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Asymmetric Mannich Reaction of Aryl Methyl Ketones with Cyclic Imines Benzo[*e*][1,2,3]oxathiazine 2,2-Dioxides Catalyzed by Cinchona Alkaloid-based Primary Amines

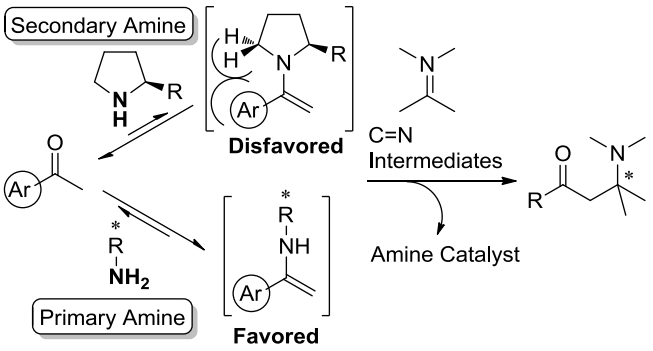
Xiao-Yu Cui, Hui-Xin Duan, Yongna Zhang,* and You-Qing Wang*[a]

Dedication ((optional))

Abstract: Aryl ketones represent problematic substrates for asymmetric Mannich reactions due to a large steric hindrance exhibited by this compound species. A highly enantioselective direct Mannich reaction of aryl methyl ketones with cyclic imines benzo[*e*][1,2,3]oxathiazine 2,2-dioxides could be successfully carried out, utilizing a combination of cinchona alkaloid derived primary amines with TFA, for the primary amines feature a superior catalytic efficacy over secondary amines with a variety of sterically hindered carbonyl compounds as substrates. The reaction proceeded well with various cyclic imines in 89-97% *ee*, and with various aryl methyl ketones in 85-98% *ee*. Moreover, aryl carbonyl of a Mannich product could be transformed to ketoxime, further undergoing a Beckmann rearrangement to produce an amide compound while maintaining enantioselectivity.

Introduction

Mannich reactions are particularly useful techniques in organic chemistry for the synthesis of β-amino carbonyl derivatives, via formation of new carbon-carbon bonds.[1] Corresponding asymmetric Mannich-type reactions have been the subject of extensive investigations over the past decades, and a number of highly enantioselective catalytic methodologies have been reported.[2] Within this area, in the last ten years, organocatalysis has played a crucial role in the development of asymmetric Mannich reactions. Particularly the activation of carbonyl nucleophiles using chiral secondary amine derivatives has been an area of research that has attracted significant attention.[2c,2d] Considering for depending on the formation of highly reactive enamine intermediates, efficient Mannich donors mainly consist of alkyl aldehydes or ketones.[2-3] In sharp contrast, aryl ketones, e.g. acetophenone and tetralone derivatives, represent challenging substrates that have been explored to a much lesser extent. The presence of α-aryl functionalities in the carbonyl compounds results in twisted and less reactive enamines intermediates due to low orbital overlap between the enamine double bond and the nitrogen lone pair as a consequence of bigger steric hindrance (Scheme 1).[4] Applications of aryl methyl ketones in the asymmetric Mannich reaction via Brønsted acid catalysis was realized by Gong[5] and Rueping[6]. Unfortunately, the substrate scope was narrow (no more than two acetophenone derivatives could be used as Mannich donors) and the corresponding enantioselectivities were modest (34-86% *ee*).[5-6] Using Brønsted base catalysis, an enolate-mediated three-component Mannich reaction of unfunctionalized aryl ketones was reported by Zhao and co-works.[7] Wang & Loh *et al.* demonstrated a highly enantioselective Mannich reaction of *N*-sulfonyl cyclic ketimines with ketones using amino sulfonohydrazides as organocatalysts. Here, only one example of acetophenone as a donor provided a moderate *ee* (80%).[8] More recently, our group reported the highly enantioselective direct Mannich reaction of acetophenone derivatives with seven-membered imines catalyzed by (*S*)-azetidine-2-carboxylic acid.[9] Although this reaction proceeds via an enamine-based organocatalysis, four-membered (*S*)-azetidine-2-carboxylic acid was chosen as a catalyst rather than the most common five-membered (*S*)-proline. This resulted in a reasonable reactivity so as to loss a few *ee* values. Furthermore, aryl β-ketoacids have been successfully employed as enolate equivalents instead of aryl methyl ketone donors through decarboxylative Mannich reactions.[10] Aryl methyl ketones, such as acetophenone, are simple, cheap, and easily accessible chemicals widely used in organic synthesis. In this regard, the direct extension to acetophenone derivatives in asymmetric Mannich reactions would be of particular interest.[11-12]



Scheme 1. Secondary and primary amine catalysis through enamine intermediate in Mannich reactions of aryl methyl ketones.

Widening the scope of either the acceptors or the donors employable in the asymmetric Mannich addition is a crucial feature to gain access to the diversity of products and reaction types. Compared with the most extensively studied acyclic imine

