−112.1 °C; 93% ee; HPLC analysis (Chiralpak IA hexane/i-PrOH = 80/20, 0.8 mL/min), t_R (minor) 10.269 min, t_R (major) 8.819 min; $[\alpha]_D^{20}$ = +111.8 (*c* = 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.49−7.42 (m, 2H), 7.39−7.36 (m, 2H), 7.29−7.22 (m, 1H), 7.14−7.06 (m, 1H),

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7.05−6.98 (m, 1H), 6.98−6.94 (m, 1H), 6.93−6.85 (m, 1H), 6.43−6.38 (m, 1H), 6.36−6.30 (m, 1H), 4.74 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.27 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 139.3, 135.7, 131.5, 129.0, 128.8, 127.3, 126.0, 124.3, 122.7 (q, J = 244 Hz), 121.5, 121.2, 116.9, 114.9, 111.6, 106.3, 62.9 (q, J = 29.4 Hz); IR (film) 3372, 1764, 1624, 1503, 1303, 1259, 1197, 1113, 990, 915, 751, 692 cm^{-1}; HRMS (EI-TOF) calcd for $C_{19}H_{13}F_3N_2O_2$ 358.0929, found 358.0929.

*(R)-6-Fluoro-3-(5-phenyl-1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5i**).* Thirty-four milligrams, 90% yield; brown solid; mp 131.7−133.6 °C; 94% ee; HPLC analysis (Chiralpak IA hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 13.915 min, t_R (major) 11.501 min; $[\alpha]_D^{20}$ = +142.1 (c = 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.46 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.7 Hz, 2H), 7.31−7.24 (m, 1H), 6.96 (dd, J = 8.9, 4.9 Hz, 1H), 6.69 (dd, J = 8.8, 2.7 Hz, 1H), 6.65−6.54 (m, 1H), 6.45−6.39 (m, 1H), 6.37−6.31 (m, 1H), 4.85 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.34 (d, J = 17.8 Hz, 1F), −110.23 to −119.82 (m, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.6, 158.9, 135.9, 135.4 (d, J = 2 Hz), 131.5, 129.8 (d, J = 109 Hz), 129.0, 127.4, 124.3, 121.1, 118.0 (d, J = 9.9 Hz), 111.6, 107.5 (d, J = 24 Hz), 106.3, 102.1 (d, J = 27.6 Hz), 62.5 (q, J = 29.2 Hz); IR(film) 3370, 1763, 1636, 1514, 1332, 1198, 1104, 992, 843, 758 cm^{-1}; HRMS (EI-TOF) calcd for $C_{19}H_{12}F_4N_2O_2$ 376.0835, found 376.0830.

*(R)-6-Chloro-3-(5-phenyl-1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5j**).* Thirty-five milligrams, 90% yield; purple solid; mp 158.6−160 °C; 90% ee; HPLC analysis (Chiralpak IA, hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 12.923 min, t_R (major) 10.875 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.46 (dd, J = 8.2, 1.1 Hz, 2H), 7.41−7.35 (m, 2H), 7.29−7.23 (m, 1H), 6.99−6.91 (m, 2H), 6.85 (dd, J = 8.6, 2.2 Hz, 1H), 6.42 (dd, J = 3.7, 2.8 Hz, 1H), 6.33 (dd, J = 3.7, 2.8 Hz, 1H), 4.89 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.27 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 137.8, 135.9, 131.5, 131.1, 129.8, 129.0, 127.4, 124.3, 122.8 (q, J = 285 Hz), 121.0, 120.9, 117.9, 114.8, 111.7, 106.3, 62.6 (q, J = 29 Hz); IR (film) 3370, 3071, 1765, 1620, 1498, 1455, 1392, 1310, 1278, 1200, 1119, 1083, 990, 931, 908, 850, 801, 784, 757, 693, 649 cm^{-1}; HRMS (EI-TOF) calcd for $C_{19}H_{12}ClF_3N_2O_2$ 392.0539, found 392.0537.

