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Catalytic Asymmetric Decarboxylative Mannich Reaction of Malonic Acid Half Esters with Cyclic Aldimines: Access to Chiral β-Amino Esters and Chroman-4-amines

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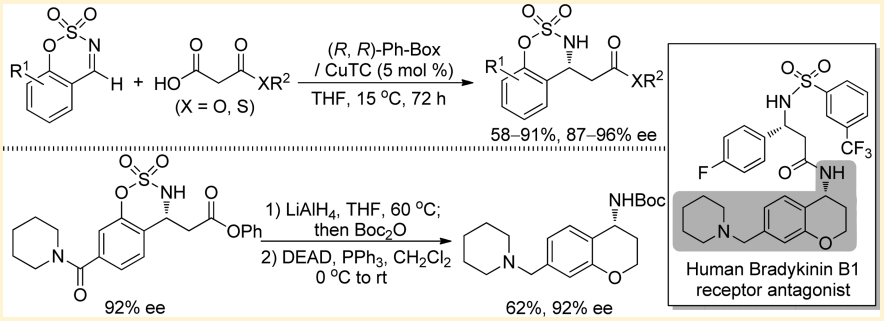
Supporting Information



ABSTRACT: An enantioselective decarboxylative Mannich reaction of malonic acid half esters (MAHEs) with cyclic aldimines has been accomplished by employing the copper(I)/(*R*,*R*)-Ph-Box complex as chiral catalyst. The desired β-amino esters were obtained in good to high yields with excellent enantioselectivities. Furthermore, one of the corresponding Mannich products could be readily transformed into chiral chroman-4-amines without loss of enantioselectivity, which is a key intermediate of the human Bradykinin B1 receptor antagonist.

INTRODUCTION

Optically pure β-amino acids and their derivatives are key structural units for the synthesis of β-peptides, β-lactam antibiotics, and many other important chiral drugs.[1] Consequently, the development of efficient methods for the construction of these useful building-blocks has become the subject of intensive research in the fields of synthetic and medicinal chemistry.[2] Although many stoichiometric and catalytic approaches have been developed to make chiral β-amino acids, catalytic asymmetric Mannich reaction of simple esters with imines represents a simple and attractive means of accessing chiral β-amino esters.[3] However, the formation of ester enolates under mild conditions is challenging due to the high pK_a value of the α-proton in simple esters. Accordingly, the utility of ester equivalents, such as malonic acid half oxyesters or thioesters, have proven to be highly effective in many asymmetric transfromations.[4] Within this context, Ricci's and Tan's groups described the catalytic asymmetric Mannich reaction of aldimines with malonic acid half thioesters by using cinchona derivatives or chiral bicyclic guanidine catalysts (Scheme 1a),[5,6] whereas the groups of Shibata,[7] Nakamura,[8] and Ma[9] reported the cinchona-sulfonamide and amino-thiourea catalyzed enantioselective decarboxylative Mannich reaction of ketimines with malonic acid half esters (Scheme 1b and c). All such studies mainly focused on the use of small organic molecules as chiral catalysts. In sharp contrast, the complementary metal-catalyzed decarboxylative Mannich reaction of these ester enolate equivalents for the enantioselective synthesis of β-amino acids has not been reported so far.

Herein we present a Cu-catalyzed asymmetric decarboxylative Mannich reaction of malonic acid half esters with cyclic aldimines. This reaction proceeds smoothly with excellent enantioselectivity to afford highly functionalized chiral β-amino esters (Scheme 1d). Furthermore, the potential application of this metal-catalyzed asymmetric decarboxylative Mannich reaction was further exemplified in a highly enantioselective synthesis of chiral chroman-4-amine derivatives.

RESULTS AND DISCUSSION

Preparation of Starting Substates. Cyclic aldimines and malonic acid half esters could be conveniently synthesized according to the known methods in the literatures.[10,11] The condensation reaction of salicylaldehyde with freshly prepared sulfamoyl chloride gave the corresponding cyclic aldimines **1**, whereas the ring opening of Meldrum's acid with (thio)phenols led to formation of malonic acid half esters in high yields.

Optimization of the Reaction Conditions. Our study commenced with cyclic aldimine (benzo[*e*][1,2,3]oxathiazine 2,2-dioxide) **1a** and malonic acid half oxyester **2a** as the model

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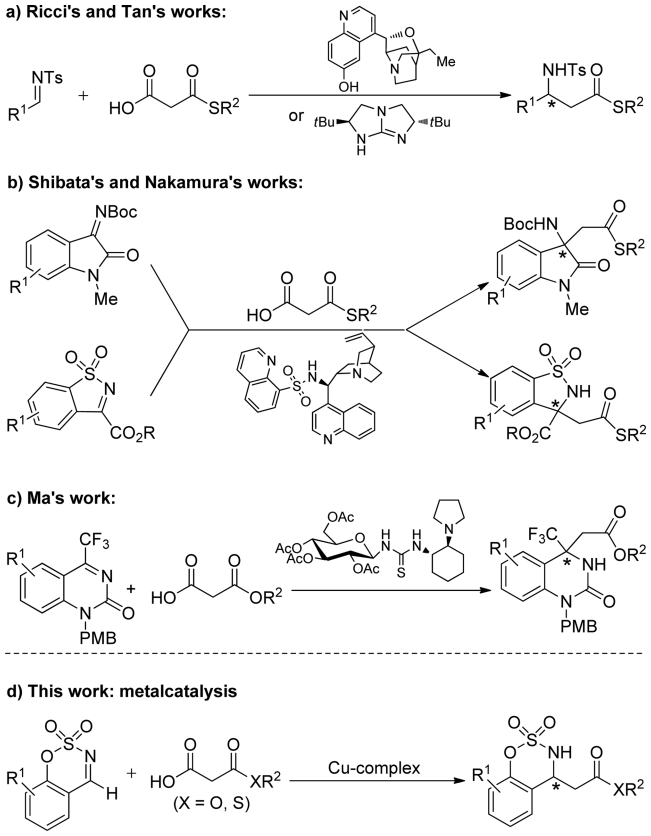
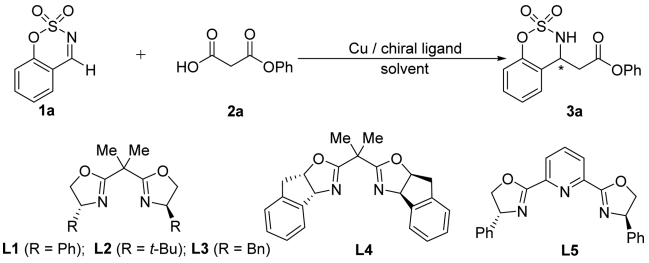
Scheme 1. Enantioselective Decarboxylative Mannich Reaction of MAHEs with Imines



substrates, and the results are listed in Table 1. In an initial experiment, a $Cu(OTf)_2$/(*R*, *R*)-Ph-Box (**L1**) complex in THF at room temperature delivered the corresponding protected *β*-amino esters **3a** in 42% yield with 68% ee (entry 1). Subsequently, a series of other copper salts, including $Cu(OAc)_2$, CuI, CuBr, and CuTC, were further evaluated (entries 2−5). We were gratified to find that the CuTC/(*R*,*R*)-Ph-Box system provided the Mannich product **3a** with the highest enantioselectivity (90% ee) (entry 5). When the reaction was performed at a lower temperature (15 °C), the ee value could be further improved to 95% (entry 6). Next, other representative chiral bis(oxazoline) ligands **L2**−**L5** were also tested for this model reaction (entries 7−10). The results showed that the use of these ligands gave rise to either significantly lower enantioselectivities or reactivities. In addition, the screening of solvents revealed that this asymmetric decarboxylative Mannich reaction is highly sensitive to the solvent used (entries 11−15). Among the solvents tested, THF was found to be the best solvent for this reaction, whereas all the other solvents resulted in a substantial decrease in the yield and/or enantioselectivity. Last, the effect of catalyst loading was examined, and reducing the amount of Cu-complex from 5 to 2 mol% caused a drop in yield (87−78%) and enantioselectivity (95−88% ee) (entry 16).