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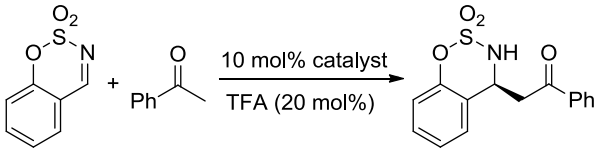
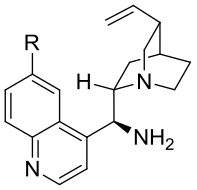
acceptors, cyclic imines have been rarely explored for enantioselective Mannich reactions.[2] A variety of reports can be found in the literature describing a few highly enantioselective Mannich reactions of cyclic imines in organocatalysis to construct *N*-heterocycles with β-carbonyl groups.[9,10c,10d,10e,13-14] The catalytic asymmetric addition to cyclic sulfonyl imines **1** has been shown to be an efficient method for the synthesis of chiral benzo-fused cyclic sulfamidate heterocycles,[15] which can undergo a nucleophilic displacement to convert optically active amines.[16] Moreover, our group reported the highly enantioselective direct Mannich reaction of alkyl ketones with cyclic sulfonyl imines **1** using a cinchona alkaloid derived primary amine as an organocatalyst.[14b] Primary amines as catalysts generally feature a small steric hindrance compared to secondary amines.[17] Therefore, we anticipate that the use of sterically less-hindered primary amines may result in a higher observed activity for Mannich additions of less flexible aryl methyl ketones (Scheme 1). In an effort to continue the studies on Mannich reactions of cyclic imines,[9,14] we hereby report highly enantioselective Mannich reactions of cyclic sulfonyl imines **1** with aryl methyl ketones catalyzed by combining a cinchona alkaloid derived primary amine with TFA.

Results and Discussion

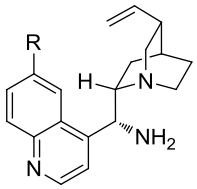
Cinchona-based primary amine catalysts have been successfully developed for the functionalization of carbonyl compounds in asymmetric reactions.[17b,17c,17e] Therefore, for the investigation of catalysts, we focused our studies on the primary amines **C1-4** that are, easily derived from natural cinchona alkaloids. The Mannich reactions were optimized using six-membered cyclic imine **1a** and acetophenone **2a** as the model substrates, and results were listed in Table 1. First, the catalytic effects of four cinchona alkaloid derived primary amines **C1-4** were examined (entries 1-4). All primary amine catalysts were effective in promoting the Mannich reactions, with quinine-derived primary amine **C2** demonstrating the best enantioselectivity (entry 2). Next, we investigated the effect of reaction temperature on the reaction outcome. When the temperature was decreased to 10 °C, the *ee* was found to be slightly improved while retaining reactivity (entry 5). Interestingly, increasing the temperature to 40 °C resulted in an improved 83% yield and 98% *ee* (entry 6). The subsequent screening different solvent demonstrated that the reaction worked well in aromatic solvents (entries 12-15). More specifically, *p*-xylene furnished the best results compared to other solvents tested, and the reaction time could be shortened significantly, with full conversion achieved after 24 hours (entry 15). Upon comparing the optical rotation of the Mannich product **3aa**, we found that the compound exhibits an opposite sign than what has been reported in the literature, indicating that enantiomers are obtained.[10d] Therefore, the absolute configuration of compound **3aa** could be assigned (*S*-configuration).



1a **2a** **3aa**



C1: R = H
C2: R = OMe



C3: R = H
C4: R = OMe

Table 1. Optimization of reaction conditions.[a]

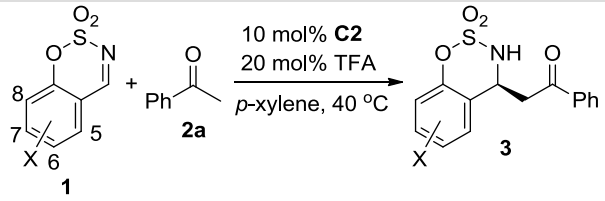
Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	**C1**	Toluene	25	96	51	94
2	**C2**	Toluene	25	96	64	96
3	**C3**	Toluene	25	96	39	-84[d]
4	**C4**	Toluene	25	96	57	-91[d]
5	**C2**	Toluene	10	96	66	98
6	**C2**	Toluene	40	96	83	98
7	**C2**	DCE	40	96	52	87
8	**C2**	$CHCl_3$	40	96	69	90
9	**C2**	THF	40	96	0	-
10	**C2**	CH_3CN	40	96	19	45
11	**C2**	MeOH	40	96	31	57
12	**C2**	Benzene	40	96	48	94
13	**C2**	*o*-xylene	40	19	94	95
14	**C2**	*m*-xylene	40	96	92	96
15	**C2**	*p*-xylene	40	24	98	97

[a] Unless otherwise noted, reactions were conducted with imine **1a** (0.1 mmol), acetophenone **2a** (0.5 mmol), primary amine **C1-4** (0.01 mmol, 10 mol%) and TFA (0.02 mmol, 20 mol%) in 1.0 mL of solvent. [b] Isolated yield. [c] Determined by HPLC using a chiral column. [d] The minus *ee* value indicates that the opposite enantiomer was obtained as the major form.

Various cyclic imines **1** were tested with acetophenone **2a** as precursor for this Mannich reaction under optimized reaction conditions (Table 1, entry 15) and the results can be found summarized in Table 2. The corresponding Mannich products **3** were obtained in excellent yields and high enantioselectivities using different substituted cyclic imines **1** bearing either electron-donating or electron-withdrawing substituents on the phenyl ring (entries 1-7). Additionally, cyclic imines **1i-l**, bearing two substituent groups on the phenyl ring, were also found to be suitable for this Mannich reaction, affording slightly lower

enantioselectivities (89-93% *ee*) than those of the non-substituented cyclic imines (entries 8-11). Moreover, a cyclic imine **1l** bearing two *tert*-butyl groups on the phenyl ring acting as a strong steric hindrance of the substrate, proved to be suitable for this reaction type to afford good yield and high enantioselectivities (93% *ee*), even though an increased reaction time was required to complete the sequence (entry 11). When a cyclic imine **1m** bearing a diethylamino group was used, the reaction failed to proceed (entry 12).