*(R)-6-Methyl-3-(5-phenyl-1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5k**).* Thirty-three milligrams, 87% yield; purple solid; mp 125.4−126.7 °C; 92% ee; HPLC analysis (Chiralpak IA, hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 16.254 min, t_R (major) 11.436 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.45 (d, J = 7.4 Hz, 2H), 7.37 (d, J = 7.7 Hz, 2H), 7.29−7.22 (m, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.75 (s, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.44−6.38 (m, 1H), 6.37−6.31 (m, 1H), 4.71 (s, 1H), 2.31 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.28 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 137.4, 136.0, 135.6, 131.6, 129.0, 128.4, 127.3, 124.3, 123.0 (q, J = 285 Hz), 121.8, 121.7, 116.6, 115.4, 111.6, 106.3, 62.9 (q, J = 29 Hz), 21.0; IR (film) 3453, 3373, 2924, 1754, 1623, 1516, 1487, 1455, 1320, 1287, 1204, 1124, 1073, 993, 905, 861, 801, 783, 757, 692, 650 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{15}F_3N_2O_2$ 372.1086, found 372.1082.

*(R)-7-Methyl-3-(5-phenyl-1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5l**).* Thirty-four milligrams, 91% yield; purple solid; mp 136.8−137.5 °C; 91% ee; HPLC analysis (Chiralpak OD-H, hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 26.310 min, t_R (major) 12.983 min; $[\alpha]_D^{20}$ = +37.3 (c = 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.48−7.42 (m, 2H), 7.41−7.34 (m, 2H), 7.29−7.23 (m, 1H), 6.94−6.79 (m, 3H), 6.40 (t, J = 3.2 Hz, 1H), 6.32 (t, J = 3.2 Hz, 1H), 4.64 (s, 1H), 2.27 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.25 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 139.4, 135.5, 131.6, 131.3, 129.0, 127.2, 126.5, 126.2, 124.3, 122.8 (q, J = 254.5 Hz), 121.6, 117.3, 114.9, 111.6, 106.3, 63.0 (q, J = 29.5 Hz), 20.6; IR (film) 3375, 2929, 1752, 1522, 1301, 1196, 1126, 1010, 811, 757, 692 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{15}F_3N_2O_2$ 372.1086, found 372.1089.

*(R)-3-(5-(4-Chlorophenyl)-1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5m**).* Thirty-three milligrams, 85% yield; purple solid; mp 139.2−140.1 °C; 92% ee; HPLC analysis (Chiralpak IA, hexane/i-PrOH = 80/20, 0.8 mL/min), t_R (minor) 10.153 min, t_R (major) 8.178 min; $[\alpha]_D^{20}$ = +116.4 (c = 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.40−7.32 (m, 4H), 7.15−7.06 (m, 1H), 7.01 (dd, J = 8.1, 1.2 Hz, 1H), 6.96 (dd, J = 7.9, 1.4 Hz, 1H), 6.93−6.87 (m, 1H), 6.42−6.37 (m, 1H), 6.36−6.31 (m, 1H), 4.73 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.25 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 139.3, 134.5, 133.0, 130.1, 129.1, 128.7, 126.1, 125.5, 124.7 (q, J = 81.2 Hz), 122.0, 121.2, 116.9, 114.9, 111.7, 106.7, 62.9 (q, J = 29.3 Hz); IR (film) 3377, 1752, 1502, 1302, 1198, 986, 825, 747 cm^{-1}; HRMS (EI-TOF) calcd for $C_{19}H_{12}ClF_3N_2O_2$ 392.0539, found 392.0534.

*(R)-3-(5-(4-Chlorophenyl)-1H-pyrrol-2-yl)-6-fluoro-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5n**).* Forty milligrams, 96% yield; purple solid; mp 171.5−172.3 °C; 94% ee; HPLC analysis (Chiralpak IA, hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 15.609 min, t_R (major) 12.565 min; $[\alpha]_D^{20}$ = +74.7 (c = 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.40−7.32 (m, 4H), 7.00−6.93 (m, 1H), 6.73−6.66 (m, 1H), 6.63−6.55 (m, 1H), 6.40 (dd, J = 3.7, 2.8 Hz, 1H), 6.34 (dd, J = 3.8, 2.7 Hz, 1H), 4.86 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.29 (d, J = 18.5 Hz, 1F), −112.70 to −116.82 (m, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (d, J = 242.7 Hz), 159.6, 135.4, 134.8, 133.1, 129.9, 129.7 (d, J = 11.3 Hz), 129.1, 125.5, 124.6 (q, J = 92 Hz), 121.6, 118.0 (d, J = 91 Hz), 111.7, 107.6 (d, J = 23.6 Hz), 106.7, 102.1 (d, J = 27.9 Hz), 62.5 (q, J = 29.3 Hz); IR (film) 3362, 1752, 1637, 1514, 1332, 1193, 1104, 992, 779 cm^{-1}; HRMS (EI-TOF) calcd for $C_{19}H_{11}ClF_4N_2O_2$ 410.0445, found 410.0448.

