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Asymmetric Formal Aza-Diels–Alder Reaction of Trifluoromethyl Hemiaminals with Enones Catalyzed by Primary Amines

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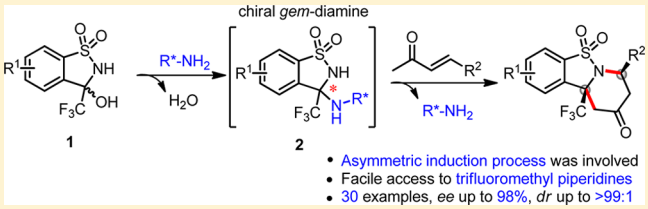
Supporting Information

ABSTRACT: A primary amine-catalyzed asymmetric formal aza-Diels–Alder reaction of trifluoromethyl hemiaminals with enones was developed via a chiral *gem*-diamine intermediate. This novel protocol allowed facile access to structurally diverse trifluoromethyl-substituted piperidine scaffolds with high stereoselectivity. The utility of this method was further demonstrated through a concise approach to biologically active 4-hydroxypiperidine. More importantly, a stepwise mechanism involving an asymmetric induction process was proposed to rationalize the positive correlation between the chirality of the *gem*-diamine intermediate and the formal aza-Diels–Alder product.



INTRODUCTION

Piperidine scaffold as a privileged substructure is widely found in natural products and pharmaceutically active molecules (Figure 1).[1] Meanwhile, fluorine as a unique element has been extensively exploited in drug design and development.[2] Consequently, the incorporation of these two important medicinal building blocks would provide a wide range of promising drug candidates. Very recently, a significant enhancement of pharmaceutical activity was observed when a trifluoromethyl-substituted piperidine was introduced to the janus kinase inhibitors (Figure 1).[3] Despite the potential pharmaceutical application of this trifluoromethylpiperidine structure, the development of related asymmetric reactions is largely lagging due to a limited availability of trifluoromethylated substrates and robust chiral catalysts.[4] In this context, a primary amine-catalyzed formal aza-Diels–Alder reaction of a trifluoromethyl hemiaminal was disclosed.

The asymmetric aza-Diels–Alder reaction is one of the most efficient and direct methods to access chiral aza-heterocycles. In this area, a tremendous development has been seen since the pioneering work of Yamamoto, Kobayashi and Jørgensen.[5] Among the various transformations, the formal aza-Diels–Alder (FADA) reaction of cyclic imines with enones has drawn increasing attention recently due to its utility in the construction of fused aza-heterocyclic compounds.[6] In 2013, a general FADA reaction catalyzed by primary aminothioureas was reported by Jacobsen et al. to synthesize indolo- and benzoquinolizidine derivatives (Scheme 1a).[6b] In the same year, the aza-Diels–Alder reaction of cyclic *N*-sulfonyl imines was developed by He and Kang (Scheme 1b).[6c] Very recently, primary aminothioureas were also employed by the Ye group in the FADA reaction of 3H-indoles and enones (Scheme 1a).[6d] Herein, a trifluoromethyl hemiaminal was utilized as a precursor of cyclic imines to contruct a variety of trifluoromethylpiperidine scaffolds (Scheme 1c).[7] Additionally, a chiral *gem*-diamine **2**, detected in this transformation, was considered as a critical intermediate to provide the final FADA product.[8]

Gem-diamine (methylenediamine) as an important intermediate in the Mannich reaction was first proposed by Wagner in 1949.[9] The corresponding transition state was later present by Butler and Fernandez (Scheme 2a).[10] According to the previously reported mechanism, we envisioned that a chiral *gem*-diamine intermediate, involved in the reaction, might provide an enantioenriched Mannich product via an asymmetric induction process. Indeed, we found that the in situ generated chiral intermediate in this formal aza-Diels–Alder reaction could afford the FADA products with high stereocontrol (Scheme 2b).

RESULTS AND DISCUSSION

We began our study by investigating the FADA reaction of trifluoromethyl hemiaminal **1a** with enone **3a** using various amine catalysts (Table 1). To better understand the relationship between the *de* values of intermediate **2** with the *ee* values of product **4aa**, the reaction was performed in $CDCl_3$ and monitored by ^{19}F NMR. Initially, we carried out this reaction in the presence of previously used catalyst (*S*)-2-amino-*N*-methyl-3-phenylpropanamide (**cat A**) and acid additive 2,6-difluorobenzoic acid.[7a] Unfortunately, only a trace of product was detected (entry 1, Table 1). To our delight, replacing the acid additive with a stronger acid *p*-nitrobenzoic acid (PNBA) provided the corresponding product with good yield and a promising *ee* value (entry 1, Table 1). Interestingly, a simple

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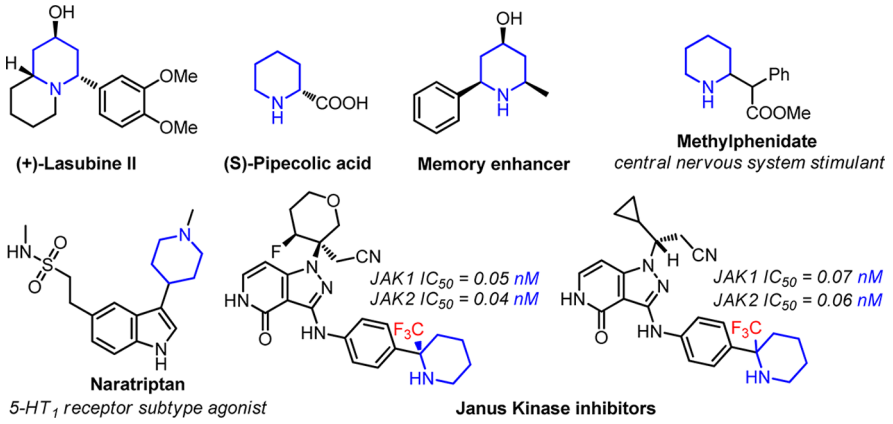
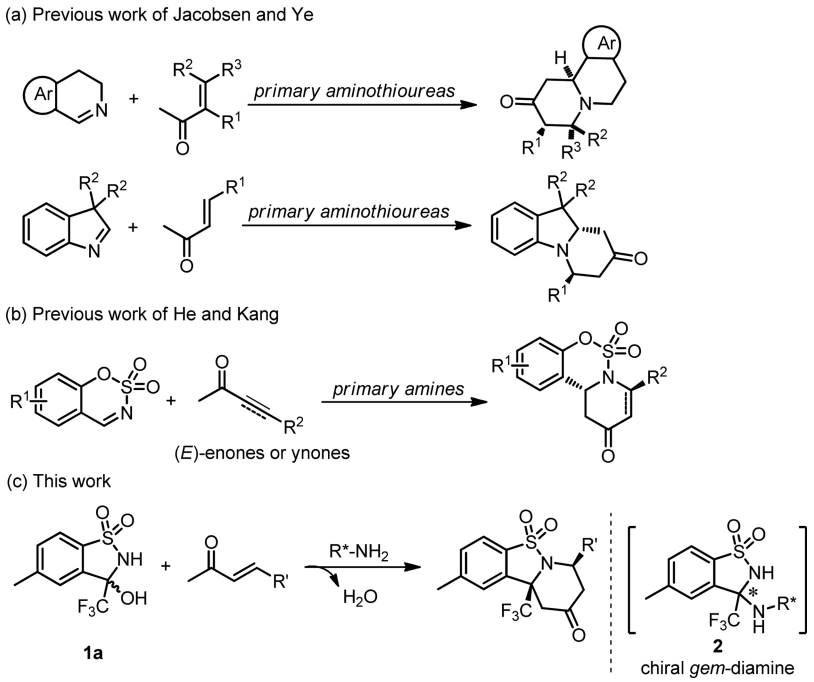
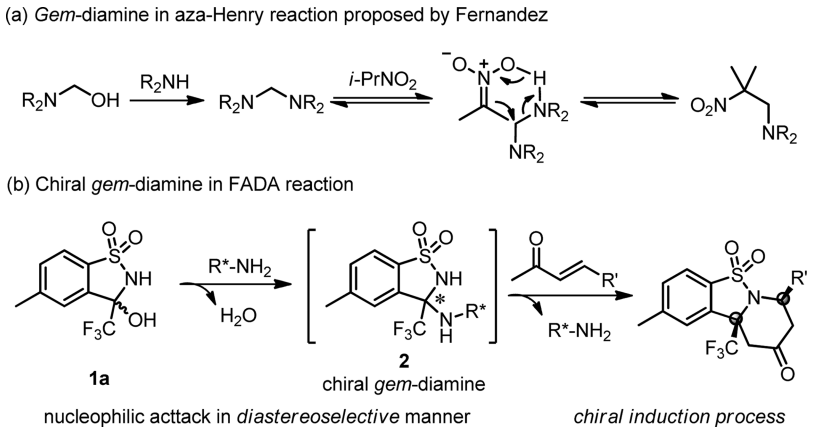


Figure 1. Chiral piperidine scaffold in bioactive compounds and commercially available drugs.

Scheme 1. Formal Aza-Diels–Alder Reaction of Cyclic Imines with Enones



Scheme 2. *Gem*-Diamine Intermediate in Mannich Reaction and FADA Reaction



primary amine (*R*)-1-phenylethanamine (**cat B**) could also give a moderate enantioselectivity (entry 2, Table 1), whereas a secondary amine catalyst (*S*)-*N*-((*S*)-1-hydroxy-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (**cat C**) caused a detrimental effect on the *ee* value of product (entry 3, Table 1). To further optimize this FADA reaction, a series of primary amine

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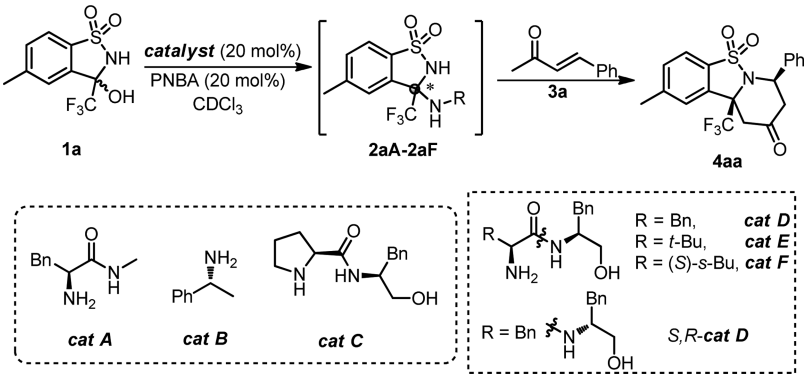
Table 1. Optimization of the Enantioselective FADA Reaction of Trifluoromethyl Hemiaminal with Enone[a]



entry	catalyst	2	*de* of 2 (%)[b]	*ee* of 4aa (%)[c]	yield (%)[d]
1[e]	**cat A**	**2aA**	77	85 (n.d.)	82 (trace)
2	**cat B**	**2aB**	50	64	77
3	**cat C**	**2aC**	28	23	72
4	**cat D**	**2aD**	90	87	82
5	*S,R*-**cat D**	*S,R*-**2aD**	69	76	70
6	**cat E**	**2aE**	96	88	91
7	**cat F**	**2aF**	97	93	93