Table 2. Substrate scope of cyclic imines for asymmetric Mannich reaction.[a]

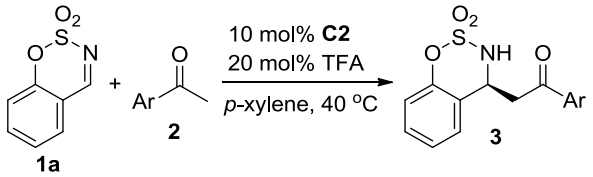


Entry	X (**1**)	Time (h)	**3**	Yield (%)[b]	*ee* (%)[c]
1	6-OMe (**1b**)	40	**3ba**	99	93
2	7-OMe (**1c**)	63	**3ca**	90	93
3	8-OMe (**1d**)	22	**3da**	99	94
4	6-Me (**1e**)	22	**3ea**	98	94
5	6-F (**1f**)	24	**3fa**	97	95
6	6-Cl (**1g**)	20	**3ga**	99	94
7	6-Br (**1h**)	17	**3ha**	99	94
8	6,8-Cl_2 (**1i**)	17	**3ia**	99	91
9	6,8-Br_2 (**1j**)	25	**3ja**	99	89
10	6-Cl, 8-Br (**1k**)	23	**3ka**	87	91
11	6,8-*t*Bu_2 (**1l**)	66	**3la**	92	93
12	6-NEt_2 (**1m**)	96	-	0	-

[a] Reaction conditions: imine **1** (0.15 mmol), acetophenone **2a** (0.75 mmol), **C2** (0.015 mmol, 10 mol%) and TFA (0.03 mmol, 20 mol%) in *p*-xylene (1.5 mL) at 40°C. [b] Isolated yield. [c] Determined by HPLC using a chiral column.

Next, various aryl methyl ketones were examined for this asymmetric Mannich reaction by using imine **1a** as an electron-acceptor. As listed in Table 3, much various aryl methyl ketones, e.g. with both electron-withdrawing and electron-donating substituents in different positions on the phenyl rings or heteroaryl groups bearing various N-, O-, S-heteroatoms, were found to be well tolerated, and the corresponding Mannich products could be produced with high enantioselectivities. Furthermore, we found that the electronic nature of the substituents affected on the reactivity. For example, the substituted electron-donating aryl methyl ketones in the *para*-position on the phenyl ring (entries 5-6) afforded better yields and shorter reaction times than electron-withdrawing substituents (entries 1-4). Furthermore, the relative reactivity of the aryl methyl ketones decreased in the order: Br>Cl>F. This order is the exact opposite of the electronegativity of halogen atoms. The *ortho*-substituted aryl methyl ketone **2i** resulted in a relatively lower yield and enantioselectivity than the *para*- or *meta*- substituted species, likely due to the effect of steric repulsion (entry 8 *vs* 6 or 7). Aryl methyl ketones bearing two substituents on the phenyl ring were also applicable to this Mannich reaction. As expected, ketone **2k** bearing *ortho*-chlorine on the phenyl group resulted in a lower activity (entries 9-10). Using the 2-naphthyl-derived ketone **2l** resulted in a quantitative yield with high *ee* values (entry 11). Noteworthy, several heteroaryl methyl ketones **2m**, **2n**, **2o** and **2p** were also found to be suitable and the desired Mannich reaction products **3am**, **3an** and **3ap** were obtained in high yields and with high enantioselectivities (entries 12-13 and 15). However the corresponding product **3ao** bearing a S-heteroatom was obtained in only moderate yield but with high enantioselectivity (entry 14).

Table 3. Substrate scope of aryl methyl ketones for asymmetric Mannich reaction.[a]



Entry	Ar (**2**)	Time (h)	**3**	Yield (%)[b]	*ee* (%)[c]
1	*p*-Br-C_6H_4 (**2b**)	96	**3ab**	86	95
2	*p*-Cl-C_6H_4 (**2c**)	96	**3ac**	71	96
3	*p*-F-C_6H_4 (**2d**)	96	**3ad**	56	94
4	*p*-NO_2-C_6H_4 (**2e**)	96	**3ae**	66	90
5	*p*-MeO-C_6H_4 (**2f**)	18	**3af**	88	93
6	*p*-Me-C_6H_4 (**2g**)	40	**3ag**	99	92
7	*m*-Me-C_6H_4 (**2h**)	40	**3ah**	99	96
8	*o*-Me-C_6H_4 (**2i**)	96	**3ai**	35	88
9	3,4-Me_2-C_6H_4 (**2j**)	16	**3aj**	96	96
10	2,4-Cl_2-C_6H_4 (**2k**)	96	**3ak**	32	85
11	2-naphthyl (**2l**)	48	**3al**	99	95
12	2-pyridinyl (**2m**)	20	**3am**	92	94
13	2-furanyl (**2n**)	36	**3an**	92	95
14	2-thienyl (**2o**)	108	**3ao**	51	93
15	3-thienyl (**2p**)	36	**3ap**	90	98

[a] Reaction conditions: imine **1** (0.15 mmol), acetophenone **2a** (0.75

mmol), **C2** (0.015 mmol, 10 mol%) and TFA (0.03 mmol, 20 mol%) in *p*-xylene (1.5 mL) at 40°C. [b] Isolated yield. [c] Determined by HPLC using a chiral column.

A proposed transition state for the enantioselective Mannich addition to give *S* adducts **3** as the major enantiomer is shown in Figure 1. Both sulfone oxygen atoms of imines **1** can form two hydrogen bonds with organocatalyst to creat a good chiral environment.[3c] Nucleophilic carbon of enamines formed from aryl methyl ketones and primary amine attacks the imines **1** from the *Si*-face. The predominant production of *S* adducts **3** is reasonably explained by this transition-state model.