*(R)-3-(5-(4-Chlorophenyl)-1H-pyrrol-2-yl)-6-methyl-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5o**).* Thirty-five milligrams, 86% yield; purple solid; mp 106.2−107.5 °C; 92% ee; HPLC analysis (Chiralpak IA, hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 12.517 min, t_R (major) 8.024 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.40−7.31 (m, 4H), 6.88 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 1.2 Hz, 1H), 6.68 (dd, J = 8.2, 1.2 Hz, 1H), 6.42−6.37 (m, 1H), 6.34 (dd, J = 3.7, 2.7 Hz, 1H), 4.67 (s, 1H), 2.31 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.26 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 137.4, 136.1, 134.5, 132.9, 130.1, 129.2, 128.3, 125.5, 123.7 (q, J = 295 Hz), 121.8, 116.6, 115.4, 111.7, 107.0, 106.7, 62.9 (q, J = 29 Hz), 21.0; IR (film) 3455, 3378, 2924, 1752, 1623, 1516, 1503, 1321, 1287, 1205, 1124, 1096, 1069, 1012, 993, 906, 861, 827, 802, 776, 732 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{14}ClF_3N_2O_2$ 406.0696, found 406.0700.

*(R)-3-(5-(4-Chlorophenyl)-1H-pyrrol-2-yl)-7-methyl-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5p**).* Thirty-six milligrams, 89% yield; yellow solid; mp 145.3−146.6 °C; 97% ee; HPLC analysis (Chiralpak IA, hexane/i-PrOH = 90/10, 0.8 mL/min), t_R (minor) 71.170 min, t_R (major) 58.643 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.41−7.32 (m, 4H), 6.90 (d, J = 8.0 Hz, 1H), 6.87−6.80 (m, 2H), 6.41−6.37 (m, 1H), 6.35−6.31 (m, 1H), 4.63 (s, 1H), 2.27 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.22 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 139.4, 134.4, 132.9, 131.4, 130.1, 129.2, 126.6, 126.1, 125.5, 122.1, 122.9 (q, J = 285 Hz), 117.3, 114.9, 111.7, 106.7, 63.0 (q, J = 29.2 Hz), 20.6; IR (film) 3376, 2923, 1754, 1522, 1415, 1301, 1196, 1125, 1012, 827, 777, 732 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{14}ClF_3N_2O_2$ 406.0696, found 406.0698.

*(R)-3-(5-(p-Tolyl)-1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5q**).* Thirty-four milligrams, 92% yield; purple solid; mp 127.5−128.9 °C; 94% ee; HPLC analysis (Chiralpak IA, hexane/i-PrOH = 80/20, 0.8 mL/min), t_R (minor) 10.974 min, t_R (major) 8.918 min; $[\alpha]_D^{20}$ = +320.6 (c = 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.13−7.06 (m, 1H), 7.00 (dd, J = 8.1, 1.2 Hz, 1H), 6.95 (dd, J = 7.9, 1.3 Hz, 1H), 6.92−6.85 (m, 1H), 6.37−6.34 (m, 1H), 6.33−6.29 (m, 1H), 4.75 (s, 1H), 2.35 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.29 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 139.3, 137.1, 135.8, 129.6, 128.8, 128.8, 126.0, 124.2, 122.9 (q, J = 285.1 Hz), 121.1, 121.0, 116.9, 114.9, 111.5, 105.7, 61.4 (q, J = 29.4 Hz), 21.1; IR (film) 3371, 3018, 2922, 2858, 1763, 1624, 1503, 1436,

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1301, 1258, 1196, 1113, 1071, 989, 914, 818, 776, 747 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{15}F_3N_2O_2$ 372.1086, found 372.1082.