Scope of the Catalytic Asymmetric Decarboxylative Mannich Reaction. Under the optimal conditions, the scope of the reaction was explored with a variety of cyclic aldimines **1** and malonic acid half esters **2**. As shown in Scheme 2, for various cyclic aldimines, the position and electronic properties of the substituents on the phenyl ring have a limited effect on enantioselectivity of the Mannich reaction. Regardless of

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol%)	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	$Cu(OTf)_2$/**L1** (5)	THF	25	96	42	68
2	$Cu(OAc)_2$/**L1** (5)	THF	25	60	79	87
3	CuI/**L1** (5)	THF	25	60	75	87
4	CuCl/**L1** (5)	THF	25	60	74	86
5	CuTC/**L1** (5)	THF	25	60	83	90
6	**CuTC/L1(5)**	**THF**	**15**	**72**	**87**	**95**
7	CuTC/**L2** (5)	THF	15	96	68	14
8	CuTC/**L3** (5)	THF	15	96	40	39
9	CuTC/**L4** (5)	THF	15	96	75	8
10	CuTC/**L5** (5)	THF	15	96	62	3
11	CuTC/**L1** (5)	MTBE	15	96	68	83
12	CuTC/**L1**(5)	1,4-dioxane	15	96	75	86
13	CuTC/**L1** (5)	DCM	15	72	0	-
14	CuTC/**L1**(5)	CH_3CN	15	72	40	30
15	CuTC/**L1**(5)	toluene	15	72	0	-
16	CuTC/**L1**(2)	THF	15	96	78	88

[a]General reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), and catalyst (2−5 mol %) in solvent for the stated time. [b]Yield of product averaged over two runs. [c]Determined by HPLC analysis on a chiral stationary phase. CuTC = copper(I) thiophene-2-carboxylate, THF = tetrahydrofuran, MTBE = *tert*-butyl methyl ether.

whether there were electron-neutral, -donating, or -withdrawing groups on the phenyl ring, the decarboxylative Mannich reactions proceeded smoothly to give the desired products **3a**−**m** in good to high yields (72−89%) with high enantioselectivities (88−96% ee). 2-Naphthaldehyde-derived imine was also a good substrate, providing the desired product **3n** in 90% yield with 87% ee. Subsequently, this protocol was extended to the use of a series of malonic acid half esters **2**. For a malonic acid half thioester, the reaction also took place to afford the Mannich product **3o** in a moderate yield (58%) with high enantioselectivity (96% ee). The use of malonic acid half oxyesters with different phenolic ester substituents, such as methyl, methoxyl, chloro, and bromo, gave rise to the corresponding *β*-amino esters **3p**−**s** in high yields (82−91%) and enantioselectivities (90−95% ee). Notably, the product **3s** was isolated as a crystalline compound (>99.9% ee), and the structure was characterized by X-ray crystallographic analysis. The absolute configuration for the stereogenic carbon center formed in the Mannich reaction is of *R* stereochemistry.[12] Remarkably, even at a loading of 5 mol%, the CuTC/(*R*,*R*)-Ph-Box (L1) complex could also deliver comparable results (78% yield and 93% ee) when the model reaction was run on 2.0 mmol scale for an extended reaction time (96 h) by sequential addition of malonic acid half esters **2a** (Scheme 3).

Further Synthetic Transformation of the Mannich Product into Chroman-4-amine. Chiral chroman-4-amines

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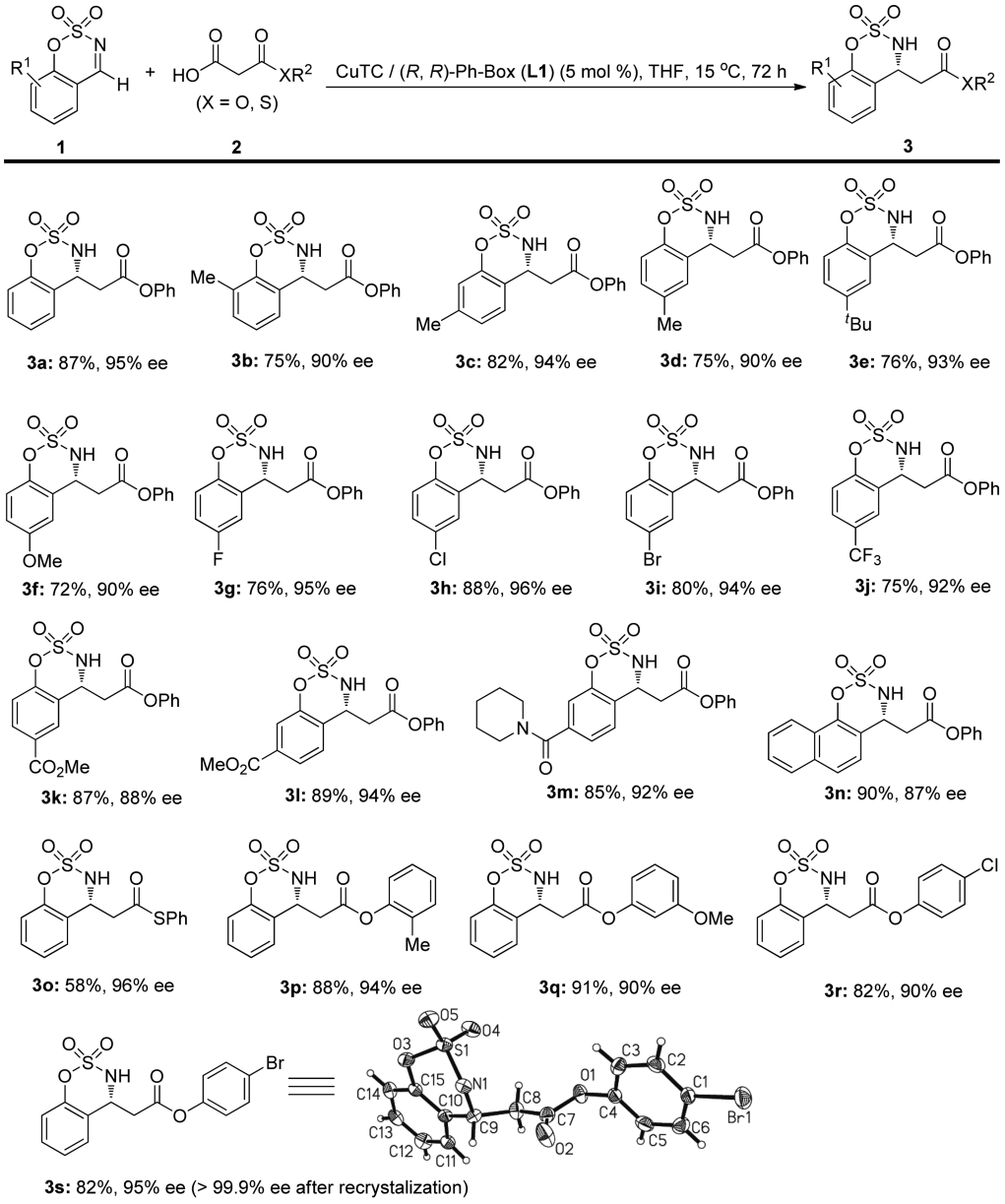
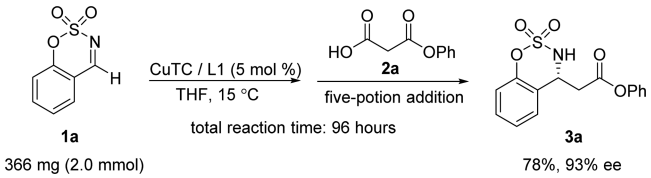
Scheme 2. Scope for Cu-Catalyzed Asymmetric Decarboxylative Mannich Reaction of Cyclic Aldimines 1 with Malonic Acid Half Esters 2[a,b]



[a]Yield of products averaged over two runs. [b]The ee values determined by HPLC analysis on a chiral stationary phase.

Scheme 3. Scaled-up DMR of Cyclic Aldimines 1a with Malonic Acid Half Esters 2a



have been utilized as core scaffolds in an increasing number of recent drug discovery programs.[13] To demonstrate the potential application of our protocol, a short-step chemical transformation of the decarboxylative Mannich adduct **3m** was carried out for the preparation of chiral chroman-4-amine **5**, which is a key intermediate of the human Bradykinin B1 receptor antagonist (Scheme 4). Direct reduction of sulfonamide, amide, and ester groups of **3m** with $LiAlH_4$, followed by protection with Boc_2O, furnished the intermediate **4**. To avoid the risk of racemization, the compound **4** was directly subjected into the Mitsunobu cyclization. The desired product **5** was obtained in 62% total yield without detectable loss of enantioselectivity.