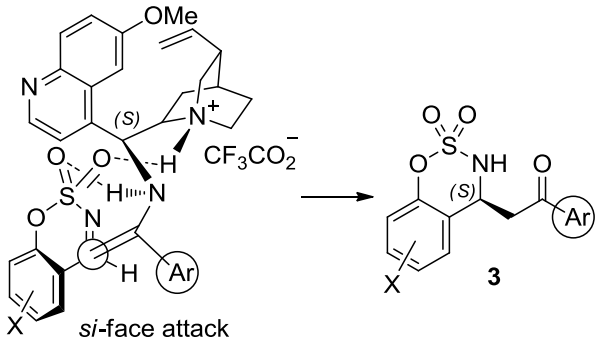
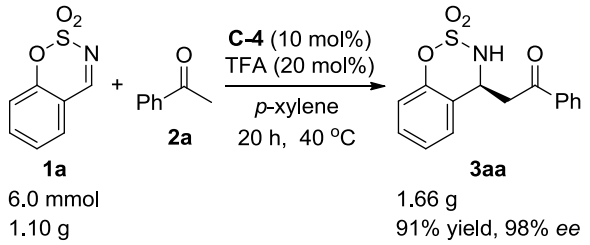


Figure 1. Proposed transition state and observed *S* adducts **3**.

To evaluate the overall practicability of the present synthetic method, this Mannich reaction was also performed on a gram scale (Scheme 2). The Mannich product **3aa** was obtained in 91% yield with 98% *ee* after flash column chromatographic purification. The reaction on this larger scale proceeded smoothly, without any detrimental effects on enantioselectivity. Compared with the decarboxylative Mannich reaction of β-ketoacid to obtain Mannich product **3aa**,[10d] this direct Mannich reaction of aryl methyl ketones can be carried out with: easily obtained acetophenone used as a substrate[18] and the reaction proceeds with higher operational simplicity and with higher *ee* values.



Scheme 2. Mannich reaction of cyclic imine **1a** with acetophenone **2a** at a gram scale.

The further transformation of the obtained, highly enantio-rich Mannich products **3** was studied, and an example can be found illustrated in Scheme 3. The carbonyl group of compound **3aa** could be easily transformed into the corresponding ketoxime in the presence of hydroxylamine hydrochloride and potassium acetate. The $AlCl_3$ catalyzed Beckmann rearrangement[19] of ketoxime **4** provided the amide **5** in 94% yield. The enantioselectivity of amide **5** was determined to be 98% *ee* as judged by chiral HPLC. This finding indicates that the optical purity can indeed be completely retained throughout the entire process.

Conclusions

In conclusion, we have successfully developed a highly enantioselective Mannich reaction of aryl methyl ketones with cyclic sulfonyl imine benzo[*e*][1,2,3]oxathiazine 2,2-dioxides. The combination of cinchona alkaloid derived primary amine with TFA was found to be the most efficient organocatalyst for this Mannich addition. A range of different aryl methyl ketones bearing moieties with different electronic properties and steric hindrance characteristics could be successfully employed in this highly enantioselective reaction types..

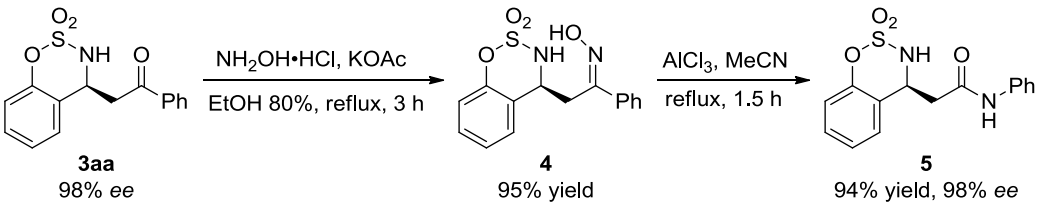
Experimental Section

General methods

^{1}H NMR, and ^{13}C NMR spectra were recorded on Bruker DRX-400/300 spectrometers. Chemical shifts were recorded in ppm (δ), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26, DMSO δ 2.50, acetone δ 2.05), carbon (chloroform δ 77.0, DMSO δ 39.5). Flash column chromatography was performed on silica gel (200-300 mesh). TLC analysis was performed using glass-backed plates coated with 0.2 mm silica. After elution, plate was visualized under at 254 nm UV illumination. The following abbreviations were used for elution solvents: PE = petroleum ether, EA = ethyl acetate. All commercially available compounds were used as provided without further purification. The solvents were distilled from appropriate drying agents prior to use, unless otherwise noted. Cyclic imines **1** were prepared according to our published papers.[14b,15d]

Typical procedure and data of asymmetric Mannich reaction (Table 1, 2 and 3)

To the mixture of quinine-NH_2 **C2** (0.015 mmol, 10 mol%) and cyclic imine **1** (0.15 mmol) in *p*-xylene (1.45 mL) was added the solution of TFA (0.03 mmol, 20 mol%) in *p*-xylene (0.05 mL). After the reaction mixture was heated to 40°C, acetophenone (0.75 mmol) was added. This reaction mixture was stirred in showed reaction time. Direct purification reaction mixture by column chromatography on a silica gel gave the desired Mannich products. The enantiomeric excess was determined by HPLC. Racemic Mannich products were obtained with the combination of 10 mol% benzyl amine and 20 mol% TFA.



Scheme 3. Transformation of Mannich product **3aa**.

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3aa**):[10d] White solid; m.p. 127.1-128.0 °C; R_f = 0.35 (CH_2Cl_2); 97% *ee*, $[\alpha]^{25}_D$ = 48.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.96 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.33-7.28 (m, 1H), 7.15 (d, *J* = 4.2 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 1H), 5.91 (s, 1H), 5.42 (dd, *J* = 7.3, 3.7 Hz, 1H), 4.28 (dd, *J* = 18.2, 7.3 Hz, 1H), 3.41 (dd, *J* = 18.2, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 151.3, 136.2, 134.2, 129.6, 128.9, 128.3, 126.0, 125.5, 121.7, 119.2, 53.7, 41.8; HPLC (Chiralcel IC column, hexane/*i*PrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 8.6 min (major, *S*), t_2 = 16.7 min (minor).