*(R)-6-Fluoro-3-(5-(p-tolyl)-1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5r**).* Thirty-eight milligrams, 96% yield; purple solid; mp 177.5−178.8 °C; 91% ee; HPLC analysis (Chiralpak IA, hexane/i-PrOH = 80/20, 0.8 mL/min), t_R (minor) 9.707 min, t_R (major) 8.123 min; $[\alpha]_D^{20}$ = +388 (*c* = 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 6.99−6.93 (m, 1H), 6.69 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.63−6.54 (m, 1H), 6.40−6.35 (m, 1H), 6.34−6.28 (m, 1H), 4.82 (s, 1H), 2.36 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.33 (s, 3F), −115.28 (dd, *J* = 8.3, 5.3 Hz, 1F); ^{13}CNMR (100 MHz, $CDCl_3$) δ 160.1 (d, *J* = 242.8 Hz), 159.6, 137.3, 136.1, 135.4, 129.9 (d, *J* = 11.3 Hz), 129.7, 128.7, 124.3, 122.6 (q, *J* = 253.3 Hz), 120.6, 118.0 (d, *J* = 9.9 Hz), 111.5, 107.5 (d, *J* = 23.8 Hz), 105.8, 102.1 (d, *J* = 27.5 Hz), 62.5 (q, *J* = 29.6 Hz), 21.2; IR (film) 3461, 3437, 3344, 3084, 1751, 1639, 1516, 1496, 1412, 1327, 1276, 1244, 1191, 1166, 1104, 1052, 992, 868, 852, 817, 777, 726, 669 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{14}F_4N_2O_2$ 390.0991, found 390.0994.

*(R)-7-Methyl-3-(5-(p-tolyl)-1H-pyrrol-2-yl)-3-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5s**).* Thirty-three milligrams, 86% yield; purple solid; mp 150.1−151.5 °C; 93% ee; HPLC analysis (Chiralpak AD-H, hexane/i-PrOH = 90/10, 0.6 mL/min), t_R (minor) 32.464 min, t_R (major) 25.012 min; $[\alpha]_D^{20}$ = +236 (*c* = 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.36−7.31 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.93−6.78 (m, 3H), 6.38−6.33 (m, 1H), 6.32−6.28 (m, 1H), 4.64 (s, 1H), 2.35 (s, 3H), 2.26 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.24 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 139.3, 137.1, 135.7, 131.2, 129.6, 128.8, 126.4, 126.2, 124.2, 122.9 (q, *J* = 284.6 Hz), 121.1, 117.2, 114.9, 111.5, 105.8, 63.0 (q, *J* = 29.1 Hz), 21.1, 20.6; IR (film) 3373, 2923, 1752, 1520, 1414, 1301, 1265, 1196, 1125, 1010, 816, 775, 731 cm^{-1}; HRMS (EI-TOF) calcd for $C_{21}H_{17}F_3N_2O_2$ 386.1242, found 386.1244.

*3-(1H-Pyrrol-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5t**).* Ten milligrams, 45% yield; brown solid; mp 149.8−151.3 °C; 9% ee; HPLC analysis (Chiralpak OD-H hexane/i-PrOH = 80/20, 0.8 mL/min), t_R (minor) 24.182 min, t_R (major) 18.875 min; $[\alpha]_D^{20}$ = −4 (*c* = 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.08−7.01 (m, 2H), 6.92−6.78 (m, 3H), 6.22−6.08 (m, 2H), 5.16 (d, *J* = 1.6 Hz, 1H), 4.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 140.8, 132.1, 125.5, 125.3, 20.8, 119.4, 117.0, 115.2, 108.8, 108.3, 53.5; IR (film) 3402, 3375, 1748, 1502, 1305, 1196, 1090, 903, 802, 722 cm^{-1}; HRMS (EI-TOF) calcd for $C_{12}H_{10}N_2O_2$ 214.0742, found 214.0743.