Study on the Mechanism of the Decarboxylative Mannich Reaction. To cast some light on the mechanism, NMR and ESI/MS methods were used to study this decarboxylative Mannich reaction. First, we conducted ^{13}C NMR spectroscopic experiments of CuTC/(*R*,*R*)-Ph-Box complex, substrates, and their mixtures in THF-d_8, respectively. As shown in Figure 1c, when 1.0 equiv of MAHE **2a** was added

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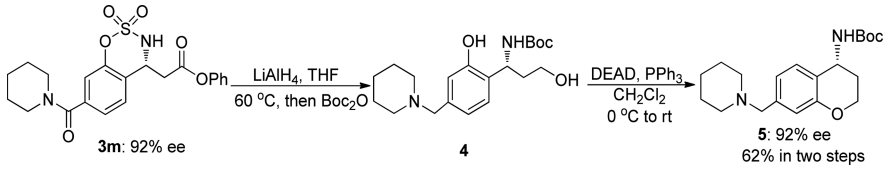
Scheme 4. Further Synthetic Transformation of the Decarboxylative Mannich Product 3m into Chroman-4-amine 5



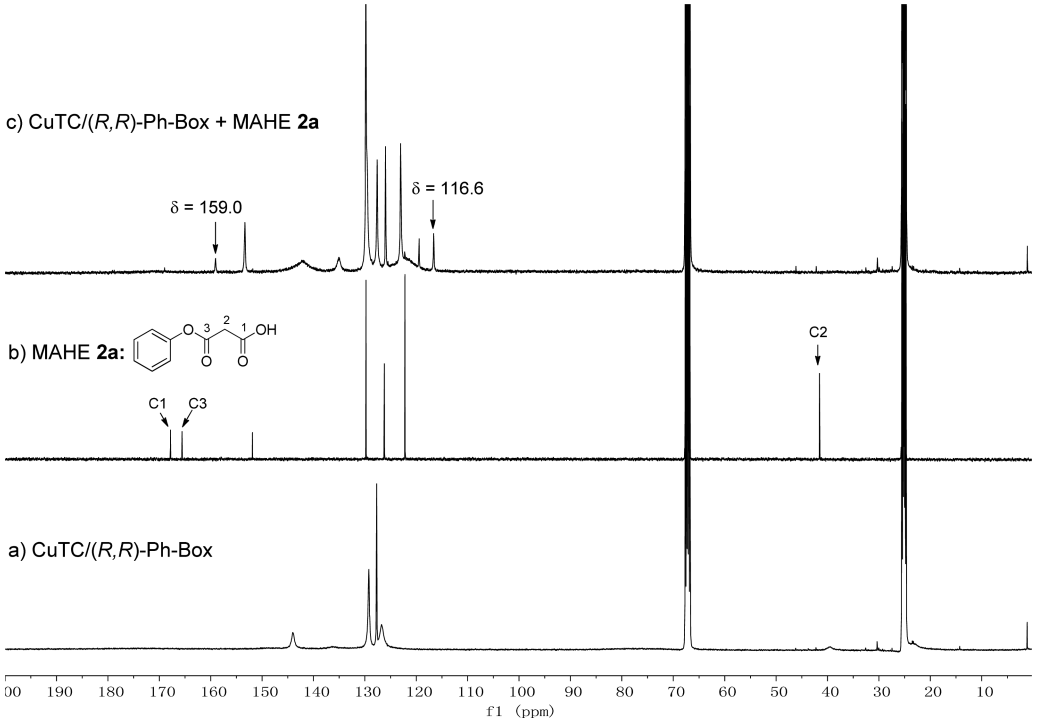


Figure 1. ^{13}C NMR spectra in THF-d_8 (0.5 mL) of (a) CuTC/(*R*,*R*)-Ph-Box complex (0.3 mmol); (b) MAHE **2a** (0.3 mmol); (c) 1:1 mixture of CuTC/(*R*,*R*)-Ph-Box complex and MAHE **2a** (0.3 mmol, 15 min later).

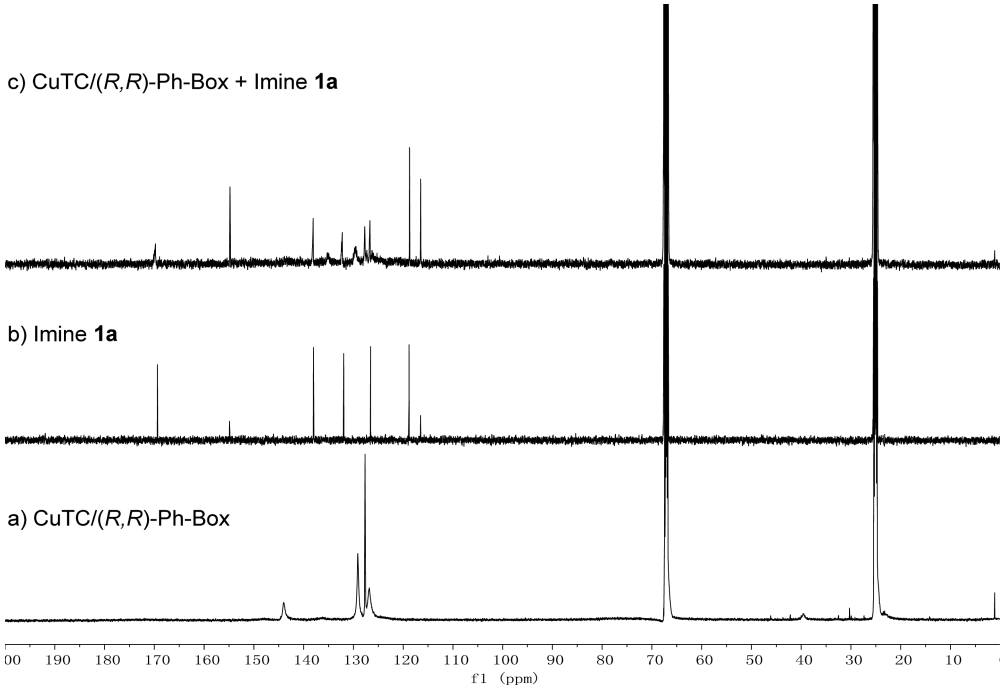


Figure 2. ^{13}C NMR spectra in THF-d_8 (0.5 mL) of (a) CuTC/(*R*,*R*)-Ph-Box complex (0.3 mmol); (b) aldimine **1a** (0.3 mmol); (c) 1:1 mixture of CuTC/(*R*,*R*)-Ph-Box complex and aldimine **1a** (0.3 mmol, 15 min later).

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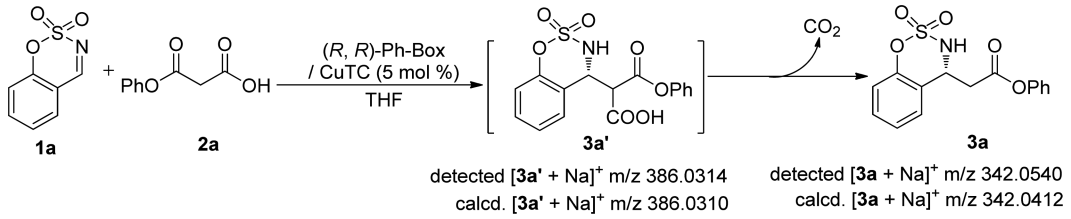
Scheme 5. HRMS Analysis of the Mannich Reaction of Cyclic Aldimine 1a and MAHE 2a