(*S*)-2-(6-methoxy-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3ba**):[10d] White solid; m.p. 114.3-115.1 °C; R_f = 0.22 (CH_2Cl_2); 93% *ee*, $[\alpha]^{25}_D$ = -4.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.96 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.10 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.94-6.91 (m, 2H)), 5.87 (d, *J* = 7.9 Hz, 1H), 5.38 (td, *J* = 7.8, 3.6 Hz, 1H), 4.26 (dd, *J* = 18.2, 7.7 Hz, 1H), 3.38 (dd, *J* = 18.2, 3.7 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 149.0, 136.1, 135.2, 134.1, 130.2, 128.8, 128.2, 126.3, 121.1 118.8, 53.6, 42.1, 20.8; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 9.6 min (major, *S*), t_2 = 17.9 min (minor).

(*S*)-2-(7-methoxy-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3ca**): White solid; m.p. 144.0-144.5 °C; R_f = 0.15 (CH_2Cl_2); 93% *ee*, $[\alpha]^{25}_D$ = 50.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 8.09 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.69 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 5.94 (d, *J* = 8.0 Hz, 1H), 5.34 (td, *J* = 7.5, 3.8 Hz, 1H), 4.22 (dd, *J* = 18.1, 7.3 Hz, 1H), 3.78 (s, 3H), 3.36 (dd, *J* = 18.1, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 160.3, 151.9, 136.2, 134.1, 128.9, 128.2, 126.5, 113.2, 112.3, 103.8, 55.6, 53.3, 41.7; HRMS (ESI): m/z calculated for $C_{16}H_{15}NNaO_5S$ $[M+Na]^+$ 356.0569, found: 356.0542; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 11.9 min (major, *S*), t_2 = 23.9min (minor).

(*S*)-2-(8-methoxy-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3da**): White solid; m.p. 174.5-175.5 °C; R_f = 0.20 (PE/EA, 3:1); 94% *ee*, $[\alpha]^{25}_D$ = 38.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H), 7.65-7.60 (m, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.07 (t, J = 8.1 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.70 (d, J = 7.9 Hz, 1H), 5.85 (d, J = 7.9 Hz, 1H), 5.40 (td, J = 7.6, 3.6 Hz, 1H), 4.28 (dd, J = 18.2, 7.2 Hz, 1H), 3.89 (s, 3H), 3.40 (dd, J = 18.2, 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 149.0, 136.1, 134.1, 128.9, 125.1, 122.6, 116.9, 111.9, 56.2, 53.8, 41.6; HRMS (ESI): m/z calculated for $C_{16}H_{15}NNaO_5S$ $[M+Na]^+$ 356.0569, found: 356.0540; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 16.4 min (major, *S*), t_2 = 43.6 min (minor).

(*S*)-2-(6-methyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3ea**):[10d] White solid; m.p. 112.5-113.5 °C; R_f = 0.45 (PE/EA, 3:1); 94% *ee*, $[\alpha]^{25}_D$ = 4.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.97 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.96-6.93 (m, 2H), 5.77 (d, *J* = 7.9 Hz, 1H), 5.37 (td, *J* = 7.7, 3.5 Hz, 1H), 4.27 (dd, *J* = 18.2, 7.5 Hz, 1H), 3.40 (dd, *J* = 18.2, 3.6 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 149.0, 136.1, 135.2, 134.1, 130.2, 128.9, 128.2, 126.2, 121.1, 118.8, 53.6, 42.1, 20.8; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 11.1 min (major, *S*), t_2 = 22.1 min (minor).

(*S*)-2-(6-fluoro-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3fa**):[10d] White solid; m.p. 86.2-87.1 °C; R_f = 0.17 (CH_2Cl_2); 95% *ee*, $[\alpha]^{25}_D$ = 53.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H), 7.66-7.60 (m, 1H), 7.50 (t, *J* = 7.40 Hz, 2H), 7.04-7.00 (m, 2H), 6.89-6.86 (m, 1H), 5.94 (d, *J* = 8.3 Hz, 1H), 5.38 (td, *J* = 7.5, 3.9 Hz, 1H), 4.23 (dd, *J* = 18.3, 7.1 Hz, 1H), 3.43 (dd, *J* = 18.3, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 159.3 (d, $^1J_{F\text{-}C}$ = 244.2 Hz), 147.0 (d, $^4J_{F\text{-}C}$ = 2.7 Hz), 135.9, 134.3, 128.9, 128.2, 123.2 (d, $^3J_{F\text{-}C}$ = 7.0 Hz), 120.7 (d, $^3J_{F\text{-}C}$ = 8.4 Hz), 116.6 (d, $^2J_{F\text{-}C}$ = 23.5 Hz), 112.7 (d, $^2J_{F\text{-}C}$ = 24.8 Hz), 53.4 (d, $^4J_{F\text{-}C}$ = 1.6 Hz), 41.7; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 7.6 min (major, *S*), t_2 = 13.2 min (minor).

(*S*)-2-(6-chloro-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3ga**):[10d] White solid; m.p. 102.9-103.5 °C; R_f = 0.33 (CH_2Cl_2); 94% *ee*, $[\alpha]^{25}_D$ = -8.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.29-7.26 (m, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 5.95 (d, *J* = 8.3 Hz, 1H), 5.38 (td, *J* = 7.7, 3.8 Hz, 1H), 4.25 (dd, *J* = 18.3, 7.2 Hz, 1H), 3.43 (dd, *J* = 18.3, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 149.7, 135.9, 134.3, 130.7, 129.7, 128.9, 128.2, 125.9, 123.2, 120.5, 53.3, 41.7; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 7.1 min (major, *S*), t_2 = 12.0 min(minor).