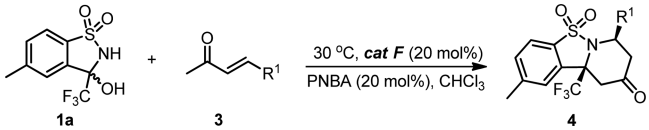
[a]The reaction of **1a** (0.1 mmol) with **3a** (0.2 mmol) was performed in the presence of **catalyst** (20 mol %) and *p*-nitrobenzoic acid (PNBA) (20 mol %) in $CDCl_3$ (1.0 mL) at room temperature for 36 h; Unless noted otherwise, *dr* ≥ 10:1 by ^{1}H NMR analysis. [b]The *de* value of intermediate **2** was determined by ^{19}F NMR. [c]The *ee* value of the product **4aa** was determined by HPLC on a chiral stationary phase. [d]Yield of isolated product **4aa**. [e]The data in the parentheses was obtained when 2,6-difluorobenzoic acid (20 mol %) used in place of PNBA.

catalysts with multiple sites for hydrogen bonding were tested. Pleasingly, the employment of the primary amine catalyst (2*S*,3*S*)-2-amino-*N*-((*S*)-1-hydroxy-3-phenyl-propan-2-yl)-3-methyl-pentanamide (**cat F**) afforded a satisfactory result with 93% *ee* and 93% yield (entry 7, Table 1). Moreover, according to this optimization table, the *ee* value of product **4aa** was well consistent with the *de* value of intermediate **2**, which was determined by ^{19}F NMR.[11] This finding suggests that this aza-Diels–Alder reaction might proceed via a chiral *gem*-diamine intermediate **2** to afford the final product through an asymmetric induction process.

With the efficient organocatalyst **cat F** in hand, we next examined the generality of the primary amine-catalyzed FADA reaction with various enones **3** under optimal conditions (Table 2). Enones with para-substituted aromatic rings were found to give the respective quaternary piperidines with uniformly excellent diastereoselectivity and enantioselectivity regardless of the electronic nature of the substituent (entries 2–8, Table 2). Although the enantioselectivity was largely independent of the aromatic substitution pattern, a slight erosion of diastereoselectivity was observed for the ortho substituted enone **3m** (entries 9–13, Table 2). Remarkably, the primary amine-catalyzed protocol was also compatible with other aryl and alkyl substituted enones (entries 14–18, Table 2). Specifically, piperidines **4aq** and **4ar** bearing silyl ether functionality, allowing for various derivatization reactions, could still be obtained with high *ee* values, albeit with a lower diastereoselectivties (entries 17–18, Table 2).

Having surveyed the scope of enones in this asymmetric FADA reaction, our attention was turned to hemiaminals **1** (Table 3). The electronic effect in this case seemed to be apparent for the depressed enantioinduction in the electron-deficient hemiaminals. However, the enantiomeric excess of products **4ca** and **4da** could be improved by a facile manipulation of washing and filtration. Variation of the

Table 2. Scope of Enones 3 in the Enantioselective FADA Reaction[a]



entry	4	R^1	*ee* (%)[b]	*dr*[c]	yield (%)[d]
1	**4aa**	Ph	93	10:1	99
2	**4ab**	4-FC_6H_4	94	10:1	99
3	**4ac**	4-ClC_6H_4	94	9:1	99
4	**4ad**	4-BrC_6H_4	94	9:1	94
5	**4ae**	4-CNC_6H_4	96	13:1	98
6	**4af**	4-$CF_3C_6H_4$	95	12:1	99
7	**4ag**	4-$NO_2C_6H_4$	94	17:1	92
8	**4ah**	4-MeC_6H_4	93	18:1	98
9	**4ai**	3-ClC_6H_4	91	15:1	97
10	**4aj**	3-$CF_3C_6H_4$	93	12:1	99
11	**4ak**	3-MeC_6H_4	90	11:1	99
12	**4al**	3-$OMeC_6H_4$	93	14:1	99
13[e]	**4am**	2-MeC_6H_4	93	6:1	99
14	**4an**	3,4-$OMeC_6H_3$	92	11:1	99
15	**4ao**	2-Naphthyl	92	26:1	95
16	**4ap**	2-Thienyl	89	22:1	91
17[e]	**4aq**	$(CH_2)_3OTBDPS$	93	9:1	93
18[e]	**4ar**	$(CH_2)_4OTBDPS$	94	7:1	83

[a]The reaction of **1a** (0.3 mmol) with **3** (0.6 mmol) was performed in the presence of **cat F** (20 mol %) and PNBA (20 mol %) in $CHCl_3$ (3.0 mL) at 30 °C for 48 h. [b]The *ee* value of the product **4** was determined by HPLC on a chiral stationary phase. [c]The *dr* value (cis/trans) of product was determined by ^{1}H NMR. [d]Yield of isolated product. [e]The reaction was performed at 20 °C for 60 h.

aromatic substituent position in substrates **1** had little effect on the efficiency of this process (Table 3, **4ga–4ha**). The

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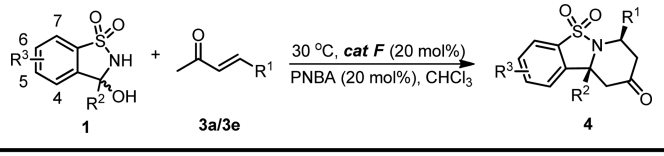
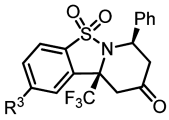
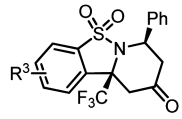
Table 3. Scope of Hemiaminals 1 in the Enantioselective FADA Reaction[a]

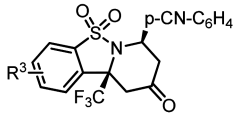




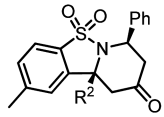
4ba[b], R^3 = H, 27:1 *dr*, 92% *ee*, 92% yield
4ca[c], R^3 = F, 54:1 dr, 86(97)% *ee*, 93(82)% yield
4da[c], R^3 = Cl, 46:1 *dr*, 86(97)% *ee*, 95(86)% yield
4ea, R^3 = *t*-Bu, 15:1 *dr*, 93% *ee*, 99% yield
4fa[b], R^3 = OMe, 19:1 *dr*, 91% *ee*, 91% yield



4ga, R^3 = 4-F, 75:1 *dr*, 90% *ee*, 96% yield
4ha, R^3 = 6-Me, 44:1 *dr*, 89% *ee*, 96% yield



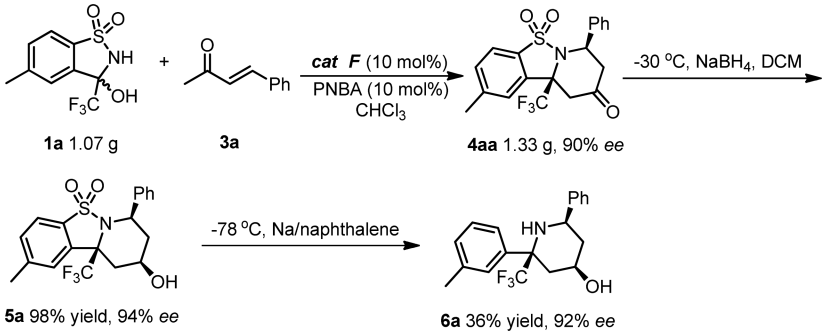
4ce, R^3 = 5-F, >99:1 *dr*, 92% *ee*, 87% yield
4de, R^3 = 5-Cl, 18:1 *dr*, 93% *ee*, 94% yield
4he, R^3 = 6-Me, 10:1 *dr*, 94% *ee*, 97% yield



4ia, R^2 = CF_2H, 4:1 *dr*, 94% *ee*, 95% yield
4ja, R^2 = C_2F_5, 3:1 *dr*, 98% *ee*, 99% yield

[a]The reaction of **1** (0.3 mmol) with **3** (0.6 mmol) was performed in the presence of **cat F** (20 mol %) and PNBA (20 mol %) in $CHCl_3$ (3.0 mL) at 30 °C for 48 h. The *ee* value of the product **4** was determined by HPLC on a chiral stationary phase. The *dr* value (cis/trans) of product was determined by ^1H NMR. The product was obtained by column chromatography. [b]The reaction was performed at 20 °C for 60 h. [c]The data in parentheses was observed by washing the product with mixed solvent (PE/EA = 6/1).

Scheme 3. Synthetic Utility of the Primary Amine-Catalyzed FADA Reaction



generality of this methodology was further demonstrated by the crossover reaction of enone **3e** with various hemiaminals (Table 3, **4ce**−**4he**). Finally, changing the trifluoromethyl group to difluoromethyl and perfluoroethyl groups in substrates **1** greatly decreased the diastereoselectivity (Table 3, **4ia**−**4ja**).

To probe the scalability of the primary amine-catalyzed aza-Diels−Alder reaction, a scaled-up reaction was performed as illustrated in Scheme 3. The optically active trifluoromethylpiperidine scaffold was furnished with 90% *ee* in the presence of 10 mol % catalyst. From the cyclization product, the bioactive 4-hydroxypiperidine **6a** was easily accessed by a facile sequence of sodium borohydride reduction and sultam ring cleavage, without tedious protection and deprotection steps.

To gain insight into the reaction mechanism, the relationship between the *ee* values of product **4aa** and the catalyst was next explored.[12] As depicted in the Figure 2a, an excellent linear correlation was observed. According to the previous study of Houk and List, we attempted to interpret this linear correlation as evidence for the monomolecular catalyzed mechanism in the stereocontrol step.[13] Additionally, the Mannich adduct **4ag′** was detected in the formal aza-Diels−Alder reaction, which might illustrate a stepwise mechanism in this transformation (Figure 2b).[14] On the basis of these findings and the absolute configuration of product **4ak**,[15] a possible reaction mechanism was proposed as shown in the Figure 2c. A nucleophilic addition of primary amine catalyst to the hemiaminal **1a** provides a diastereomerically enriched *gem*-diamine intermediate **2aF**. Subsequent reaction of **2aF** with enone affords the Mannich adduct via asymmetric induction and regenerates the catalyst. The generated chiral Mannich adduct undergoes an intramolecular aza-Michael addition giving the final cyclized product **4aa** in the presence of **cat F**.