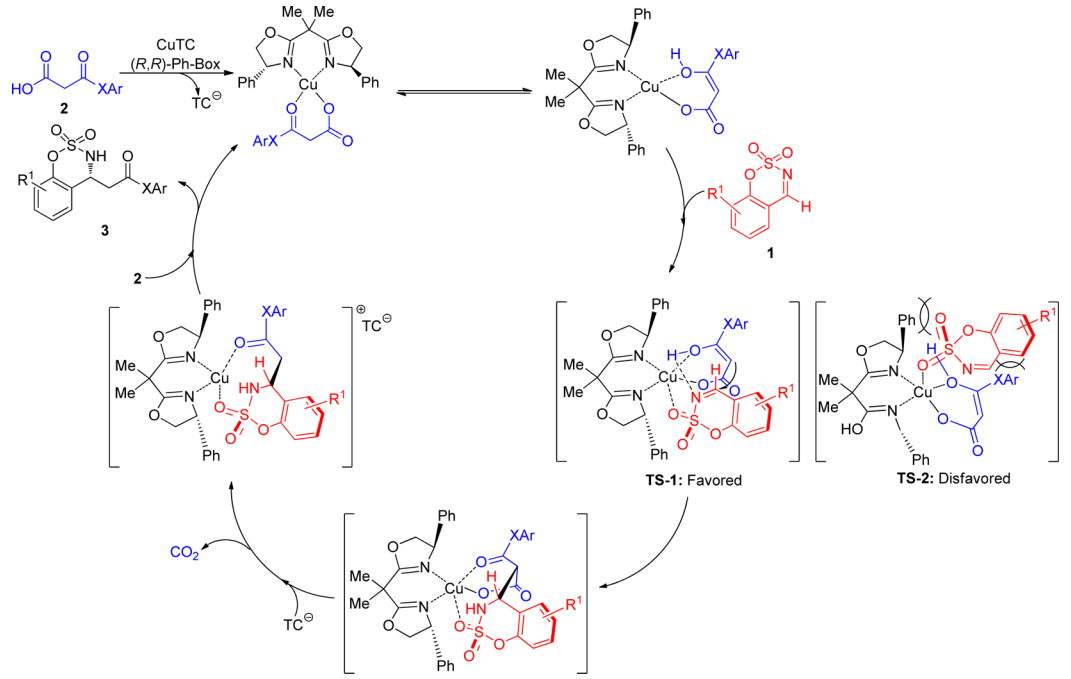


Figure 3. Proposed mechanism for the Cu-catalyzed decarboxylative Mannich reaction.

to the CuTC/(*R*,*R*)-Ph-Box complex, the original peaks of C1, C2, and C3 (δ = 167.8, 41.6, 165.6) of MAHE remarkably decreased or vanished, indicating that the coordination of MAHE to CuTC/(*R*,*R*)-Ph-Box occurred. Meanwhile, the appearance of two new peaks at 159.0 and 116.6 ppm suggests that the coordinated MAHE could undergo a process of deprotonative enolization and generate the reactive ester enolate. In sharp contrast, new peaks in the ^{13}C NMR spectra could not be observed when 1.0 equiv of cyclic aldimine **1a** was added to the CuTC/(*R*,*R*)-Ph-Box complex (Figure 2). In addition, the high resolution mass spectroscopy (HRMS-ESI) analysis of the model reaction under optimal conditions was carried out (Scheme 5). Two signal peaks were detected at *m*/*z* 386.0314 and 342.0540, which correspond to the Mannich intermediate (**3a**′) and the decarboxylative product (**3a**), respectively. A control experiment was simultaneously conducted in the absence of catalyst CuTC/(*R*,*R*)-Ph-Box. However, neither **3a** nor **3a**′ was observed even with the prolonged reaction time. These ESI/MS experimental results provide some preliminary evidence that the Mannich addition of MAHEs to cyclic aldimines could occur prior to the decarboxylation.

On the basis of our experimental results and the previous reports,[14] we proposed the mechanism of the catalytic decarboxylative Mannich reaction as shown in Figure 3. The Cu-(*R*,*R*)-Ph-Box complex undergoes the coordination reaction with the MAHEs **2** and affords the square-planar complexes. Subsequently, the sulfonyl oxygen of cyclic aldimines **1** is chelated to the metal center in the axial position with a concomitant hydrogen-bond interaction between the ester enol and aldimine, leading to the square pyramidal transition states (**TS-1** and **TS-2**). The sterically favored **TS-1** allows the nucleophilic attack of MAHEs from the *Re* face of cyclic aldimines which predominantly delivers the *R* enantiomer. The decarboxylation of the Mannich adducts gives the corresponding intermediate, which exchanges with the new reactant MAHE and releases the final product **3**.

■ CONCLUSION

In summary, we have successfully developed a metal-catalyzed enantioselective decarboxylative Mannich reaction of malonic acid half esters with cyclic aldimines. In the presence of CuTC/(*R*, *R*)-Ph-Box, the Mannich reaction proceeded smoothly to afford a series of β-amino esters in 58−91% yields with 87−96% ee. Synthetic transformation of the Mannich adduct gave rise to the formation of chiral chroman-4-amine without detectable loss of enantiopurity, which is a key intermediate of the human Bradykinin B1 receptor antagonist. Further applications of MAHEs-derived synthons to other transformations are underway in our laboratory, the results of which will be reported in due course.

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EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR were recorded at 600 MHz (^{1}H NMR), 150 MHz (^{13}C NMR). Chemical shifts were reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.15 ppm; THF-d_8: δ_C = 25.12, 67.21 ppm). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), and dt (doublet of triplets). High-resolution mass spectrometry (HRMS) spectra were obtained on a micro TOF-QII instrument.

Materials. Tetrahydrofuran (THF), methyl *tert*-butyl ether (MTBE), 1,4-dioxane and toluene was distilled from sodium/benzophenone prior to use; CH_2Cl_2 (dichloromethane, DCM) was distilled from CaH_2; acetonitrile (CH_3CN) was distilled from P_2O_5. All purchased reagents and ligands (**L1**–**L5**) were used without further purification. Malonic acid half esters **2** were prepared according to the literature and their characterization data were in agreement with reported values.[11]

Representative Procedure for the Preparation of Cyclic Aldimines. Anhydrous formic acid (40.0 mmol, 1.814 g, 1.5 mL) was added dropwise to neat chlorosulfonyl isocyanate (40.0 mmol, 5.660 g, 3.5 mL) at 0 °C with rapid stirring. The resulting viscous suspension was stirred at 0 °C for 3h and afforded the $ClSO_2NH_2$. To a solution of salicylaldehyde (15.0 mmol) in DMA (100 mL) at 0 °C was carefully added freshly prepared $ClSO_2NH_2$ (4.61 g, 40.0 mmol) in small portions and the resulting solution was stirred for 24 h. The reaction was quenched carefully with ice-cold H_2O (100 mL) and the mixture was transferred to a separating funnel containing CH_2Cl_2 (200 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), filtered through a short pad of silica using CH_2Cl_2 as eluent and concentrated in vacuum. The residue was purified via flash column chromatography on silica gel (eluting with petroleum ether/ethyl acetate, v/v = 6/1). The substrates **1a**, **1d**, **1f**, and **1h** are known compounds, and their characterization data were in agreement with reported values. The analysis data for unknown substrates are listed as followed.

*8-Methylbenzo[e][1,2,3]oxathiazine 2,2-Dioxide (**1b**).* mp 89–90 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 2.40 (s, 3H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 168.0, 152.6, 139.1, 128.5, 125.6, 115.2, 100.0, 14.5; IR (KBr) ν: 3683, 2920, 1600, 1381, 1272, 1245, 1171, 872, 764, 726 cm^{-1}; HRMS (APCI) found: m/z 198.0200 [M+H]$^+$; calcd. for $C_8H_7NO_3S$ + H 198.0225.

*7-Methylbenzo[e][1,2,3]oxathiazine 2,2-Dioxide (**1c**).* mp 76–77 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.09 (s, 1H), 2.50 (s, 3H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 167.4, 154.4, 150.4, 130.6, 127.2, 118.8, 113.2, 22.4; IR (KBr) ν: 3453, 2923, 1603, 1546, 1384, 1234, 1190, 1117, 955, 872, 785, 750 cm^{-1}; HRMS (APCI) found: m/z 198.0215 [M+H]$^+$; calcd. for $C_8H_7NO_3S$ + H 198.0225.

*6-(tert-Butyl)benzo[e][1,2,3]oxathiazine 2,2-Dioxide (**1e**).* mp 77–78 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.78 (dd, J = 8.7, 2.1 Hz, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 1.36 (s, 9H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 168.1, 152.2, 149.8, 135.2, 127.3, 118.1, 114.9, 34.8, 31.1; IR (KBr) ν: 3450, 1640, 1486, 1443, 1388, 1277, 1186, 1117, 976, 872, 775 cm^{-1}; HRMS (APCI) found: m/z 240.0675 [M+H]$^+$; calcd. for $C_{11}H_{13}NO_3S$ + H 240.0694.

*6-Fluorobenzo[e][1,2,3]oxathiazine 2,2-Dioxide (**1g**).* mp 139–141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.43–7.38 (m, 1H), 7.33 (dd, J = 6.8, 2.9 Hz, 1H), 7.24 (dd, J = 9.1, 4.0 Hz, 1H); ^{19}F NMR (565 MHz, $CDCl_3$) δ −113.3 (td, J = 7.1, 4.2 Hz); ^{13}C{H}-NMR (150 MHz, $CDCl_3$) δ 166.5, 159.2 (d, $^1J_{F-C}$ = 249.4 Hz), 150.2, 124.8 (d, $^2J_{F-C}$ = 24.2 Hz), 120.6 (d, $^3J_{F-C}$ = 7.9 Hz), 116.3 (d, $^2J_{F-C}$ = 24.4 Hz), 115.9 (d, $^3J_{F-C}$ = 8.0 Hz); IR (KBr) ν: 3674, 2922, 1742, 1562, 1475, 1386, 1348, 1260, 1185, 1152, 848, 761 cm^{-1}; HRMS (APCI) found: m/z 201.9965 [M+H]$^+$; calcd. for $C_7H_4FNO_3S$ + H 201.9974.