(*S*)-2-(6-bromo-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3ha**):[10d] White solid; m.p. 103.1-104.0 °C; R_f = 0.26 (CH_2Cl_2); 94% *ee*, $[\alpha]^{25}_D$ = -26.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.96 (m, 2H), 7.67-7.62 (m, 1H), 7.54-7.49 (m, 2H), 7.43 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.29 (d, *J* = 1.6 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 5.85 (d, *J* = 8.3 Hz, 1H), 5.38 (td, *J* = 7.6, 3.8 Hz, 1H), 4.25 (dd, *J* = 18.3, 7.1 Hz, 1H), 3.44 (dd, *J* = 18.3, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 150.2, 135.8, 134.3, 132.5, 128.9, 128.2, 123.6, 120.8, 118.1, 53.1, 42.0; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 7.3 min (major, *S*), t_2 = 12.7 min (minor).

(*S*)-2-(6,8-dichloro-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3ia**): White solid; m.p. 111.8-112.3 °C; R_f = 0.28 (CH_2Cl_2); 91% *ee*, $[\alpha]^{25}_D$ = 40.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H), 7.67-7.62 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.39 (d, *J* = 2.3 Hz, 1H), 7.06-7.05 (m, 1H), 6.12 (d, *J* = 8.3 Hz, 1H), 5.39 (td, *J* = 7.4, 3.8 Hz, 1H), 4.25 (dd, *J* = 18.4, 7.0 Hz, 1H), 3.44 (dd, *J* = 18.4, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 145.9, 135.7, 134.4, 130.3, 130.1, 129.0, 128.2, 125.0, 124.6, 124.3, 53.4, 41.7; HRMS (ESI): m/z

calculated for $C_{15}H_{11}Cl_2NNaO_4S$ $[M+Na]^+$ 393.9684, found: 393.9679; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 6.0 min (major, *S*), t_2 = 10.3 min (minor).

(*S*)-2-(6,8-dibromo-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3ja**): White solid; m.p. 165.4-166.1 °C; R_f = 0.41 (CH_2Cl_2); 89% *ee*, $[\alpha]^{25}_D$ = 46.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.4 Hz, 2H), 7.55-7.48 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.11 (s, 1H), 5.97 (dd, *J* = 17.2, 9.0 Hz, 1H), 5.26 (d, *J* = 2.8 Hz, 1H), 4.12 (dd, *J* = 18.4, 7.1 Hz, 1H), 3.30 (dd, *J* = 18.4, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 147.3, 135.7, 134.4, 128.9, 128.3, 128.0, 125.0, 117.9, 113.8, 53.3, 41.9; HRMS (ESI): m/z calculated for $C_{15}H_{11}Br_2NNaO_4S$ $[M+Na]^+$ 483.8653, found: 483.8629; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 6.3 min (major, *S*), t_2 = 11.1 min (minor).

(*S*)-2-(8-bromo-6-chloro-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3ka**): White solid; m.p. 140.1-141.0 °C; R_f = 0.40 (CH_2Cl_2); 91% *ee*, $[\alpha]^{25}_D$ = 43.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H), 7.68-7.61 (m, 1H), 7.57-7.50 (m, 3H), 7.09 (dd, *J* = 2.2, 0.7 Hz, 1H), 5.96-5.91(m, 1H), 5.40-5.34 (m, 1H), 4.25 (dd, *J* = 18.5, 6.7 Hz, 1H), 3.46 (dd, *J* = 18.4, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 146.8, 135.6, 134.4, 132.9, 130.7, 129.0, 128.2, 125.1, 124.6, 113.5, 53.4, 41.8; HRMS (ESI): m/z calculated for $C_{15}H_{11}BrClNNaO_4S$ $[M+Na]^+$ 437.9178, found: 439.9181; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 6.2 min (major, *S*), t_2 = 10.7 min (minor).

(*S*)-2-(6,8-di-tert-butyl-2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-phenylethan-1-one (**3la**): White solid; m.p. 127.9-128.3 °C; R_f = 0.40 (PE/EA, 5:1); 93% *ee*, $[\alpha]^{25}_D$ = -7.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.96 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 2.2 Hz, 1H), 6.99 (d, *J* = 2.1 Hz, 1H), 5.81 (d, *J* = 7.4 Hz, 1H), 5.41 (td, *J* = 7.8, 3.6 Hz, 1H), 4.30 (dd, *J* = 17.9, 8.2 Hz, 1H), 3.34 (dd, *J* = 17.9, 3.7 Hz, 1H), 1.43 (s, 9H), 1.24 (s, 9H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 148.1, 147.6, 139.4, 136.3, 134.0, 128.8, 128.2, 124.3, 121.9, 120.9, 54.0, 42.8, 35.1, 34.6, 31.3, 30.0; HRMS (ESI): m/z calculated for $C_{23}H_{29}NNaO_4S$ $[M+Na]^+$ 439.1749, found: 439.1739; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 5.9 min (major, *S*), t_2 = 7.7 min (minor).

(*S*)-1-(4-bromophenyl)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)ethan-1-one (**3ab**):[10d] White solid; m.p. 140.4-141.2 °C; R_f = 0.54 (PE/EA, 3:1); 95% *ee*, $[\alpha]^{25}_D$ = 30.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.34-7.29 (m, 1H), 7.19-7.14 (m, 2H), 7.03 (d, *J* = 8.2 Hz, 1H), 5.90-5.88 (m, 1H), 5.42 (td, *J* = 7.8, 3.4 Hz, 1H), 4.25 (dd, *J* = 18.1, 7.8 Hz, 1H), 3.34 (dd, *J* = 18.1, 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 151.0, 134.8, 132.2, 129.7, 129.6, 129.5, 126.1, 125.5, 121.3, 119.1, 53.5, 42.2; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 7.9 min (major, *S*), t_2 = 15.3min (minor).