CONCLUSIONS

In conclusion, we have unveiled a primary amine-catalyzed formal aza-Diels−Alder reaction of hemiaminals via a critical intermediate chiral *gem*-diamine **2**. This highly efficient methodology permits a straightforward route to a wide range

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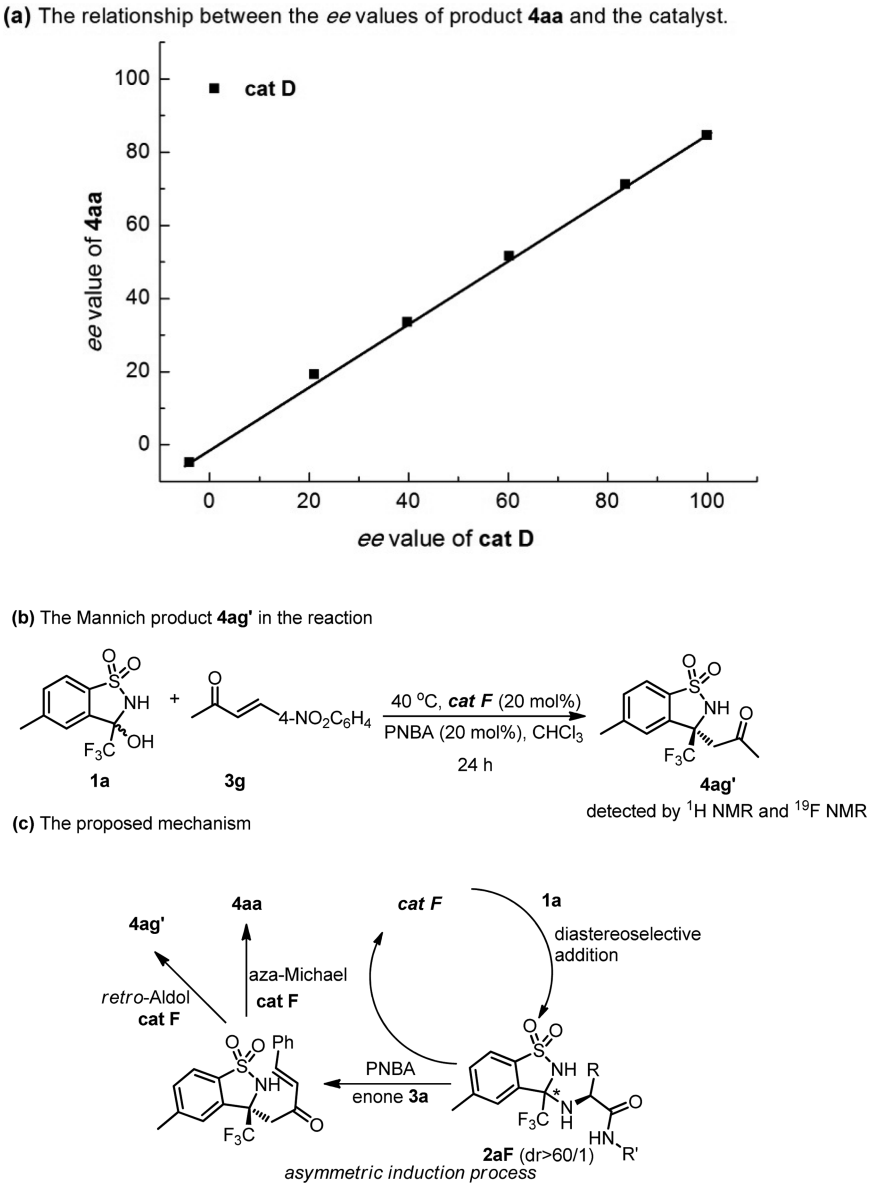

Figure 2. Mechanistic observations and the proposed mechanism.

of pharmaceutically active trifluoromethylpiperidine scaffolds. Moreover, an interestingly positive correlation between the chirality of the *gem*-diamine intermediate and the formal aza-Diels–Alder product was observed in this process. Further application of this primary amine catalyst in other transformations is currently under active investigation in our laboratory.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR and ^{13}C NMR were recorded on a 400 MHz Spectrometer (^{1}H NMR: 400 MHz, ^{19}F NMR: 376 MHz, ^{13}C NMR: 100 MHz) using TMS as the reference. The chemical shifts (δ) and coupling constants (J) were expressed in ppm and Hz, respectively. Commercially available compounds were used without further purification. All solvents were purified according to the standard procedures unless otherwise noted. Substrate **1a**–**1j**,[7a] **3a**–**3p**,[6c] **3q**–**3r**,[16] **cat A**[17] and **cat C**–**F**[7a] was prepared according to the literature procedures.

General Working Procedure for the Asymmetric FADA Reaction. To a mixture of cyclic hemiaminal **1a** (80 mg, 0.3 mmol) and enone **3a** (88 mg, 0.6 mmol) in 3.0 mL of chloroform was added **cat F** (16 mg, 0.06 mmol) and *p*-nitrobenzoic acid (10 mg, 0.06 mmol). After stirring the mixture at 30 °C for 48 h (for **4am**, **4aq**, **4ar**, **4ba**, **4fa**, the reaction was performed at 20 °C for 60 h), the solvent was evaporated in vacuo. Purification of the residue by column chromatography (PE/ethyl ether = 5/1–1/2) afforded the desired FADA product **4aa** in 99% yield with 93% *ee*. (Chiralcel OD-H, *i*-PrOH/hexane = 30/70, 1.0 mL/min, λ = 215 nm: t_R = 25.5 min (minor), t_R = 33.4 min (major)).

Experimental Data of FADA Products, Catalysts and Substrates. *(7R,10aR)-2-Methyl-7-phenyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4aa**).* The title product was obtained as a white solid in 99% yield (117.2 mg), mp 169–171 °C; $[\alpha]_D^{20}$ 74.8 (c = 0.3, EtOAc); HPLC Chiralcel OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 25.5 min (minor), t_R = 33.4 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.70 (d, J = 8.0 Hz, 1H), 7.53–7.48 (m, 3H), 7.44–7.40 (m, 2H), 7.37–7.31 (m, 2H), 5.21–5.17 (dd, J = 4.5 Hz, 11.1 Hz, 1H), 3.41–3.37 (d, J = 17.2 Hz, 1H), 3.09–3.02 (dd, J = 11.3 Hz, 18.8 Hz, 1H), 2.88–2.84 (d, J = 17.2 Hz, 1H), 2.82–2.76 (dd, J = 4.1 Hz, 19.0 Hz, 1H), 2.51 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.79 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 145.4, 139.0, 133.3, 132.8, 132.1, 128.9, 128.6,

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127.1, 125.6−122.8 (q, J = 284.1 Hz), 124.5, 121.6, 67.7−66.8 (q, J = 30.8 Hz), 56.7, 45.5, 43.5, 21.9. IR (film, ν/cm^{-1}) 2924, 1735, 1704, 1688, 1656, 1599, 1561, 1544, 1510, 1459, 1399, 1366, 1323, 1260, 1222, 1205, 1177, 1104, 1063, 995, 953, 819, 767; HRMS (ESI) m/z calcd for $C_{19}H_{16}F_3NO_3S$ [M + Na]$^+$ 418.0701, found 418.0705.

*(7R,10aR)-7-(4-Fluorophenyl)-2-methyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ab**).* The title product was obtained as a white solid in 99% yield (122.7 mg), mp 84−87 °C; $[\alpha]_D^{20}$ 76.4 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 27.3 min (minor), t_R = 31.9 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.70 (d, J = 8.04 Hz, 1H), 7.52−7.48 (m, 3H), 7.32 (s, 1H), 7.12−7.08 (m, 2H), 5.20−5.16 (dd, J = 4.6 Hz, 11.4 Hz, 1H), 3.42−3.37 (d, J = 17.2 Hz, 1H), 3.05−2.98 (dd, J = 11.6 Hz, 18.6 Hz, 1H), 2.87−2.83 (d, J = 17.2 Hz, 1H), 2.80−2.74 (m, 1H), 2.51 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.78, −113.1 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 163.9−161.4 (d, J = 246.1 Hz), 145.5, 134.84−134.81 (d, J = 3.3 Hz), 133.1, 132.8, 131.5, 129.02−128.94 (d, J = 8.3 Hz), 128.4−119.9 (q, J = 284.0 Hz), 124.46−124.45 (d, J = 1.5 Hz), 121.6, 116.0−115.8 (d, J = 21.7 Hz); IR (film, ν/cm^{-1}) 2925, 1735, 1655, 1605, 1560, 1542, 1510, 1323, 1298, 1226, 1205, 1178, 1097, 1065, 995, 953, 829, 758, 712; HRMS (ESI) m/z calcd for $C_{19}H_{15}F_4NO_3S$ [M + Na]$^+$ 436.0606, found 436.0610.

*(7R,10aR)-7-(4-Chlorophenyl)-2-methyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ac**).* The title product was obtained as a white solid in 99% yield (127.8 mg), mp 162−165 °C; $[\alpha]_D^{20}$ 88.3 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 231 nm, t_R = 30.8 min (minor), t_R = 41.1 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.71 (d, J = 8.0 Hz, 1H), 7.52−7.50 (d, J = 8.0 Hz, 1H), 7.47−7.45 (d, J = 8.4 Hz, 2H), 7.40−7.38 (d, J = 8.2 Hz, 2H), 7.32 (s, 1H), 5.19−5.15 (dd, J = 4.6 Hz, 11.4 Hz, 1H), 3.42−3.37 (d, J = 17.2 Hz, 1H), 3.04−2.97 (dd, J = 11.1 Hz, 18.1 Hz, 1H), 2.87−2.83 (d, J = 17.2 Hz, 1H), 2.80−2.74 (dd, J = 4.4 Hz, 18.6 Hz, 1H), 2.52 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.76 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 145.6, 137.6, 134.5, 133.1, 132.9, 131.8, 129.2, 128.5, 125.6−122.8 (q, J = Hz), 124.5, 121.6, 67.4−67.1 (q, J = 30.6 Hz), 56.1, 45.3, 43.5, 21.9; IR (film, ν/cm^{-1}) 2924, 1735, 1688, 1656, 1639, 1599, 1562, 1544, 1525, 1510, 1492, 1460, 1410, 1323, 1222, 1205, 1177, 1065, 1014, 952, 820, 768, 714; HRMS (ESI) m/z calcd for $C_{19}H_{15}ClF_3NO_3S$ [M + Na]$^+$ 452.0311, found 452.0313.