*3-Methyl-3-(1H-pyrrol-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5u**).* Ten milligrams, 41% yield; yellow solid; mp 149.7−150.6 °C; 20% ee; HPLC analysis (Chiralpak OD-H hexane/i-PrOH = 85/15, 0.8 mL/min), t_R (minor) 17.573 min, t_R (major) 15.141 min; $[\alpha]_D^{20}$ = +6 (*c* = 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.06−7.00 (m, 1H), 7.00−6.96 (m, 1H), 6.88−6.80 (m, 2H), 6.76−6.72 (m, 1H), 6.40−5.79 (m, 2H), 4.21 (s, 1H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 140.7, 131.6, 130.7, 125.3, 120.4, 119.0, 116.6, 115.0, 108.6, 106.9, 57.1, 25.7; IR (film) 3364, 1752, 1619, 1501, 1207, 1089, 735 cm^{-1}; HRMS (EI-TOF) calcd for $C_{13}H_{12}N_2O_2$ 228.0899, found 228.0900.

*3-Phenyl-3-(1H-pyrrol-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5v**).* Fourteen milligrams, 47% yield; gray solid; mp 180−181.7 °C; 66% ee; HPLC analysis (Chiralpak OD-H hexane/i-PrOH = 80/20, 0.8 mL/min), t_R (minor) 11.912 min, t_R (major) 23.024 min; $[\alpha]_D^{20}$ = −8 (*c* = 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.33 (s, 5H), 7.03−6.97 (m, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.86−6.78 (m, 3H), 6.18−6.11 (m, 1H), 6.01 (t, *J* = 3.8 Hz, 1H), 4.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 140.9, 138.5, 131.6, 129.4, 128.8, 128.7, 126.8, 125.1, 120.6, 119.4, 116.6, 115.2, 109.5, 108.5, 64.5; IR (film) 3583, 3368, 3060, 1755, 1619, 1501, 1448, 1422, 1298, 1197, 1114, 1034, 912, 733, 699 cm^{-1}; HRMS (EI-TOF) calcd for $C_{18}H_{14}N_2O_2$ 290.1055, found 290.1058.

*3-(Difluoromethyl)-3-(1H-pyrrol-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**5w**).* Twenty-one milligrams, 80% yield; purple solid; mp 127.5−129 °C; 70% ee; HPLC analysis (Chiralpak OD-H hexane/i-PrOH = 80/20, 0.8 mL/min), t_R (minor) 11.646 min, t_R (major) 13.978 min; $[\alpha]_D^{20}$ = −101.8 (*c* = 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.11−7.03 (m, 1H), 7.01−6.91 (m, 2H), 6.91−6.79 (m, 2H), 6.37 (t, J_{H-F} = 56.0 Hz, 1H), 6.22 (s, 1H), 6.15 (dd, *J* = 6.1, 2.8 Hz, 1H), 4.66 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −127.24 (dd, J_{F-F} = 276.5 Hz, J_{F-H} = 54.6 Hz, 1F), −133.45 (dd, J_{F-F} = 276.4 Hz, J_{F-H} = 55.0 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 139.7, 129.5, 125.8, 121.0, 120.6, 116.9, 116.4, 115.6, 113.9 (t, *J* = 247 Hz), 111.4, 109.3, 62.0 (t, *J* = 44 Hz); IR (film) 3384, 2917, 1743, 1622, 1503, 1436, 1368, 1304, 1229, 1201, 1081, 1028, 905, 852, 802, 729 cm^{-1}; HRMS (EI-TOF) calcd for $C_{13}H_{10}F_2N_2O_2$ 264.0710, found 264.0709.

Scalable Preparation of 5a with Low Catalyst Loading. To a solution of benzoxazinone **3a** (0.43 g, 2 mmol) and pyrrole **4a** (0.16 g, 2.4 mmol) in toluene (20 mL) was added catalyst (*R*)-**1g** with the appointed loading as shown in Scheme 1. The resulting mixture was stirred at room temperature for the corresponding time under a nitrogen atmosphere. After the reaction was complete, the reaction mixture was quenched with aq $NaHCO_3$ and extracted with toluene. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed under reduced pressure, the residue was subjected to a silica gel column (petroleum ether/ethyl acetate) to afford the desired product **5a**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02848.

Details of the theory calculations and copies of ^{1}H, ^{13}C, and ^{19}F NMR and HPLC traces (PDF)

Crystallographic data for **5a** (CIF)

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Notes

The authors declare no competing financial interest.

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