*6-Bromobenzo[e][1,2,3]oxathiazine 2,2-Dioxide (**1i**).* mp 118–120 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.84 (dd, J = 8.8, 2.1 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 166.3, 153.3, 140.2, 133.0, 120.4, 118.7, 116.5; IR (KBr) ν: 3659, 3032, 1605, 1550, 1463, 1380, 1342, 1211, 1179, 1127, 1071, 1021, 912, 826, 764 cm^{-1}; HRMS (APCI) found: m/z 261.9158 [M+H]$^+$; calcd. for $C_7H_4BrNO_3S$ + H 261.9174.

*6-(Trifluoromethyl)benzo[e][1,2,3]oxathiazine 2,2-Dioxide (**1j**).* mp 89–90 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.93–8.03 (m, 2H), 7.45 (d, J = 8.5 Hz, 1H); ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.7(s); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 166.4, 156.3, 134.1, 128.9 (q, $^2J_{F-C}$ = 34.5 Hz), 128.1, 122.6 (q, $^1J_{F-C}$ = 273.4 Hz), 119.7, 115.1; IR (KBr) ν: 3659, 3067, 1615, 1580, 1485,1391, 1350, 1317, 1212, 1187, 1130, 1069, 1021, 927, 824, 762 cm^{-1}; HRMS (APCI) found: m/z 251.9964 [M+H]$^+$; calcd. for $C_8H_4F_3NO_3S$ + H 251.9942.

*Methyl Benzo[e][1,2,3]oxathiazine-6-carboxylate 2,2-Dioxide (**1k**).* mp 118–119 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.40 (s, 1H), 8.39 (s, 1H), 7.36 (d, J = 9.1 Hz, 1H), 3.98 (s, 3H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 167.0, 164.3, 157.0, 138.2, 132.5, 128.4, 118.9, 114.9, 52.8; IR (KBr) ν: 3682, 2848, 1728, 1615, 1528, 1493, 1442, 1393, 1291, 1185, 839, 758 cm^{-1}; HRMS (APCI) found: m/z 242.0114 [M+H]$^+$; calcd. for $C_9H_7NO_5S$ + H 242.0123.

*Methyl Benzo[e][1,2,3]oxathiazine-7-carboxylate 2,2-Dioxide (**1l**).* mp 102–103 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.06 (dd, J = 8.0, 1.2 Hz, 1H), 7.91 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 4.00 (s, 3H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 166.9, 164.2, 154.0, 138.1, 130.8, 126.8, 119.7, 117.8, 53.2; IR (KBr) ν: 3658, 2957, 1726, 1609, 1552, 1492, 1437, 1392, 1290, 1224, 1195, 1084, 980, 929, 840, 761 cm^{-1}; HRMS (APCI) found: m/z 242.0110 [M+H]$^+$; calcd. for $C_9H_7NO_5S$ + H 242.0123.

*(2,2-Dioxidobenzo[e][1,2,3]oxathiazin-7-yl)(piperidin-1-yl)-methanone (**1m**).* mp 155–156 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.40 (dd, J = 7.8, 0.8 Hz, 1H), 7.27 (d, J = 4.4 Hz, 1H), 3.71 (s, 2H), 3.29 (s, 2H), 1.70 (s, 4H), 1.54 (s, 2H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 167.1, 166.6, 154.3, 145.7, 131.2, 124.3, 116.9, 115.4, 48.6, 43.3, 26.5, 25.4, 24.3; IR (KBr) ν: 3659, 2935, 2858, 1613, 1545, 1497, 1444, 1391, 1282, 1231, 1190, 1096, 1007, 959, 874, 819, 761 cm^{-1}; HRMS (APCI) found: m/z 295.0733 [M+H]$^+$; calcd. for $C_{13}H_{14}N_2O_4S$ + H 295.0753.

*Naphtho[2,1-e][1,2,3]oxathiazine 2,2-Dioxide (**1n**).* mp 190–191 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.76 (s, 1H), 8.40 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.82–7.74 (m, 2H), 7.71 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 168.1, 153.5, 137.7, 131.6, 128.3, 128.2, 125.7, 123.5, 123.1, 122.7, 110.6; IR (KBr) ν: 3659, 2935, 1633, 1595, 1548, 1496, 1461, 1381, 1335, 1272, 1225, 1088, 1024, 994, 884, 813, 782 cm^{-1}; HRMS (APCI) found: m/z 234.0214 [M+H]$^+$; calcd. for $C_{11}H_7NO_3S$ + H 234.0225.

General Procedure for Asymmetric Decarboxylative Mannich Reaction of Malonic Acid Half Esters with Cyclic Aldimines. CuTC (0.95 mg, 5 mol%) and (*R*, *R*)-Ph-box (1.75 mg, 5 mol%) were added into a 10 mL flask equipped with a stirring bar under air atmosphere in THF (1.0 mL). After the reaction was stirred at 15 °C for 1 h, the cyclic aldimines **1** (0.10 mmol), malonic acid half esters **2** (0.15 mmol) were then added into the reaction system. After completion of the reaction (monitored by TLC), the reaction was quenched with 5% brine. The mixture was extracted by ethyl acetate (5 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica gel (eluting with petroleum ether/ethyl acetate, v/v = 15/1 to 7/1) to give the Mannich product **3**. The enantiomeric excess was determined by HPLC analysis on a Chiralcel column.

*Phenyl (R)-2-(2,2-Dioxido-3,4-dihydrobenzo[e][1,2,3]oxathiazin-4-yl)acetate (**3a**).* 27 mg; 87% yield; 95% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 14.2 min (minor) and t_R = 19.7 min (major)]; mp 93–95 °C; $[\alpha]_D^{25}$ = +48.2 (c 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (dd, J = 14.9, 7.2 Hz, 3H), 7.19–7.11 (m, 3H), 6.96 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 7.9 Hz, 2H), 5.70 (d, J = 8.7 Hz, 1H), 5.15 (td, J = 8.2, 3.8 Hz, 1H), 3.49 (dd, J = 17.0, 7.6 Hz, 1H), 3.13 (dd, J = 17.0, 3.8 Hz, 1H); ^{13}C{H}NMR (150 MHz,

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$CDCl_3$) δ 169.7, 151.4, 150.1, 130.2, 129.7, 126.5, 126.0, 125.7, 121.3, 120.6, 119.3, 54.0, 38.1; IR (KBr) ν: 3268, 2926, 1746, 1677, 1597, 1420, 1182, 1104, 915, 757, 689 cm^{-1};HRMS (ESI) found: m/z 342.0412 $[M+Na]^+$; calcd. for $C_{15}H_{13}NO_5S$ + Na 342.0412.

*Phenyl (R)-2-(8-Methyl-2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]-oxathiazin-4-yl)acetate (**3b**).* 24 mg; 75% yield; 90% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 11.4 min (minor) and t_R = 16.0 min (major)]; mp 118−120 °C; $[\alpha]_D^{25}$ = +26.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.8 Hz, 2H), 7.18−7.11 (m, 2H), 7.07−6.99 (m, 2H), 6.89 (d, *J* = 7.9 Hz, 2H), 5.65 (d, *J* = 8.5 Hz, 1H), 5.13 (td, *J* = 7.9, 3.7 Hz, 1H), 3.48 (dd, *J* = 17.0, 7.6 Hz, 1H), 3.12 (dd, *J* = 17.0, 3.7 Hz, 1H), 2.20 (s, 3H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.8, 150.1, 145.0, 131.6, 129.7, 128.8, 126.5, 124.9, 123.4, 121.4, 120.4, 54.1, 38.1, 15.7; IR (KBr) ν: 3270, 2960, 2850, 1744, 1487, 1460, 1422, 1371, 1261, 1193, 1153, 1019, 936, 871, 792, 740 cm^{-1}; HRMS (ESI) found: m/z 356.0569 $[M+Na]^+$; calcd. for $C_{16}H_{15}NO_5S$ + Na 356.0569.