*(7R,10aR)-7-(4-Bromophenyl)-2-methyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ad**).* The title product was obtained as a white solid in 94% yield (133.5 mg), mp 182−185 °C; $[\alpha]_D^{20}$ 83.9 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 231 nm, t_R = 29.3 min (minor), t_R = 40.3 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.71 (d, J = 8.0 Hz, 1H), 7.57−7.53 (m, 2H), 7.52−7.50 (d, J = 8.0 Hz, 1H), 7.42−7.38 (m, 2H), 7.32 (s, 1H), 5.17−5.13 (dd, J = 4.6 Hz, 11.4 Hz, 1H), 3.41−3.37 (d, J = 17.3 Hz, 1H), 3.03−2.96 (dd, J = 12.7 Hz, 19.9 Hz, 1H), 2.87−2.82 (d, J = 17.2 Hz, 1H), 2.80−2.74 (dd, J = 4.6 Hz, 18.7 Hz, 1H), 2.52 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.76 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 145.6, 138.1, 133.1, 132.9, 132.1, 131.8, 128.8, 125.6−122.7 (q, J = 284.2 Hz), 124.5, 122.7, 121.6, 67.4−67.1 (q, J = 30.7 Hz), 56.2, 45.26−45.24 (d, J = 2.4 Hz), 43.5, 21.9; IR (film, ν/cm^{-1}) 2926, 1735, 1598, 1543, 1489, 1410, 1324, 1206, 1178, 1155, 1067, 1011, 952, 820, 713; HRMS (ESI) m/z calcd for $C_{19}H_{15}BrF_3NO_3S$ [M + Na]$^+$ 495.9806, found 495.9803.

*4-((7R,10aR)-2-Methyl-5,5-dioxido-9-oxo-10a-(trifluoromethyl)-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-yl)-benzonitrile (**4ae**).* The title product was obtained as white solid in 98% yield (123.8 mg), mp 172−175 °C; $[\alpha]_D^{20}$ 84.2 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 50.3 min (minor), t_R = 64.2 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−77.72 (m, 3H), 7.67−7.64 (d, J = 8.4 Hz, 2H), 7.54−7.52 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 5.26−5.22 (dd, J = 4.7 Hz, 11.4 Hz, 1H), 3.44−3.40 (d, J = 17.3 Hz, 1H), 3.03−2.96 (dd, J = 11.5 Hz, 18.6 Hz, 1H), 2.89−2.85 (d, J = 17.4 Hz, 1H), 2.82−2.77 (dd, J = 4.0 Hz, 18.7 Hz, 1H), 2.53 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.69 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 145.9, 144.3, 133.1, 133.0, 132.8, 131.5, 127.9, 125.6−122.7 (q, J = 284.0 Hz), 124.5, 121.7, 118.3, 112.7, 67.5−66.9 (q, J = 30.8 Hz), 56.3, 44.8, 43.6, 22.0; IR (film, ν/cm^{-1}) 1775, 1736, 1703, 1687, 1655, 1638, 1626, 1561, 1544, 1524, 1510, 1477, 1460, 1323, 1177, 1155, 824; HRMS (ESI) m/z calcd for $C_{20}H_{15}F_3N_2O_3S$ [M + Na]$^+$ 443.0653, found 443.0651.

*(7R,10aR)-2-Methyl-10a-(trifluoromethyl)-7-(4-(trifluoromethyl)-phenyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4af**).* The title product was obtained as white solid in 99% yield (137.3 mg), mp 187−190 °C; $[\alpha]_D^{20}$ 77.6 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 27.1 min (minor), t_R = 31.1 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.70 (m, 1H), 7.68−7.64 (m, 4H), 7.52−7.50 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 5.27−5.23 (dd, J = 4.7 Hz, 11.4 Hz, 1H), 3.43−3.39 (d, J = 17.2 Hz, 1H), 3.06−2.98 (dd, J = 11.5 Hz, 18.6 Hz, 1H), 2.88−2.84 (d, J = 17.4 Hz, 1H), 2.83−2.77 (dd, J = 4.7 Hz, 18.8 Hz, 1H), 2.52 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.67, −75.73 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 145.7, 143.1, 133.2, 132.9, 131.7, 131.0−130.7 (q, J = 32.3 Hz), 127.5, 126.05−125.97 (q, J = 3.8 Hz), 125.6−122.8 (q, J = 284.0 Hz), 125.3−122.5 (q, J = 270.6 Hz), 124.50−124.49 (d, J = 1.5 Hz), 121.7, 67.5−67.2 (q, J = 30.7 Hz), 56.3, 45.2, 43.6, 21.9; IR (film, ν/cm^{-1}) 2928, 1737, 1599, 1422, 1327, 1158, 1126, 1067, 1017, 953, 838, 713; HRMS (ESI) m/z calcd for $C_{20}H_{15}F_6NO_3S$ [M + Na]$^+$ 486.0575, found 486.0579.

*(7R,10aR)-2-Methyl-7-(4-nitrophenyl)-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ag**).* The title product was obtained as white solid in 92% yield (121.2 mg), mp 112−115 °C; $[\alpha]_D^{20}$ 75.0 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 52.0 min (major), t_R = 60.7 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.26 (m, 2H), 7.74−7.71 (m, 3H), 7.54−7.52 (m, 1H), 7.35 (s, 1H), 5.31−5.27 (dd, J = 4.1 Hz, 11.6 Hz, 1H), 3.46−3.42 (d, J = 17.2 Hz, 1H), 3.05−2.97 (m, 1H), 2.92−2.88 (d, J = 17.4 Hz, 1H), 2.86−2.80 (m, 1H), 2.54 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.71 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 148.0, 146.1, 145.9, 133.0, 131.3, 128.1, 125.6−122.7 (q, J = 284.0 Hz), 124.52−124.50 (d, J = 1.5 Hz), 124.3, 121.7, 67.8−66.9 (q, J = 30.8 Hz), 56.1, 44.86−44.83 (d, J = 2.5 Hz), 43.6, 21.9; IR (film, ν/cm^{-1}) 2925, 1736, 1602, 1525, 1349, 1323, 1179, 1155, 1108, 1065, 996, 953, 861, 820, 752, 713; HRMS (ESI) m/z calcd for $C_{19}H_{15}F_3N_2O_5S$ [M + Na]$^+$ 463.0551, found 463.0550.

*(7R,10aR)-2-Methyl-7-(p-tolyl)-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ah**).* The title product was obtained as white solid in 98% yield (120.7 mg), mp 152−155 °C; $[\alpha]_D^{20}$ 73.3 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 231 nm, t_R = 22.6 min (minor), t_R = 36.4 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.69 (d, J = 8.0 Hz, 1H), 7.49−7.47 (d, J = 8.0 Hz, 1H), 7.42−7.40 (d, J = 8.0 Hz, 2H), 7.31 (s, 1H), 7.23−7.21 (d, J = 8.0 Hz, 2H), 5.17−5.13 (dd, J = 4.5 Hz, 11.3 Hz, 1H), 3.41−3.36 (d, J = 17.2 Hz, 1H), 3.08−3.00 (dd, J = 11.4 Hz, 18.8 Hz, 1H), 2.87−2.83 (d, J = 17.3 Hz, 1H), 2.79−2.73 (dd, J = 4.4 Hz, 18.9 Hz, 1H), 2.50 (s, 3H), 2.36 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.80 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 145.3, 138.4, 136.0, 133.3, 132.7, 132.2, 129.6, 128.5−122.8 (q, J = 284.1 Hz), 127.0, 124.5, 121.6, 67.7−66.8 (q, J = 30.7 Hz), 56.5, 45.6, 43.5, 21.9, 21.2; IR (film, ν/cm^{-1}) 2926, 1734, 1688, 1599, 1544, 1511, 1460, 1324, 1206, 1177, 1154, 1066, 952, 817, 711; HRMS (ESI) m/z calcd for $C_{20}H_{18}F_3NO_3S$ [M + Na]$^+$ 432.0857, found 432.0859.

*(7R,10aR)-7-(3-Chlorophenyl)-2-methyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ai**).* The title product was obtained as white solid in 97% yield (124.8 mg), mp 94−97 °C; $[\alpha]_D^{20}$ 75.8 (c = 0.3, EtOAc); HPLC Chiralpak IC, hexane:2-propanol = 70:30, flow rate = 0.8 mL/min, T = 23 °C, UV = 231 nm, t_R = 11.0 min (minor), t_R = 16.0 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.70 (d, J = 8.0 Hz, 1H), 7.51−

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7.49 (m, 1H), 7.46−7.43 (m, 2H), 7.38−7.34 (m, 1H), 7.32−7.30 (m, 2H), 5.16−5.12 (dd, J = 4.6 Hz, 11.4 Hz, 1H), 3.41−3.36 (d, J = 17.2 Hz, 1H), 3.02−2.95 (m, 1H), 2.87−2.83 (d, J = 17.6 Hz, 1H), 2.79−2.74 (m, 1H), 2.51 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.76 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 145.6, 141.2, 134.5, 133.1, 132.8, 131.7, 130.3, 128.8, 127.3, 125.5−122.7 (q, J = 283.9 Hz), 125.2, 124.4, 121.6, 67.7−66.8 (q, J = 30.6 Hz), 56.2, 45.23−45.21 (d, J = 2.3 Hz), 43.5, 21.9; IR (film, ν/cm^{-1}) 1735, 1595, 1317, 1271, 1221, 1203, 1176, 1151, 1062, 995, 950, 891, 809, 782, 721; HRMS (ESI) m/z calcd for $C_{19}H_{15}ClF_3NO_3S$ [M + Na]$^+$ 452.0311, found 452.0314.

*(7R,10aR)-2-Methyl-10a-(trifluoromethyl)-7-(3-(trifluoromethyl)-phenyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4aj**).* The title product was obtained as white solid in 99% yield (137.2 mg), mp 81−84 °C; $[\alpha]_D^{20}$ 66.8 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 231 nm, t_R = 21.7 min (major), t_R = 25.7 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.77 (d, J = 7.6 Hz, 1H), 7.72−7.69 (m, 2H), 7.62−7.54 (m, 2H), 7.51−7.49 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 5.26−5.22 (dd, J = 4.6 Hz, 11.5 Hz, 1H), 3.42−3.38 (d, J = 17.2 Hz, 1H), 3.04−2.96 (dd, J = 11.3 Hz, 18.9 Hz, 1H), 2.89−2.85 (d, J = 17.3 Hz, 1H), 2.82−2.76 (dd, J = 4.1 Hz, 18.8 Hz, 1H), 2.51 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.61, −75.80 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 145.7, 140.2, 133.0, 132.9, 131.7−130.6 (q, J = 32.2 Hz), 131.6, 130.4, 129.6, 128.4−119.9 (q, J = 284.9 Hz), 127.9−119.7 (q, J = 270.7 Hz), 125.6−125.4 (q, J = 6.7 Hz), 124.48−124.47 (d, J = 1.2 Hz), 124.10−123.99 (q, J = 3.6 Hz), 121.5, 67.7−66.8 (q, J = 30.7 Hz), 56.3, 45.21−45.18 (d, J = 2.2 Hz), 43.5, 21.8; IR (film, ν/cm^{-1}) 2927, 1736, 1600, 1455, 1330, 1207, 1157, 1126, 1074, 996, 955, 909, 809; HRMS (ESI) m/z calcd for $C_{20}H_{15}F_6NO_3S$ [M + Na]$^+$ 486.0575, found 486.0570.