(*S*)-1-(4-chlorophenyl)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)ethan-1-one (**3ac**):[10d] White solid; m.p. 117.6-118.5 °C; R_f = 0.57 (PE/EA, 3:1); 96% *ee*, $[\alpha]^{25}_D$ = 27.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.34-7.29 (m, 1H), 7.19-7.15 (m, 2H), 7.04 (d, *J* = 8.2 Hz, 1H), 5.88 (d, *J* = 7.9 Hz, 1H), 5.42 (td, *J* = 7.8, 3.5 Hz, 1H), 4.26 (dd, *J* = 18.1, 7.8 Hz, 1H), 3.34 (dd, *J* = 18.1, 3.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 151.1, 140.7, 134.4, 129.6, 129.2, 126.0, 125.5, 121.3, 119.1, 53.5, 42.1; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 8.0 min (major, *S*), t_2 = 15.6min (minor).

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-(4-fluorophenyl)ethan-1-one (**3ad**):[10d] White solid; m.p. 104.5-105.3 °C; R_f = 0.51 (PE/EA, 3:1); 95% *ee*, $[\alpha]^{25}_D$ = 28.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02-7.98 (m, 2H), 7.31-7.29 (m, 1H), 7.19-7.13 (m, 4H), 7.05 (d, *J* = 8.2 Hz, 1H), 5.88 (s, 1H), 5.43-5.41 (m, 1H), 4.26 (dd, *J* = 18.1, 7.6 Hz, 1H), 3.36 (dd, *J* = 18.1, 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 166.3 (d, $^1J_{F\text{-}C}$ = 255.2 Hz), 151.1, 132.6 (d, $^4J_{F\text{-}C}$ = 3.0 Hz), 131.0 (d, $^3J_{F\text{-}C}$ = 9.5 Hz), 129.6, 125.7 (d, $^2J_{F\text{-}C}$ = 37.7 Hz), 121.4, 119.1, 116.01 (d, $^2J_{F\text{-}C}$ = 21.9 Hz), 53.6, 42.0; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 7.8 min (major, *S*), t_2 = 14.7min (minor).

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-(4-nitrophenyl)ethan-1-one (**3ae**)**:** White solid; m.p. 117.6-118.3 °C; R_f = 0.41 (PE/EA, 3:1); 90% *ee*, $[\alpha]^{25}_D$ = 10.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36-8.33 (m, 2H), 8.15 (d, *J* = 8.9 Hz, 2H), 7.38-7.33 (m, 1H), 7.23-7.16 (m, 2H), 7.09 (d, *J* = 8.7 Hz, 1H), 5.57 (d, *J* = 7.8 Hz, 1H), 5.47 (td, *J* = 7.7, 3.4 Hz, 1H), 4.38 (dd, *J* = 18.2, 8.2 Hz, 1H), 3.39 (dd, *J* = 18.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 151.0, 150.8, 140.4, 129.9, 129.4, 126.2, 125.7, 124.1, 121.0, 119.2, 53.4, 43.3; HRMS (ESI): m/z calculated for $C_{15}H_{13}NNaO_4S$ $[M+Na]^+$ 371.0314, found: 371.0314; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 19.5 min (major, *S*), t_2 = 32.6 min (minor).

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-(4-methoxyphenyl)ethan-1-one (**3af**):[10d] White solid; m.p. 144.5-145.3 °C; R_f = 0.37 (PE/EA, 3:1); 93% *ee*, $[\alpha]^{25}_D$ = 86.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.7 Hz, 2H), 7.32-7.26 (m, 1H), 7.15-7.10 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.09 (d, *J* = 7.7 Hz, 1H), 5.41-5.35 (m, 1H), 4.22 (dd, *J* = 17.9, 7.2 Hz, 1H), 3.88 (s, 3H), 3.34 (dd, *J* = 17.9, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 164.3, 151.2, 130.7, 129.5, 129.2, 125.9, 125.4, 121.7, 119.0, 114.0, 55.6, 53.8, 41.1; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 14.3 min (major, *S*), t_2 = 27.1min (minor).

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-(*p*-tolyl)ethan-1-one (**3ag**):[10d] White solid; m.p. 140.1-141.0 °C; R_f = 0.57 (PE/EA, 3:1); 92% *ee*, $[\alpha]^{25}_D$ = 54.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.28-7.26 (m, 3H), 7.14-7.10 (m, 2H), 7.02 (d, *J* = 8.2 Hz, 1H), 5.41-5.37 (m, 2H), 4.23 (dd, *J* = 18.1, 7.3 Hz, 1H), 3.36 (dd, *J* = 18.0, 3.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 151.1, 145.2, 133.6, 129.5, 129.5, 128.3, 126.0 125.4, 121.6, 119.0, 53.6, 41.6, 21.7; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 10.7 min (major, *S*), t_2 = 22.2min (minor).

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-(*m*-tolyl)ethan-1-one (**3ah**):[10d] White solid; m.p. 135.8-136.5 °C; R_f = 0.56 (PE/EA, 3:1); 97% *ee*, $[\alpha]^{25}_D$ = 53.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.76 (m, 2H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.39-7.35 (m, 1H), 7.33-7.28 (m, 1H), 7.15 (dd, *J* = 10.5, 2.5 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 5.98 (d, *J* = 8.2 Hz, 1H), 5.41 (td, *J* = 7.7, 3.7 Hz, 1H), 4.27 (dd, *J* = 18.2, 7.3 Hz, 1H), 3.40 (dd, *J* = 18.2, 3.7 Hz, 1H), 2.41 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 151.2, 138.8, 136.1, 134.9, 129.5, 128.73, 128.70, 125.9, 125.44, 125.42, 121.6, 119.0, 53.6, 41.8, 21.3; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 9.9 min (major, *S*), t_2 = 19.4 min (minor).