*Phenyl (R)-2-(7-Methyl-2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]-oxathiazin-4-yl)acetate (**3c**).* 27 mg; 82% yield; 94% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 16.7 min (minor) and t_R = 23.8 min (major)]; mp 162−163 °C; $[\alpha]_D^{25}$ = +51.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 2H), 6.77 (s, 1H), 5.63 (s, 1H), 5.10 (s, 1H), 3.46 (dd, *J* = 16.9, 7.5 Hz, 1H), 3.10 (dd, *J* = 16.9, 3.6 Hz, 1H), 2.27 (s, 3H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.8, 151.3, 150.1, 140.8, 129.7, 126.5, 126.5, 125.7, 121.4, 119.5, 117.5, 53.9, 38.0, 21.1; IR (KBr) ν: 3449, 2960, 1738, 1703, 1626, 1490, 1404, 1383, 1261, 1190, 1161, 1104, 1020, 944, 804, 746 cm^{-1}; HRMS (ESI) found: m/z 356.0565 $[M+Na]^+$; calcd. for $C_{16}H_{15}NO_5S$ + Na 356.0569.

*Phenyl (R)-2-(6-Methyl-2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]-oxathiazin-4-yl)acetate (**3d**).* 24 mg; 75% yield; 90% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 14.4 min (minor) and t_R = 19.7 min (major)]; mp: 129−132 °C; $[\alpha]_D^{25}$ = +64.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.7 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.96 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 5.62 (d, *J* = 6.6 Hz, 1H), 5.10 (d, *J* = 1.4 Hz, 1H), 3.46 (dd, *J* = 16.9, 8.0 Hz, 1H), 3.10 (dd, *J* = 16.9, 3.5 Hz, 1H), 2.26 (s, 3H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.7, 150.1, 149.3, 135.5, 130.7, 129.7, 126.5, 126.3, 121.3, 119.0, 54.0, 38.3, 20.9; IR (KBr) ν: 3277, 2926, 1750, 1592, 1490, 1426, 1374, 1282, 1258, 1183, 1115, 1025, 901, 854, 817, 752 cm^{-1}; HRMS (ESI) found: m/z 356.0567 $[M+Na]^+$; calcd. for $C_{16}H_{15}NO_5S$ + Na 356.0569.

*Phenyl (R)-2-(6-(tert-Butyl)-2,2-dioxido-3,4-dihydrobenzo[e]-[1,2,3]oxathiazin-4-yl)acetate (**3e**).* 24 mg; 76% yield; 93% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 10.4 min (minor) and t_R = 13.2 min (major)]; mp 117−119 °C; $[\alpha]_D^{25}$ = +73.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 2H), 7.17 (dd, *J* = 8.4, 5.1 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.88−6.82 (m, 2H), 5.61 (s, 1H), 5.17 (d, *J* = 2.3 Hz, 1H), 3.55 (dd, *J* = 16.8, 7.5 Hz, 1H), 3.15 (dd, *J* = 16.8, 3.6 Hz, 1H), 1.24 (s, 9H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.8, 150.1, 149.3, 148.9, 129.7, 127.3, 126.5, 122.7, 121.3, 119.6, 118.8, 54.4, 38.1, 34.7, 31.5; IR (KBr) ν: 3281, 3058, 2961, 2870, 1730, 1592, 1492, 1324, 1269, 1236, 1150, 930, 830, 751 cm^{-1}; HRMS (ESI) found: m/z 398.1036 $[M+Na]^+$; calcd. for $C_{19}H_{21}NO_5S$ + Na 398.1038.

*Phenyl 2-(6-Methoxy-2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]-oxathiazin-4-yl)acetate (**3f**).* 25 mg; 72% yield; 90% *ee*; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 17.4 min (minor) and t_R = 23.5 min (major)]; mp: 133−135 °C; $[\alpha]_D^{25}$ = +67.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.8 Hz, 2H), 7.23 (dd, *J* = 13.7, 6.3 Hz, 1H), 7.04−6.92 (m, 3H), 6.87 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.75 (d, *J* = 2.0 Hz, 1H), 5.67 (s, 1H), 5.17 (s, 1H), 3.79 (s, 3H), 3.54 (dd, *J* = 17.0, 7.8 Hz, 1H), 3.18 (dd, *J* = 17.0, 3.4 Hz, 1H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.6, 156.9, 150.1, 145.0, 129.6, 126.4, 121.3, 120.0, 115.2, 111.2, 55.9, 54.1, 38.2; IR (KBr) ν: 3449, 2924, 2852, 1748, 1631, 1492, 1422, 1381, 1253, 1168, 1033, 852, 813, 751 cm^{-1}; HRMS (ESI) found: m/z 372.0518 $[M+Na]^+$; calcd. for $C_{16}H_{15}NO_6S$ + Na 372.0518.

*Phenyl (R)-2-(6-Fluoro-2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]-oxathiazin-4-yl)acetate (**3g**).* 26 mg; 76% yield; 95% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 9.7 min (minor) and t_R = 12.5 min (major)]; mp 127−128 °C; $[\alpha]_D^{25}$ = +37.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.00−6.95 (m, 1H), 6.95−6.86 (m, 4H), 5.68 (s, 1H), 5.10 (s, 1H), 3.44 (dd, *J* = 17.1, 7.6 Hz, 1H), 3.10 (dd, *J* = 17.1, 3.8 Hz, 1H); ^{19}F NMR (565 MHz, $CDCl_3$) δ −115.23 (dd, *J* = 12.5, 7.6 Hz); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.5, 159.4 (d, $^1J_{F-C}$ = 246.3 Hz), 150.0, 147.2 (d, $^4J_{F-C}$ = 2.6 Hz), 129.6, 126.5, 122.1 (d, $^3J_{F-C}$ = 6.9 Hz), 121.2, 120.8 (d, $^3J_{F-C}$ = 8.4 Hz), 117.1 (d, $^2J_{F-C}$ = 23.5 Hz), 112.7 (d, $^2J_{F-C}$ = 25.1 Hz), 53.8, 37.9; IR (KBr) ν: 3450, 1741, 1630, 1592, 1485, 1419, 1381, 1274, 1284, 1192, 1160, 1023, 939, 851, 749 cm^{-1}; HRMS (ESI) found: m/z 360.0320 $[M+Na]^+$; calcd. for $C_{15}H_{12}FNO_5S$ + Na 360.0318.

*Phenyl (R)-2-(6-Chloro-2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]-oxathiazin-4-yl)acetate (**3h**).* 30 mg; 88% yield; 96% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 10.0 min (minor) and t_R = 12.7 min (major)]; mp 120−122 °C; $[\alpha]_D^{25}$ = +80.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.8 Hz, 2H), 7.26 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.22−7.15 (m, 2H), 6.93 (d, *J* = 8.4 Hz, 3H), 5.69 (s, 1H), 5.13 (dd, *J* = 6.8, 3.6 Hz, 1H), 3.50 (dd, *J* = 17.2, 7.3 Hz, 1H), 3.15 (dd, *J* = 17.1, 3.6 Hz, 1H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.5, 150.0, 150.0, 130.9, 130.3, 129.8, 126.7, 126.0, 122.2, 121.3, 120.8, 53.8, 37.8; IR (KBr) ν: 3267, 1747, 1592, 1477, 1429, 1374, 1190, 1168, 1114, 820, 785, 750 cm^{-1}; HRMS (ESI) found: m/z 376.0023 $[M+Na]^+$; calcd. for $C_{15}H_{12}ClNO_5S$ + Na 376.0022.

*Phenyl (R)-2-(6-Bromo-2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]-oxathiazin-4-yl)acetate (**3i**).* 31 mg; 80% yield; 94% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 10.2 min (minor) and t_R = 12.9 min (major)]; mp 140−141 °C; $[\alpha]_D^{25}$ = +82.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.34 (d, *J* = 1.4 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 1H), 5.69 (d, *J* = 8.9 Hz, 1H), 5.12 (td, *J* = 8.3, 3.8 Hz, 1H), 3.49 (dd, *J* = 17.1, 7.5 Hz, 1H), 3.14 (dd, *J* = 17.1, 3.8 Hz, 1H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.6, 150.5, 150.0, 133.2, 129.8, 129.0, 126.6, 122.6, 121.3, 121.0, 118.3, 53.7, 37.9; IR (KBr) ν: 3448, 1746, 1634, 1475, 1428, 1401, 1189, 1168, 1115, 841, 815, 780, 749 cm^{-1}; HRMS (ESI) found: m/z 419.9513 $[M+Na]^+$; calcd. for $C_{15}H_{12}BrNO_5S$ + Na 419.9517.