*(7R,10aR)-2-Methyl-7-(m-tolyl)-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ak**).* The title product was obtained as white solid in 99% yield (122.1 mg), mp 164−167 °C; $[\alpha]_D^{20}$ 54.7 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 231 nm, t_R = 21.1 min (minor), t_R = 28.0 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.68 (d, J = 8.0 Hz, 1H), 7.49−7.47 (d, J = 8.0 Hz, 1H), 7.35−7.28 (m, 4H), 7.16−7.14 (d, J = 7.1 Hz, 1H), 5.16−5.12 (dd, J = 4.6 Hz, 11.3 Hz, 1H), 3.40−3.35 (d, J = 17.2 Hz, 1H), 3.06−2.99 (dd, J = 11.4 Hz, 19.0 Hz, 1H), 2.88−2.83 (d, J = 17.2 Hz, 1H), 2.79−2.73 (dd, J = 4.0 Hz, 18.9 Hz, 1H), 2.50 (s, 3H), 2.08 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.78 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 145.3, 139.0, 138.4, 133.2, 132.7, 132.1, 129.3, 128.7, 128.2−122.8 (q, J = 284.1 Hz), 127.7, 124.44−124.43 (d, J = 1.4 Hz), 124.0, 121.5, 67.7−66.8 (q, J = 30.6 Hz), 56.7, 45.52−45.50 (d, J = 2.2 Hz), 43.4, 21.8, 21.4; IR (film, ν/cm^{-1}) 2923, 1735, 1600, 1490, 1324, 1205, 1178, 1154, 1066, 953, 786; HRMS (ESI) m/z calcd for $C_{20}H_{18}F_3NO_3S$ [M + Na]$^+$ 432.0857, found 432.0860.

*(7R,10aR)-7-(3-Methoxyphenyl)-2-methyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4al**).* The title product was obtained as white solid in 99% yield (125.8 mg), mp 168−171 °C; $[\alpha]_D^{20}$ 67.3 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 231 nm, t_R = 30.5 min (minor), t_R = 36.0 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.70 (d, J = 8.0 Hz, 1H), 7.50−7.48 (d, J = Hz, 1H), 7.34−7.30 (m, 2H), 7.10−7.08 (m, 2H), 6.89−6.86 (m, 1H), 5.19−5.15 (dd, J = 4.6 Hz, 11.2 Hz, 1H), 3.81 (s, 3H), 3.40−3.36 (d, J = 17.2 Hz, 1H), 3.06−2.99 (d, J = 10.3 Hz, 18.8 Hz, 1H), 2.87−2.83 (d, J = 17.3 Hz, 1H), 2.81−2.76 (dd, J = 4.1 Hz, 18.9 Hz, 1H), 2.50 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.77 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 159.8, 145.4, 140.7, 133.2, 132.7, 132.0, 129.9, 128.4−122.7 (q, J = 284.1 Hz), 124.45−124.44 (d, J = 1.2 Hz), 121.5, 119.0, 113.9, 112.7, 67.7−66.8 (q, J = 30.6 Hz), 56.6, 55.1, 45.40−45.38 (d, J = 2.1 Hz), 43.5, 21.8; IR (film, ν/cm^{-1}) 2925, 1735, 1602, 1543, 1491, 1458, 1438, 1323, 1291, 1268, 1237, 1205, 1177, 1153, 1120, 1065, 1045, 995, 954, 907, 820, 784, 745; HRMS (ESI) m/z calcd for $C_{20}H_{18}F_3NO_4S$ [M + Na]$^+$ 448.0806, found 448.0810.

*(7R,10aR)-2-Methyl-7-(o-tolyl)-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4am**).* The title product was obtained as white solid in 99% yield (122.0 mg), mp 102−105 °C; $[\alpha]_D^{20}$ 71.6 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 18.9 min (major), t_R = 30.9 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.66 (m, 2H), 7.49−7.47 (d, J = 8.0 Hz, 1H), 7.34−7.28 (m, 2H), 7.25−7.21 (m, 1H), 7.18−7.17 (d, J = 7.4 Hz, 1H), 5.38−5.34 (dd, J = 4.2 Hz, 12.1 Hz, 1H), 3.45−3.41 (d, J = 17.4 Hz, 1H), 2.99−2.89 (m, 2H), 2.75−2.70 (m, 1H), 2.51 (s, 3H), 2.43 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.00 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 145.3, 137.1, 134.9, 133.3, 132.8, 132.3, 130.8, 128.6−122.9 (q, J = 288.5 Hz), 128.3, 127.0, 126.9, 124.5, 121.5, 67.4−67.1 (q, J = 30.6 Hz), 53.4, 44.76−44.73 (d, J = 2.4 Hz), 43.5, 21.9, 19.1; IR (film, ν/cm^{-1}) 2927, 1735, 1687, 1655, 1638, 1599, 1561, 1543, 1524, 1510, 1491, 1460, 1420, 1324, 1205, 1177, 1153, 1065, 994, 951, 821, 761; HRMS (ESI) m/z calcd for $C_{20}H_{18}F_3NO_3S$ [M + Na]$^+$ 432.0857, found 432.0859.

*(7R,10aR)-7-(3,4-Dimethoxyphenyl)-2-methyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4an**).* The title product was obtained as white solid in 99% yield (135.3 mg), mp 96−99 °C; $[\alpha]_D^{20}$ 73.6 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 31.6 min (major), t_R = 48.7 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.71 (d, J = 8.0 Hz, 1H), 7.50−7.48 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 7.09−7.08 (d, J = 2.0 Hz, 1H), 7.05−7.02 (dd, J = 2.1 Hz, 8.3 Hz, 1H), 6.90−6.88 (d, J = 8.3 Hz, 1H), 5.21−5.17 (dd, J = 4.8 Hz, 10.9 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.40−3.36 (d, J = 17.2 Hz, 1H), 3.08−3.00 (dd, J = 11.0 Hz, 18.7 Hz, 1H), 2.87−2.83 (d, J = 17.3 Hz, 1H), 2.82−2.76 (dd, J = 5.0 Hz, 19.1 Hz, 1H), 2.51 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.75 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 149.0, 148.9, 145.3, 133.1, 132.7, 131.9, 131.4, 125.6−122.7 (q, J = 284.3 Hz), 124.4, 121.4, 119.1, 111.0, 110.2, 67.3−66.7 (q, J = 30.6 Hz), 56.2, 55.7, 45.4, 43.4, 21.8; IR (film, ν/cm^{-1}) 2936, 1733, 1597, 1518, 1466, 1422, 1324, 1266, 1205, 1177, 1155, 1065, 1026, 954, 815, 766, 739; HRMS (ESI) m/z calcd for $C_{21}H_{20}F_3NO_5S$ [M + Na]$^+$ 478.0912, found 478.0917.

*(7R,10aR)-2-Methyl-7-(naphthalen-2-yl)-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ao**).* The title product was obtained as white solid in 95% yield (127.4 mg), mp 120−123 °C; $[\alpha]_D^{20}$ 100.7 (c = 0.3, EtOAc); HPLC Chiralpak IC, hexane:2-propanol = 70:30, flow rate = 0.8 mL/min, T = 23 °C, UV = 215 nm, t_R = 17.8 min (minor), t_R = 25.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.89 (m, 2H), 7.86−7.82 (m, 2H), 7.69−7.65 (m, 2H), 7.50−7.46 (m, 2H), 7.44−7.42 (d, J = 8.0 Hz, 1H), 7.29 (s,1H), 5.38−5.35 (dd, J = 4.6 Hz, 11.0 Hz, 1H), 3.41−3.36 (d, J = 17.2 Hz, 1H), 3.18−3.10 (dd, J = 11.1 Hz,18.9 Hz, 1H), 2.89−2.79 (m, 2H), 2.46 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.70 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.79, 145.39, 136.29, 133.25, 133.15, 133.08, 132.73, 131.97, 128.98, 128.16, 127.97−122.78 (q, J = 284.1 Hz), 127.71, 126.42, 126.35, 126.33, 125.62 124.43, 121.54, 67.77−66.85 (q, J = 30.6 Hz), 56.70, 45.11−45.09 (d, J = 2.0 Hz), 43.43, 21.81; IR (film, ν/cm^{-1}) 2925, 1734, 1600, 1510, 1375, 1324, 1240, 1204, 1178, 1155, 1107, 1065, 995, 953, 913, 861, 820, 748; HRMS (ESI) m/z calcd for $C_{23}H_{18}F_3NO_3S$ [M + Na]$^+$ 468.0857, found 468.0860.

*(7R,10aR)-2-Methyl-7-(thiophen-2-yl)-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ap**).* The title product was obtained as white solid in 91% yield (109.1 mg), mp 164−167 °C; $[\alpha]_D^{20}$ 90.0 (c = 0.3, EtOAc); HPLC Chiralpak IC, hexane:2-propanol = 70:30, flow rate = 0.8 mL/min, T = 23 °C, UV = 240 nm, t_R = 18.3 min (minor), t_R = 34.7 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.74 (d, J = 8.0 Hz, 1H), 7.52−7.50 (m, 1H), 7.37−7.36 (m, 1H), 7.31 (s, 1H), 7.22−7.21 (m, 1H), 7.02−6.99 (m, 1H), 5.66−5.62 (dd, J = 5.3 Hz, 9.2 Hz, 1H), 3.41−3.37 (d, J = 17.1 Hz, 1H), 3.21−3.14 (dd, J = 9.3 Hz, 18.6 Hz, 1H), 2.95−2.89 (dd, J = 5.2 Hz, 18.3 Hz, 1H), 2.86−2.82 (d, J = 17.1 Hz, 1H), 2.52 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.87 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 145.5, 142.4, 133.2,

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132.8, 132.0, 126.9, 126.8, 126.5, 125.4−122.6 (q, J = 284.0 Hz), 124.5, 121.7, 67.8−66.9 (q, J = 31.0 Hz), 51.8, 45.2, 43.3, 21.9; IR (film, ν/cm^{-1}) 2927, 1733, 1598, 1321, 1273, 1205, 1170, 1154, 1064, 950, 822; HRMS (ESI) m/z calcd for $C_{17}H_{14}F_3NO_3S_2$ [M + Na]$^+$ 424.0265, found 424.0263.