*Phenyl (R)-2-(2,2-Dioxido-6-(trifluoromethyl)-3,4-dihydrobenzo-[e][1,2,3]oxathiazin-4-yl)-acet-ate (**3j**).* 29 mg; 75% yield; 92% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 90/10, 220 nm UV detector, 1.0 mL/min, t_R = 10.6 min (minor) and t_R = 14.6 min (major)]; mp 161−163 °C; $[\alpha]_D^{25}$ = +42.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.5 Hz, 1H), 7.55 (s, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 6.6 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 2H), 5.87 (s, 1H), 5.26 (s, 1H), 3.63 (dd, *J* = 17.2, 7.1 Hz, 1H), 3.27 (d, *J* = 17.1 Hz, 1H); ^{19}F NMR (565 MHz, $CDCl_3$) δ −62.23 (s); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.6, 153.8, 150.0, 129.8, 128.0 (q, $^2J_{F-C}$ = 33.4 Hz), 127.4 (q, $^3J_{F-C}$ = 3.5 Hz), 126.7, 123.5 (q, $^3J_{F-C}$ = 3.6 Hz), 123.4 (q, $^1J_{F-C}$ = 272.2 Hz), 121.5, 121.2, 120.1, 53.9, 37.6; IR (KBr) ν: 3282, 2926, 1745, 1626, 1594, 1493, 1429, 1381, 1332, 1191, 1169, 1121, 1081, 955, 898, 833, 753 cm^{-1}; HRMS (ESI) found: m/z 410.0285 $[M+Na]^+$; calcd. for $C_{16}H_{12}F_3NO_5S$ + Na 410.0286.

*(R)-Methyl 4-(2-oxo-2-Phenoxyethyl)-3,4-dihydrobenzo[e][1,2,3]-oxathiazine-7-carboxylate 2,2-Dioxide (**3k**).* 33 mg; 87% yield; 88% *ee*; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 17.8

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min (minor) and t_R = 20.0 min (major)]; mp: 60−62 °C; $[\alpha]_D^{25}$ = +23.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06−7.96 (m, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.23 (t, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 5.96 (s, 1H), 5.26 (d, 1H), 3.93 (s, 3H), 3.64 (dd, *J* = 17.0, 6.0 Hz, 1H), 3.29−3.26 (m, 1H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.5, 165.7, 154.6, 150.1, 131.4, 129.7, 128.0, 127.5, 126.5, 121.3, 120.8, 119.4, 53.9, 52.7, 38.0; IR (KBr) ν: 3267, 2963, 1725, 1491, 1414, 1436, 1296, 1260, 1195, 1091, 1020, 820, 799 cm^{-1}; HRMS (ESI) found: *m*/*z* 400.0466 $[M+Na]^+$; calcd. for $C_{17}H_{15}NO_7S$ + Na 400.0467.

*Methyl (R)-4-(2-oxo-2-Phenoxyethyl)-3,4-dihydrobenzo[e][1,2,3]-oxathiazine-7-carboxylate 2,2-Dioxide (**3l**).* 34 mg; 89% yield; 94% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 21.6 min (minor) and t_R = 24.0 min (major)]; mp 60−62 °C; $[\alpha]_D^{25}$ = +23.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.69 (s, 1H), 7.40−7.33 (m, 3H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 2H), 5.86 (s, 1H), 5.28 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.94 (s, 3H), 3.62 (dd, *J* = 17.2, 7.4 Hz, 1H), 3.26 (dd, *J* = 17.2, 3.7 Hz, 1H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.5, 165.4, 151.5, 150.0, 132.3, 129.7, 126.6, 126.4, 126.2, 125.4, 121.3, 120.6, 54.1, 52.8, 37.9; IR (KBr) ν: 3267, 2963, 1725, 1491, 1414, 1436, 1296, 1260, 1195, 1091, 1020, 820, 799 cm^{-1}; HRMS (ESI) found: *m*/*z* 400.0466 $[M+Na]^+$; calcd. for $C_{17}H_{15}NO_7S$ + Na 400.0467.

*Phenyl (R)-2-(2,2-Dioxido-7-(piperidine-1-carbonyl)-3,4-dihydrobenzo[e][1,2,3]oxathiazin −4-yl)acetate (**3m**).* 37 mg; 85% yield; 92% ee; white solid; [determined by HPLC analysis Daicel Chirapak IB, *n*-hexane/*i*-PrOH = 40/60, 220 nm UV detector, 0.63 mL/min, t_R = 26.7 min (minor) and t_R = 19.6 min (major)]; mp 198−199 °C; $[\alpha]_D^{25}$ = +48.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.20−7.16 (m, 1H), 7.10 (dd, *J* = 20.7, 7.5 Hz, 2H), 7.02 (d, *J* = 7.7 Hz, 2H), 6.84 (s, 1H), 5.04 (s, 1H), 3.61 (s, 2H), 3.44 (dd, *J* = 16.7, 8.3 Hz, 1H), 3.20 (s, 2H), 3.05 (dd, *J* = 16.6, 3.6 Hz, 1H), 1.59 (s, 4H), 1.43 (s, 2H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 168.1, 167.4, 149.9, 149.2, 136.3, 128.5, 125.8, 125.2, 122.3, 121.3, 120.4, 116.1, 52.3, 47.8, 42.5, 38.6, 25.5, 24.4, 23.3; IR (KBr) ν: 3265, 2958, 1730, 1491, 1410, 1436, 1296, 1260, 1195, 1090, 1020, 825, 786 cm^{-1}; HRMS (ESI) found: *m*/*z* 453.1089 $[M+Na]^+$; calcd. for $C_{21}H_{22}N_2O_6S$ + Na 453.1095.

*Phenyl (R)-2-(2,2-Dioxido-3,4-dihydronaphtho[2,1-e][1,2,3]-oxathiazin-4-yl)acetate (**3n**).* 32 mg; 90% yield; 87% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 11.4 min (minor) and t_R = 17.1 min (major)]; mp 126−128 °C; $[\alpha]_D^{25}$ = +20.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21−8.13 (m, 1H), 7.88−7.81 (m, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.63−7.55 (m, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 5.82 (d, *J* = 8.2 Hz, 1H), 5.36 (m, 1H), 3.68 (dd, *J* = 17.0, 8.0 Hz, 1H), 3.27 (dd, *J* = 17.0, 3.4 Hz, 1H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.8, 150.2, 146.9, 134.0, 129.7, 127.9, 127.7, 127.6, 126.5, 125.5, 124.7, 121.9, 121.4, 121.2, 115.2, 54.6, 38.1; IR (KBr) ν: 3262, 3065, 2926, 1750, 1594, 1490, 1426, 1376, 1266, 1195, 1076, 1024, 941, 887, 805, 749 cm^{-1}; HRMS (ESI) found: *m*/*z* 392.0559 $[M+Na]^+$; calcd. for $C_{19}H_{15}NO_5S$ + Na 392.0569.

*S-Phenyl (R)-2-(2,2-Dioxido-3,4-dihydrobenzo[e][1,2,3]-oxathiazin-4-yl)ethanethioate (**3o**).* 19 mg; 58% yield; 96% ee; yellow solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 85/15, 254 nm UV detector, 0.8 mL/min, t_R = 21.4 min (minor) and t_R = 35.9 min (major)]; mp 77−78 °C; $[\alpha]_D^{25}$ = +58.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44−7.38 (m, 3H), 7.36−7.31 (m, 3H), 7.24−7.19 (m, 2H), 7.03 (d, *J* = 8.2 Hz, 1H), 5.68 (d, *J* = 8.4 Hz, 1H), 5.19 (td, *J* = 7.9, 3.9 Hz, 1H), 3.74 (dd, *J* = 16.8, 7.4 Hz, 1H), 3.22 (dd, *J* = 16.8, 3.9 Hz, 1H). ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 196.6, 151.4, 134.5, 130.2, 130.1, 129.6, 126.4, 126.1, 125.6, 120.4, 119.3, 54.4, 45.9; IR (KBr) ν: 3450, 3281, 2924, 2854, 1690, 1581, 1482, 1423, 1378, 1187, 1168, 1105, 1076, 1024, 976, 857, 750 cm^{-1}; HRMS (ESI) found: *m*/*z* 358.0180 $[M+Na]^+$; calcd. for $C_{15}H_{13}NO_4S_2$ + Na 358.0184.

*o-Tolyl (R)-2-(2,2-Dioxido-3,4-dihydrobenzo[e][1,2,3]oxathiazin-4-yl)acetate (**3p**).* 29 mg; 88% yield; 94% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 10.4 min (minor) and t_R = 14.3 min (major)]; mp 134−135 °C; $[\alpha]_D^{25}$ = +55.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 7.14−7.04 (m, 3H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 5.73 (s, 1H), 5.16 (d, *J* = 2.8 Hz, 1H), 3.53 (dd, *J* = 16.9, 7.4 Hz, 1H), 3.15 (dd, *J* = 16.9, 3.7 Hz, 1H), 1.96 (s, 3H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.5, 151.5, 148.8, 131.4, 130.2, 123.0, 127.2, 126.7, 126.1, 125.7, 121.6, 120.6, 119.4, 54.1, 37.7, 16.2; IR (KBr) ν: 3449, 3263, 1750, 1631, 1582, 1487, 1452, 1425, 1380, 1173, 1039, 864, 750 cm^{-1}; HRMS (ESI) found: *m*/*z* 356.0566 $[M+Na]^+$; calcd. for $C_{16}H_{15}NO_5S$ + Na 356.0569.

*3-Methoxyphenyl (R)-2-(2,2-Dioxido-3,4-dihydrobenzo[e][1,2,3]-oxathiazin-4-yl)acetate (**3q**).* 32 mg; 91% yield; 90% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 22.2 min (minor) and t_R = 21.7 min (major)]; mp 107−108 °C; $[\alpha]_D^{25}$ = +45.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.6 Hz, 1H), 7.28−7.25 (m, 1H), 7.23 (t, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.55 (d, *J* = 7.9 Hz, 1H), 6.50 (d, *J* = 1.8 Hz, 1H), 5.75 (s, 1H), 5.22 (s, 1H), 3.75 (s, 3H), 3.56 (dd, *J* = 17.0, 7.5 Hz, 1H), 3.19 (dd, *J* = 17.0, 3.5 Hz, 1H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.6, 160.6, 151.4, 151.0, 130.2, 130.1, 126.1, 125.7, 120.6, 119.3, 113.5, 112.2, 107.5, 55.6, 54.0, 38.1; IR (KBr) ν: 3258, 2920, 2840, 1751, 1607, 1487, 1451, 1426, 1373, 1282, 1171, 1105, 1038, 955, 861, 826, 754 cm^{-1}; HRMS (ESI) found: *m*/*z* 372.0521 $[M+Na]^+$; calcd. for $C_{16}H_{15}NO_6S$ + Na 372.0518.

*4-Chlorophenyl (R)-2-(2,2-Dioxido-3,4-dihydrobenzo[e][1,2,3]-oxathiazin-4-yl)acetate (**3r**).* 29 mg; 82% yield; 94% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 11.2 min (minor) and t_R = 14.5 min (major)]; mp 107−108 °C; $[\alpha]_D^{25}$ = +45.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 6.4 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.86 (s, 1H), 6.85 (d, *J* = 1.2 Hz, 1H), 5.59 (d, *J* = 6.7 Hz, 1H), 5.17 (s, 1H), 3.52 (dd, *J* = 17.0, 7.9 Hz, 1H), 3.14 (dd, *J* = 17.0, 2.2 Hz, 1H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.4, 151.4, 148.5, 132.0, 130.3, 129.8, 126.0, 125.7, 122.8, 120.5, 119.4, 54.1, 38.2; IR (KBr) ν: 3450, 1752, 1632, 1485, 1451, 1424, 1381, 1258, 1170, 1040, 1014, 860, 802, 755 cm^{-1}; HRMS (ESI) found: *m*/*z* 376.0025 $[M+Na]^+$; calcd. for $C_{15}H_{12}ClNO_5S$ + Na 376.0022.

*4-Bromophenyl (R)-2-(2,2-Dioxido-3,4-dihydrobenzo[e][1,2,3]-oxathiazin-4-yl)acetate (**3s**).* 32 mg; 82% yield; 95% ee; white solid; [determined by HPLC analysis Daicel Chirapak IC, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_R = 12.3 min (minor) and t_R = 16.1 min (major)]; mp 147−149 °C; $[\alpha]_D^{25}$ = +43.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.7 Hz, 2H), 7.40−7.34 (m, 1H), 7.27−7.24 (m, 2H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.64 (s, 1H), 5.25 (s, 1H), 3.60 (dd, *J* = 17.0, 7.8 Hz, 1H), 3.21 (dd, *J* = 17.0, 3.7 Hz, 1H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 169.4, 151.4, 149.1, 132.8, 130.3, 126.0, 125.7, 123.2, 120.5, 119.7, 119.4, 54.0, 38.2; IR (KBr) ν: 3269, 2927, 1750, 1588, 1486, 1451, 1426, 1375, 1283, 1257, 1191, 1171, 1106, 1017, 948, 837, 753 cm^{-1}; HRMS (ESI) found: *m*/*z* 419.9523 $[M+Na]^+$; calcd. for $C_{15}H_{12}BrNO_5S$ + Na 419.9517.

Procedure for the Further Synthetic Transformation. To a solution of $LiAlH_4$ (68 mg, 1.8 mmol) in THF (1.5 mL) at room temperature was added the **3m** (78 mg, 0.18 mmol) in THF (2 mL) dropwise over 5 min. The mixture was heated at 55 °C for 6 h, cooled naturally to room temperature, and then cooled to 0 °C with an ice bath. The reaction was quenched carefully with EtOAc (2 mL) followed by H_2O (6 mL). The aqueous layer was extracted with EtOAc (3 × 8 mL). The combined organic layers were dried by $MgSO_4$, filtered, and concentrated in vacuum. To the residue in DCM (3 mL) at room temperature was added Et_3N (18 mg, 0.18 mmol), Boc_2O (40 mg, 0.2 mmol). The mixture was stirred at room temperature for 12 h and then quenched carefully with EtOAc (2 mL) followed by H_2O (6 mL). The aqueous layer was extracted with

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EtOAc (3 × 8 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated in vacuum and obtained the crude product **4** (39 mg) as a yellow solid.

To a solution of crude product **4** (39 mg) and PPh_3 (32 mg, 0.12 mmol) in DCM (1 mL) at 0 °C was added a solution of diethyl azodicarboxylate (DEAD, 23 mg, 0.13 mmol) in DCM (2 mL). The mixture was allowed to warm to room temperature over 1 h, and then stirred for an additional 6 h. The reaction was quenched with EtOH (2 mL) and concentrated in vacuum. Purification of the residue by column chromatography [petroleum ether/EtOAc (50/1)] gave the product **5** (37 mg) as a white solid.

*tert-Butyl (R)-(7-(Piperidin-1-ylmethyl)chroman-4-yl)carbamate (**5**).* 37 mg; 62% total yield; 92% ee; white solid; mp 119−120 °C; [determined by HPLC analysis Daicel Chirapak AD, *n*-hexane/*i*-PrOH = 90/10, 254 nm UV detector, 1.0 mL/min, t_R= 5.7 min (major) and t_R= 7.0 min (minor)]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.70 (s, 1H), 4.73 (s, 2H), 4.20−4.13 (m, 1H), 4.06 (t, J = 11.1 Hz, 1H), 3.32 (s, 2H), 2.28 (s, 4H), 2.14−2.06 (m, 1H), 1.96 (d, J = 16.0 Hz, 1H), 1.52−1.46 (m, 4H), 1.40 (s, 9H), 1.34 (s, 2H); ^{13}C{H}NMR (150 MHz, $CDCl_3$) δ 155.2, 154.8, 140.1, 129.2, 121.7, 120.8, 117.6, 79.8, 63.4, 63.2, 54.5, 44.6, 29.5, 28.5, 26.0, 24.4; IR (KBr) ν: 3325, 3035, 2975, 2932, 2875, 1686, 1609, 1581, 1490, 1369, 1248, 1169, 1061, 861, 755 cm^{-1}; HRMS (ESI) found: m/z 347.2337 $[M+H]^+$; calcd. For $C_{20}H_{30}N_2O_3$ + H 347.2335.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01750.

^{1}H, ^{13}C NMR, ^{19}F NMR spectra for the substrates **1b−c**, **1e**, **1g**, **1i−n**, the products **3a−s** and **5**; HPLC analytic results for the compounds **3a−s** and **5** (PDF)

Crystallographic data for compound **3s** (CIF)

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Notes

The authors declare no competing financial interest.

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