*(7S,10aR)-7-(3-((tert-Butyldiphenylsilyl)oxy)propyl)-2-methyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo-[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4aq**).* The title product was obtained as colorless oil in 93% yield (172.2 mg); $[\alpha]_D^{20}$ 18.2 (c = 1.4, EtOAc); HPLC Chiralpak IC, hexane:2-propanol = 70:30, flow rate = 0.8 mL/min, T = 23 °C, UV = 240 nm, t_R = 6.4 min (major), t_R = 7.2 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.67 (m, 5H), 7.47−7.37 (m, 7H), 7.32 (s, 1H), 4.06−4.02 (m, 1H), 3.80−3.77 (t, J = 6.1 Hz, 2H), 3.23−3.19 (d, J = 15.4 Hz, 1H), 2.93−2.82 (m, 2H), 2.65−2.61 (m, 1H), 2.51−2.46 (m, 4H), 2.22−2.16 (m, 1H), 1.91−1.80 (m, 2H), 1.07 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.46 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 145.3, 135.5, 133.8, 133.7, 133.0, 132.6, 132.2, 129.6, 128.9−123.2 (q, J = 285.0 Hz), 127.7, 124.39−124.37 (d, J = 1.6 Hz), 121.2, 67.6−66.7 (q, J = 30.4 Hz), 62.9, 55.8, 44.1, 29.6, 29.5, 27.7, 26.8, 21.9, 19.2; IR (film, ν/cm^{-1}) 2931, 2858, 1730, 1427, 1315, 1257, 1172, 1108, 1006, 821, 739; HRMS (ESI) m/z calcd for $C_{32}H_{36}F_3NO_4SSi$ [M + Na]$^+$ 638.1984, found 638.1988.

*(7S,10aR)-7-(4-((tert-Butyldiphenylsilyl)oxy)butyl)-2-methyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]-pyridin-9(8H)-one 5,5-dioxide (**4ar**).* The title product was obtained as colorless oil in 83% yield (156.2 mg); $[\alpha]_D^{20}$ 24.7 (c = 1.0, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 231 nm, t_R = 7.0 min (major), t_R = 10.0 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.58 (m, 5H), 7.41−7.39 (m, 1H), 7.35−7.28 (m, 6H), 7.26 (s, 1H), 3.97−3.95 (m, 1H), 3.66−3.63 (t, J = 5.7 Hz, 2H), 3.22−3.18 (d, J = 15.4 Hz, 1H), 2.83−2.76 (dd, J = 12.8 Hz, 16.8 Hz, 2H), 2.49−2.46 (m, 1H), 2.42 (m, 4H), 1.99−1.97 (m, 1H), 1.60−1.52 (m, 4H), 0.98 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.24 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 145.3, 135.6, 133.98−133.97 (d, J = 4.8 Hz), 133.0, 132.6, 132.3, 129.5, 127.6, 126.1−123.3 (q, J = 285.2 Hz), 124.4, 121.3, 67.6−66.7 (q, J = 30.5 Hz), 63.5, 56.19−56.18 (d, J = 1.4 Hz), 44.3, 44.0, 32.0, 31.03, 26.9, 23.4, 21.9, 19.2; IR (film, ν/cm^{-1}) 1731, 1428, 1315, 1172, 1109, 822, 742; HRMS (ESI) m/z calcd for $C_{33}H_{38}F_3NO_4SSi$ [M + Na]$^+$ 652.2141, found 652.2144.

*(7R,10aR)-7-Phenyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ba**).* The title product was obtained as white solid in 92% yield (105.8 mg), mp 192−195 °C; $[\alpha]_D^{20}$ 76.6 (c = 0.3, EtOAc); HPLC Chiralpak IC, hexane:2-propanol = 70:30, flow rate = 0.8 mL/min, T = 23 °C, UV = 215 nm, t_R = 18.4 min (minor), t_R = 20.3 min (major); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.92−7.91 (m, 3H), 7.89−7.83 (m, 1H), 7.57−7.55 (d, J = 7.3 Hz), 7.43−7.40 (m, 2H), 7.36−7.32 (m, 1H), 5.36−5.32 (dd, J = 5.0 Hz, 11.4 Hz, 1H), 3.63−3.58 (d, J = 17.2 Hz, 1H), 3.45−3.41 (dd, J = 0.8 Hz, 17.2 Hz, 1H), 2.95−2.79 (m, 2 H); ^{19}F NMR (376 MHz, acetone-d_6) δ −76.36 (major isomer); ^{13}C NMR (100 MHz, acetone-d_6) δ 201.6, 141.4, 135.9, 135.1, 133.9, 133.0, 130.0−124.3 (q, J = 283.6 Hz), 129.4, 129.0, 128.1, 126.01−125.99 (d, J = 1.8 Hz), 122.2, 69.1−68.5 (q, J = 30.0 Hz), 58.2, 47.02−46.99 (d, J = 2.7 Hz), 43.9; IR (film, ν/cm^{-1}) 2924, 1733, 1455, 1410, 1327, 1222, 1182, 1065, 990, 947, 763; HRMS (ESI) m/z calcd for $C_{18}H_{14}F_3NO_3S$ [M + Na]$^+$ 404.0544, found 404.0545.

*(7R,10aR)-2-Fluoro-7-phenyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ca**).* The title product was obtained as white solid in 93% yield (111.8 mg), mp 183−186 °C; $[\alpha]_D^{20}$ 119.1 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 20.3 min (minor), t_R = 37.3 min (major); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.02−7.99 (dd, J = 4.8 Hz, J = 8.6 Hz, 1H), 7.80−7.77 (m, 1H), 7.67−7.62 (m, 1H), 7.56−7.54 (m, 2H), 7.43−7.40 (m, 2H), 7.36−7.32 (m, 1H), 5.37−5.33 (dd, J = 5.0 Hz, 11.3 Hz, 1H), 3.67−3.62 (d, J = 17.2 Hz, 1H), 3.51−3.46 (dd, J = 1.0 Hz, 17.2 Hz, 1H), 2.95−2.79 (m, 2H); ^{19}F NMR (376 MHz, acetone-d_6) δ −71.19, −99.41 (major isomer); ^{13}C NMR (100 MHz, acetone-d_6) δ 201.3, 167.9−165.3 (d, J = 252.4 Hz), 141.2, 137.1−137.0 (d, J = 9.6 Hz), 132.30−132.28 (d, J = 2.5 Hz), 129.8−124.1 (q, J = 283.8 Hz), 129.5, 129.1, 128.1, 125.2−124.9 (m), 121.1−120.8 (m), 113.6−113.3 (dd, J = 8.3 Hz, 25.9 Hz), 68.5−68.2 (q, J = 30.5 Hz), 58.4, 47.03−47.00 (d, J = 2.6 Hz), 43.7; IR (film, ν/cm^{-1}) 2921, 1736, 1596, 1483, 1409, 1327, 1182, 1158, 1064, 1004, 959, 923, 832, 766; HRMS (ESI) m/z calcd for $C_{18}H_{13}F_4NO_3S$ [M + Na]$^+$ 422.0450, found 422.0447.

*(7R,10aR)-2-Chloro-7-phenyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4da**).* The title product was obtained as white solid in 95% yield (118.0 mg), mp 201−204 °C; $[\alpha]_D^{20}$ 99.7 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 23.7 min (minor), t_R = 39.5 min (major); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.05 (s, 1H), 7.97−7.95 (d, J = 8.3 Hz, 1H), 7.90−7.87 (m, 1H), 7.56−7.54 (m, 2H), 7.44−7.40 (m, 2H), 7.37−7.33 (m, 1H), 5.37−5.33 (dd, J = 5.1 Hz, 11.2 Hz, 1H), 3.72−3.68 (d, J = 17.2 Hz, 1H), 3.53−3.49 (d, J = 17.3 Hz, 1H), 2.95−2.80 (m, 2H); ^{19}F NMR (376 MHz, acetone-d_6) δ −76.36 (major isomer); ^{13}C NMR (100 MHz, acetone-d_6) δ 201.3, 141.2, 140.8, 136.1, 134.8, 133.5, 129.8−124.1 (q, J = 283.6 Hz), 129.5, 129.1, 128.1, 126.36−126.35 (d, J = 1.6 Hz), 124.0, 68.7−68.4 (q, J = 30.4 Hz), 58.5, 47.08−47.05 (d, J = 2.6 Hz), 43.6; IR (film, ν/cm^{-1}) 1735, 1583, 1459, 1406, 1328, 1222, 1182, 1094, 1062, 999, 952, 898, 830, 763; HRMS (ESI) m/z calcd for $C_{18}H_{13}ClF_3NO_3S$ [M + Na]$^+$ 438.0154, found 438.0152.

*(7R,10aR)-2-(tert-Butyl)-7-phenyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ea**).* The title product was obtained as white solid in 99% yield (129.6 mg), mp 198−201 °C; $[\alpha]_D^{20}$ 72.8 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 231 nm, t_R = 14.3 min (minor), t_R = 49.1 min (major); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.94 (s, 1H), 7.92−7.90 (m, 1H), 7.82−7.80 (d, J = 8.3 Hz, 1H), 7.57−7.54 (m, 2H), 7.43−7.39 (m, 2H), 7.35−7.32 (m, 1H), 5.35−5.31 (dd, J = 4.8 Hz, 11.4 Hz, 1H), 3.76−3.71 (d, J = 17.2 Hz, 1H), 3.42−3.37 (dd, J = 0.9 Hz, 17.2 Hz, 1H), 2.88−2.81 (m, 2H), 1.41 (s, 9H); ^{19}F NMR (376 MHz, acetone-d_6) δ −76.31 (major isomer); ^{13}C NMR (100 MHz, acetone-d_6) δ 201.9, 159.4, 141.6, 134.3, 133.5, 130.4, 129.5, 129.0, 128.2, 127.3−124.5 (q, J = 283.6 Hz), 122.85−122.84 (d, J = 1.5 Hz), 121.8, 69.0−68.7 (q, J = 30.0 Hz), 58.3, 47.20−47.17 (d, J = 2.3 Hz), 44.0, 36.5, 31.4; IR (film, ν/cm^{-1}) 2965, 1735, 1598, 1458, 1410, 1367, 1326, 1222, 1192, 1158, 1111, 1060, 1001, 951, 832, 762; HRMS (ESI) m/z calcd for $C_{22}H_{22}F_3NO_3S$ [M + Na]$^+$ 460.1170, found 460.1174.

*(7R,10aR)-2-Methoxy-7-phenyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4fa**).* The title product was obtained as white solid in 91% yield (112.7 mg), mp 181−184 °C; $[\alpha]_D^{20}$ 92.4 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 25.1 min (minor), t_R = 44.8 min (major); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.81−7.79 (d, J = 8.6 Hz, 1H), 7.56−7.54 (m, 2H), 7.42−7.38 (m, 3H), 7.36−7.31 (m, 2H), 5.34−5.30 (dd, J = 5.1 Hz, 11.3 Hz, 1H), 3.98 (s, 3H), 3.66−3.62 (d, J = 17.2 Hz, 1H), 3.41−3.37 (dd, J = 1.0 Hz, 17.2 Hz, 1H), 2.87−2.81 (m, 2H); ^{19}F NMR (376 MHz, acetone-d_6) δ −76.29 (major isomer); ^{13}C NMR (100 MHz, acetone-d_6) δ 201.8, 165.2, 141.6, 136.5, 129.4, 128.9, 128.1, 127.9, 127.1−124.3 (q, J = 283.6 Hz), 123.7, 119.8, 110.02−110.01 (d, J = 1.5 Hz), 68.6−68.0 (q, J = 30.0 Hz), 58.2, 56.9, 47.07−47.05 (d, J = 2.5 Hz), 43.9; IR (film, ν/cm^{-1}) 2924, 1731, 1596, 1489, 1318, 1255, 1179, 1065, 1021, 960, 829, 765; HRMS (ESI) m/z calcd for $C_{19}H_{16}F_3NO_4S$ [M + Na]$^+$ 434.0650, found 434.0652.

*(7R,10aR)-1-Fluoro-7-phenyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide (**4ga**).* The title product was obtained as white solid in 96% yield (114.6 mg), mp 138−141 °C; $[\alpha]_D^{20}$ 60.9 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 17.8 min (minor), t_R = 55.8 min (major); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.95−7.89 (m, 1H), 7.79−7.77 (d, J = 7.6 Hz, 1H), 7.71−7.66 (m, 1H), 7.56−7.54 (d, J =

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7.4 Hz, 2H), 7.44−7.40 (dd, J = 7.1 Hz, Hz, 2H), 7.36−7.33 (m, 1H), 5.35−5.31 (dd, J = 4.9 Hz, 11.4 Hz, 1H), 3.69−3.59 (m, 2H), 2.95−2.80 (m, 2H); ^{19}F NMR (376 MHz, acetone-d_6) δ −76.28 to −76.33 (d, J = 19.1 Hz), −111.7 to −111.8 (q, J = 19.0 Hz) (major isomer); ^{13}C NMR (100 MHz, acetone-d_6) δ 201.0, 159.8−157.3 (d, J = 255.4 Hz), 141.0, 138.77−138.75 (d, J = 2.0 Hz), 136.14−136.06 (d, J = 8.0 Hz), 129.8−124.1 (q, J = 282.3 Hz), 129.5, 129.1, 128.1, 122.6−122.3 (d, J = 21.8 Hz), 120.5−120.4 (d, J = 16.8 Hz), 118.65−118.61 (d, J = 4.0 Hz), 68.6−67.7 (m), 58.5, 47.06−47.04 (d, J = 2.3 Hz), 42.04−42.00 (d, J = 3.6 Hz); IR (film, ν/cm^{-1}) 2924, 1735, 1608, 1473, 1412, 1331, 1259, 1202, 1104, 1003, 989, 951, 913, 797, 762, 725; HRMS (ESI) m/z calcd for $C_{18}H_{13}F_4NO_3S$ [M + Na]$^+$ 422.0450, found 422.0454.

(7R,10aR)-3-Methyl-7-phenyl-10a-(trifluoromethyl)-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide ***(4ha)***. The title product was obtained as white solid in 96% yield (114.2 mg), mp 176−179 °C; $[\alpha]_D^{20}$ 143.0 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 30.6 min (major), t_R = 53.3 min (minor); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.78−7.75 (m, 1H), 7.71−7.69 (m, 2H), 7.56−7.54 (m, 2H), 7.43−7.39 (m, 2H), 7.35−7.31 (m, 1H), 5.35−5.31 (dd, J = 4.9 Hz, 11.4 Hz, 1H), 3.58−3.54 (d, J = 17.2 Hz, 1H), 3.38−3.34 (dd, J = 0.9 Hz, 17.1 Hz, 1H), 2.90−2.78 (m, 2H), 2.51 (s, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ −76.43 (major isomer); ^{13}C NMR (100 MHz, acetone-d_6) δ 201.7, 144.0, 141.5, 136.0, 131.2, 130.0, 129.4, 128.9, 128.1, 127.1−124.3 (q, J = 283.5 Hz), 125.60−125.58 (d, J = 1.4 Hz), 121.9, 68.9−68.0 (q, J = 30.2 Hz), 58.1, 46.97−46.95 (d, J = 2.6 Hz), 44.0, 21.1; IR (film, ν/cm^{-1}) 2925, 1733, 1495, 1455, 1410, 1325, 1225, 1158, 1063, 990, 947, 895, 832, 766; HRMS (ESI) m/z calcd for $C_{19}H_{16}F_3NO_3S$ [M + Na]$^+$ 418.0701, found 418.0699.

(7R,10aR)-10a-(Difluoromethyl)-2-methyl-7-phenyl-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide ***(4ia)***. The title product was obtained as white solid in 95% yield (108.0 mg), mp 183−186 °C; $[\alpha]_D^{20}$ 130.3 (c = 0.2, EtOAc); HPLC Chiralpak AD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 43.0 min (major), t_R = 48.8 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.72 (d, J = 8.0 Hz, 1H), 7.54−7.53 (d, J = 7.5 Hz, 2H), 7.48−7.46 (d, J = 8.0 Hz, 1H), 7.44−7.40 (t, J = 7.2 Hz, 2H), 7.37−7.35 (m, 1H), 7.29 (s, 1H), 5.78−5.50 (t, J_{F-H} = 55.4 Hz, 1H), 5.37−5.34 (t, J = 6.7 Hz, 1H), 3.27−3.23 (d, J = 16.8 Hz, 1H), 3.16−3.09 (dd, J = 8.2 Hz, 17.9 Hz, 1H), 2.85−2.76 (q, 2H), 2.50 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.90 to −124.63 (d, J = 276.7 Hz), −125.35 to −126.08 (d, J = 276.8 Hz) (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 145.2, 139.0, 134.77−134.75 (d, J = 3.0 Hz), 132.2, 132.1, 129.0, 128.5, 127.2, 125.0, 121.4, 117.0−112.0 (t, J = 251.5 Hz), 67.1−66.6 (t, J = 23.5 Hz), 55.3, 44.03−44.00 (d, J = 3.0 Hz), 42.3, 21.9; IR (film, ν/cm^{-1}) 1730, 1599, 1494, 1456, 1372, 1311, 1225, 1193, 1166, 1076, 998, 919, 818, 761; HRMS (ESI) m/z calcd for $C_{19}H_{17}F_2NO_3S$ [M + Na]$^+$ 400.0795, found 400.0799.

(7R,10aR)-2-Methyl-10a-(perfluoroethyl)-7-phenyl-10,10a-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-9(8H)-one 5,5-dioxide ***(4ja)***. The title product was obtained as white solid in 99% yield (132.5 mg), mp 169−171 °C; $[\alpha]_D^{20}$ 89.1 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 23.3 min (minor), t_R = 36.6 min (major); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.79−7.77 (d, J = 8.0 Hz, 1H), 7.74−7.73 (d, J = 4.1 Hz, 1H), 7.67−7.65 (m, 1H), 7.56−7.54 (m, 2H), 7.42−7.38 (m, 2H), 7.35−7.31 (m, 1H), 5.36−5.32 (dd, J = 4.4 Hz, 12.4 Hz, 1H), 3.66−3.61 (dd, J = 1.8 Hz, 17.1 Hz, 1H), 3.34−3.29 (d, J = 17.2 Hz), 2.97−2.88 (m, 1H), 2.81−2.74 (m, 1H), 2.54 (s, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ −77.94, −114.62 to −115.36 (d, J = 279.4 Hz) −116.09 to −116.83 (d, J = 279.4 Hz) (major isomer); ^{13}C NMR (100 MHz, acetone-d_6) δ 201.7, 146.5, 141.4, 134.34−134.29 (d, J = 5.2 Hz), 133.8, 132.8, 129.5, 129.0, 128.4, 126.49−126.43 (d, J = 6.7 Hz), 122.1, 121.8−113.0 (m), 69.2−68.7 (q, J = 23.1 Hz), 58.8, 46.88−46.81 (d, J = 6.9 Hz), 44.9, 21.8; IR (film, ν/cm^{-1}) 2927, 1735, 1599, 1328, 1227, 1167, 1144, 1019, 932, 819, 761; HRMS (ESI) m/z calcd for $C_{20}H_{16}F_5NO_3S$ [M + Na]$^+$ 468.0669, found 468.0673.

4-((7R,10aR)-2-Fluoro-5,5-dioxido-9-oxo-10a-(trifluoromethyl)-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-yl)-benzonitrile ***(4ce)***. The title product was obtained as white solid in 87% yield (111.2 mg), mp 116−119 °C; $[\alpha]_D^{20}$ 111.7 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 43.4 min (minor), t_R = 77.3 min (major); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.08−8.04 (dd, J = 4.7 Hz, 8.6 Hz, 1H), 7.88−7.85 (m, 2H), 7.84−7.81 (m, 1H), 7.78−7.76 (m, 2H), 7.72−7.67 (m, 1H), 5.49−5.45 (dd, J = 7.6 Hz, 8.9 Hz, 1H), 3.72−3.68 (d, J = 17.2 Hz, 1H), 3.59−3.55 (dd, J = 1.1 Hz, 17.2 Hz, 1H), 2.94−2.91 (m, 2H); ^{19}F NMR (376 MHz, acetone-d_6) δ −76.48, −104.25 (major isomer); ^{13}C NMR (100 MHz, acetone-d_6) δ 200.7, 168.0−165.5 (d, J = 252.7 Hz), 146.5, 137.1−137.0 (d, J = 9.7 Hz), 133.5, 131.91−131.88 (d, J = 2.5 Hz), 129.7−124.1 (q, J = 283.7 Hz), 129.3, 125.3−125.2 (d, J = 10.0 Hz), 121.3−121.1 (d, J = 24.3 Hz), 119.2, 113.8−113.5 (d, J = 24.2 Hz), 112.9, 68.6−68.0 (q, J = 30.4 Hz), 58.3, 46.32−46.29 (d, J = 2.6 Hz), 43.6; IR (film, ν/cm^{-1}) 1734, 1596, 1484, 1328, 1182, 1065, 958, 837; HRMS (ESI) m/z calcd for $C_{19}H_{12}F_4N_2O_3S$ [M + Na]$^+$ 447.0402, found 447.0400.

4-((7R,10aR)-2-Chloro-5,5-dioxido-9-oxo-10a-(trifluoromethyl)-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-yl)-benzonitrile ***(4de)***. The title product was obtained as white solid in 94% yield (124.7 mg), mp 198−201 °C; $[\alpha]_D^{20}$ 120.1 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 53.8 min (minor), t_R = 85.4 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.79 (d, J = 8.4 Hz, 1H), 7.75−7.70 (m, 3H), 7.67−7.61 (m, 2H), 7.55 (s, 1H), 5.24−5.20 (dd, J = 4.4 Hz, 11.5 Hz, 1H), 3.45−3.41 (d, J = 17.3 Hz, 1H), 3.03−2.79 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.71 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 143.8, 141.1, 134.5, 132.9, 132.7, 132.5, 128.1−122.4 (q, J = 284.4 Hz), 127.9, 124.7, 123.2, 118.3, 112.8, 67.6−66.7 (q, J = 31.1 Hz), 56.6, 44.9, 43.3; IR (film, ν/cm^{-1}) 2922, 1734, 1584, 1505, 1467, 1408, 1328, 1223, 1179, 1123, 1094, 1063, 999, 953, 911, 850, 826, 771, 735; HRMS (ESI) m/z calcd for $C_{19}H_{12}ClF_3N_2O_3S$ [M + Na]$^+$ 463.0107, found 463.0104.

4-((7R,10aR)-3-Methyl-5,5-dioxido-9-oxo-10a-(trifluoromethyl)-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-yl)-benzonitrile ***(4he)***. The title product was obtained as white solid in 97% yield (121.9 mg), mp 219−221 °C; $[\alpha]_D^{20}$ 66.8 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23 °C, UV = 231 nm, t_R = 55.7 min (major), t_R = 122.3 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.73 (m, 2H), 7.67−7.65 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 7.59−7.57 (m, 1H), 7.45−7.43 (d, J = 8.2 Hz, 1H), 5.24−5.20 (dd, J = 4.6 Hz, 11.6 Hz, 1H), 3.45−3.41 (d, J = 17.3 Hz, 1H), 2.99−2.96 (m, 1H), 2.87−2.82 (m, 2H), 2.51 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.90 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 144.2, 143.2, 135.5, 134.1, 132.9, 129.9, 127.9, 125.6−122.7 (q, J = 284.1 Hz), 124.1, 121.8, 118.4, 112.7, 67.4−66.8 (q, J = 30.8 Hz), 56.4, 44.9, 43.7, 21.4; IR (film, ν/cm^{-1}) 2925, 1733, 1610, 1499, 1414, 1325, 1226, 1159, 1122, 1065, 990, 948, 843, 735; HRMS (ESI) m/z calcd for $C_{20}H_{15}F_3N_2O_3S$ [M + Na]$^+$ 443.0653, found 443.0648.

(7R,9R,10aR)-9-Hydroxy-2-methyl-7-phenyl-10a-(trifluoromethyl)-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide ***(5a)***. The title product was obtained according to the following procedure: To the solution of **4aa** (395 mg, 1.0 mmol) in 11 mL the mixture solvent of DCM/MeOH (10/1), $NaBH_4$ (380 mg, 10 mmol) was added in portion wise fashion at −30 °C for 2 h. The resulting suspension was stirred at −30 °C for 3 h. The reaction was quenched at −30 °C by the addition of 10 mL of saturated NH_4Cl solution. The mixture was transferred to a separatory funnel, the organic layer was collected, and the aqueous layer was extracted with 3 × 10 mL of DCM. The combined organic extracts were washed with 30 mL of saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a white solid residue. Purification of the residue by column chromatography (PE/EA = 6/1−2/1) afforded the desired reductive product **5a** as white solid in 98% yield (389.5 mg), mp 154−157 °C; $[\alpha]_D^{20}$ 50.9 (c = 0.4, EtOAc);

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HPLC Chiralpak OD-H, hexane:2-propanol = 90:10, flow rate = 0.8 mL/min, T = 23 °C, UV = 215 nm, t_R = 47.5 min (major), t_R = 57.6 min (minor); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.78−7.76 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 7.64−7.62 (m, 1H), 7.56−7.55 (d, J = 7.5 Hz, 2H), 7.39−7.35 (m, 2H), 7.30−7.26 (m, 1H), 5.21−5.16 (dd, J = 6.3 Hz, 11.5 Hz, 1H), 4.37−4.36 (d, J = 4.5 Hz), 3.97−3.90 (m, 1H), 2.72−2.67 (dd, J = 6.2 Hz, 14.4 Hz, 1H), 2.62−2.57 (dd, J = 5.6 Hz, 12.6 Hz, 1H), 2.55 (s, 3H), 2.54−2.48 (m, 1H), 2.03−1.96 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.29 (major isomer); ^{13}C NMR (100 MHz, acetone-d_6) δ 146.3, 143.2, 137.0, 133.3, 133.1, 130.3, 129.2, 128.2, 127.7, 127.5−124.6 (q, J = 283.1 Hz), 126.05−126.03 (d, J = 1.6 Hz), 121.8, 68.0−67.1 (q, J = 30.7 Hz), 63.0, 56.5, 39.8, 39.4, 21.9; IR (film, ν/cm^{-1}) 3669, 3647, 3512, 2923, 1597, 1454, 1378, 1297, 1176, 1066, 945, 817, 759; HRMS (ESI) m/z calcd for $C_{19}H_{18}F_3NO_3S$ [M + Na]$^+$ 420.0857, found 420.0861.

*(2R,4R,6R)-6-Phenyl-2-(m-tolyl)-2-(trifluoromethyl)piperidin-4-ol (**6a**).* The title product was obtained according to the following procedure: To the solution of **5a** (200 mg, 0.5 mmol) in 12 mL anhydrous DME, 0.5 M Na/Naphthaene in DME (10 mL, 5 mmol, 10 equiv) was added dropwise at −78 °C under a dry nitrogen atmosphere. The resulting suspension was stirred at −78 °C for 2 min. The reaction was quenched at −78 °C by the addition of 5 mL of 5% aqueous NaH_2PO_4. The resulting solution was concentrated and extracted with 3 × 20 mL of Et_2O. The combined organic extracts were washed with 50 mL of saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford an oily residue. Purification of the residue by column chromatography (PE/EA = 15/1−5/1) afforded the desired reductive product **6a** as colorless oil in 36% yield (61.2 mg); $[\alpha]_D^{20}$ −8.8 (c = 0.3, EtOAc); HPLC Chiralpak OD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, T = 23 °C, UV = 215 nm, t_R = 11.7 min (minor), t_R = 13.3 min (major); ^{1}H NMR (400 MHz, methanol-d_4) δ 7.45 (s, 1H), 7.41−7.39 (d, J = 7.5 Hz, 3H), 7.35−7.31 (m, 3H), 7.27−7.23 (m, 1H), 7.21−7.19 (d, J = 7.4 Hz, 1H), 3.69−3.60 (m, 2H), 3.31 (s, 1H), 2.88−2.85 (m, 1H), 2.39 (s, 3H), 1.97−1.85 (m, 2H), 1.53−1.44 (q, J = 11.6 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.89 (major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 138.6, 134.6, 129.2, 128.8, 128.7, 128.6, 127.8, 126.9−124.1 (q, J = 281.8 Hz), 126.7, 125.1, 65.7, 64.2−63.6 (q, J = 26.5 Hz), 54.0, 43.4, 36.5, 21.7; IR (film, ν/cm^{-1}) 2923, 2853, 1604, 1493, 1458, 1266, 1171, 1054, 997, 785, 760, 720; HRMS (ESI) m/z calcd for $C_{19}H_{20}F_3NO$ [M + H]$^+$ 336.1575, found 336.1578.

(S)-N-((S)-1-Hydroxy-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (cat C). The title product was obtained as a white solid in 82% yield (2.03 g, using 10 mmol starting material), mp 98−101 °C; $[\alpha]_D^{20}$ −20.8 (c = 1.2, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.86 (d, J = 7.5 Hz, 1H), 7.30−7.26 (m, 2H), 7.24−7.19 (m, 3H), 4.15−4.10 (m, 1H), 3.72−3.65 (m, 2H), 3.61−3.56 (dd, J = 6.0 Hz, 11.1 Hz, 1H), 2.99−2.86 (m, 4H), 2.78−2.72 (dd, J = 8.8 Hz, 13.8 Hz, 1H), 2.69−2.63 (m, 1H), 2.05−1.96 (m, 1H), 1.71−1.64 (m, 1H), 1.61−1.53 (m, 1H), 1.44−1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 137.7, 129.1, 128.4, 126.5, 65.2, 60.3, 52.8, 47.0, 37.0, 30.6, 25.8; IR (film, ν/cm^{-1}) 3353, 3268, 2938, 2860, 1636, 1522, 1451, 1296, 1053, 907, 744; HRMS (ESI) m/z calcd for $C_{14}H_{20}N_2O_2$ [M + H]$^+$ 249.1603, found 249.1599.

(S)-2-Amino-N-((R)-1-hydroxy-3-phenylpropan-2-yl)-3-phenylpropanamide (S,R-cat D). The title product was obtained as a white solid in 84% yield (2.52 g, using 10 mmol starting material), mp 102−105 °C; $[\alpha]_D^{20}$ −17.2 (c = 1.0, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.44 (d, J = 7.6 Hz, 1H), 7.32−7.17 (m, 10 H), 4.13−4.09 (m, 1H), 3.68−3.64 (dd, J = 3.6 Hz, 11.2 Hz, 1H), 3.57−3.52 (m, 2H), 3.18−3.14 (dd, J = 4.2 Hz, 13.7 Hz, 1H), 2.89−2.84 (dd, J = 6.9 Hz, 13.8 Hz, 1H), 2.81−2.75 (dd, J = 7.8 Hz, 13.8 Hz, 1H), 2.73−2.67 (dd, J = 8.9 Hz, 13.7 Hz, 1H), 2.15 (br, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 137.7, 137.6, 129.3, 129.2, 128.7, 128.5, 126.9, 126.6, 64.4, 56.3, 53.1, 41.0, 37.0; IR (film, ν/cm^{-1}) 3304, 3064, 3028, 2923, 1643, 1543, 1496, 1452, 1363, 1260, 1100, 1075, 1040, 917, 745; HRMS (ESI) m/z calcd for $C_{18}H_{22}N_2O_2$ [M + H]$^+$ 299.1760, found 299.1757.

*(E)-8-((tert-Butyldiphenylsilyl)oxy)oct-3-en-2-one (**3r**).* The title product was obtained as colorless oil in 65% yield, (10.85 g, using 44 mmol starting material). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.66 (d, J = 6.6 Hz, 4H), 7.43−7.32 (m, 6H), 6.80−6.73 (m, 1H), 6.06−6.02 (d, J = 16.0 Hz, 1H), 3.67−3.66 (t, J = 5.5 Hz, 2H), 2.21−2.18 (m, 5H), 1.58−1.57 (m, 4H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 148.3, 135.4, 134.7, 133.8, 131.2, 129.5, 127.5, 127.5, 63.3, 32.0, 31.8, 26.8, 26.5, 24.3, 19.1; IR (film, ν/cm^{-1}) 3064, 2935, 2860, 1674, 1629, 1467, 1428, 1361, 1256, 1106, 983, 821, 738; HRMS (ESI) m/z calcd for C24H32O2Si [M + Na]$^+$ 403.2069, found 403.2073.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00087.

Crystallographic data of compound **4ak**. (CIF)

^{1}H NMR and ^{13}C NMR spectra for all the products; HPLC profiles. (PDF)

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Notes

The authors declare no competing financial interest.

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