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-(*o*-tolyl)ethan-1-one (**3ai**):[10d] White solid; m.p. 149.9-150.6 °C; R_f = 0.58 (PE/EA, 3:1); 88% *ee*, $[\alpha]^{25}_D$ = 20.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.43 (td, *J* = 7.5, 1.0 Hz, 1H), 7.34-7.30 (m, 2H), 7.27 (s, 1H), 7.17-7.12 (m, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 5.94 (d, *J* = 8.3 Hz, 1H), 5.36 (td, *J* = 7.8, 3.6 Hz, 1H), 4.18 (dd, *J* = 18.0, 7.3 Hz,

1H), 3.38 (dd, *J* = 18.0, 3.7 Hz, 1H), 2.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 151.3, 139.0, 136.6, 132.4, 132.3, 129.6, 128.9, 126.0, 125.8, 125.4, 121.5, 119.1, 54.0, 43.9, 21.4; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 8.4 min (major, *S*), t_2 = 12.6 min (minor).

(*S*)-1-(3,4-dimethylphenyl)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)ethan-1-one (**3aj**): White solid; m.p. 124.5-125.2 °C; R_f = 0.28 (PE/EA, 5:1); 96% *ee*, $[\alpha]^{25}_D$ = 93.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.70 (m, 2H), 7.32-7.28 (m, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.14-7.11 (m, 2H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.02 (d, *J* = 8.3 Hz, 1H), 5.38 (td, *J* = 7.7, 3.7 Hz, 1H), 4.24 (dd, *J* = 18.1, 7.1 Hz, 1H), 3.38 (dd, *J* = 18.1, 3.7 Hz, 1H), 2.32 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 151.2, 144.0, 137.3, 134.0, 130.1, 129.5, 129.5, 126.0, 125.8, 125.4, 121.7, 119.0, 53.7, 41.3, 20.1, 19.8; HRMS (ESI): m/z calculated for $C_{17}H_{18}Br_2NO_4S$ $[M+H]^+$ 332.0957, found: 332.0958; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 12.3 min (major, *S*), t_2 = 24.6 min (minor).

(*S*)-1-(2,4-dichlorophenyl)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)ethan-1-one (**3ak**): White solid; m.p. 113.9-114.5 °C; R_f = 0.47 (PE/EA, 3:1); 86% *ee*, $[\alpha]^{25}_D$ = 7.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.47 (m, 2H), 7.35-7.31 (m, 2H), 7.19-7.13 (m, 2H), 7.07-7.05 (m, 1H), 5.65 (d, *J* = 8.1 Hz, 1H), 5.38 (td, *J* = 8.0, 3.6 Hz, 1H), 4.20 (dd, *J* = 18.2, 8.0 Hz, 1H), 3.45 (dd, *J* = 18.2, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 151.2, 138.7, 136.0, 132.5, 130.80, 130.77, 129.8, 127.7, 126.0, 125.5, 120.9, 119.2, 53.8, 46.2; HRMS (ESI): m/z calculated for $C_{15}H_{11}Cl_2NNaO_4S$ $[M+Na]^+$ 393.9684, found: 393.9676; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 7.9 min (major, *S*), t_2 = 16.4 min (minor).

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[e][1,2,3]oxathiazin-4-yl)-1-(naphthalen-2-yl)ethan-1-one (**3al**):[10d] White solid; m.p. 132.3-133.0 °C; R_f = 0.51 (PE/EA, 3:1); 95% *ee*, $[\alpha]^{25}_D$ = 66.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.89 (t, *J* = 8.8 Hz, 2H), 7.82-7.77 (m, 2H), 7.57-7.46 (m, 2H), 7.24-7.17 (m, 1H), 7.12-7.03 (m, 2H), 6.96 (d, *J* = 8.2 Hz, 1H), 5.94 (d, *J* = 5.8 Hz, 1H), 5.39 (d, *J* = 2.3 Hz, 1H), 4.34 (dd, *J* = 18.1, 7.4 Hz, 1H), 3.43 (dd, *J* = 18.1, 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 151.1, 135.9, 133.4, 132.3, 130.4, 129.7, 129.5, 129.0, 128.7, 127.8, 127.0, 126.1, 125.4, 123.4, 121.6, 119.0, 53.7, 42.0; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 11.6 min (major, *S*), t_2 = 21.9 min (minor).

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-(pyridin-2-yl)ethan-1-one (**3am**): White solid; m.p. 73.7-74.2 °C; R_f = 0.35 (CH_2Cl_2); 94% *ee*, $[\alpha]^{25}_D$ = -25.4 (*c* 1.0, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75-8.69 (m, 2H), 8.06 (d, *J* = 3.5 Hz, 2H), 7.74-7.68 (m, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.25 (dd, *J* = 10.8, 4.3 Hz, 1H), 7.16-7.08 (m, 1H), 5.34 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.17 (dd, *J* = 18.3, 9.8 Hz, 1H), 3.81 (dd, *J* = 18.3, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.4, 152.3, 150.8, 149.3, 137.7, 129.4, 128.1, 127.2, 125.2, 122.5, 121.5, 118.2, 52.1, 42.5; HRMS (ESI): m/z calculated for $C_{14}H_{13}N_2O_4S$ $[M+H]^+$ 305.0596, found: 305.0595; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 22.1 min (major, *S*), t_2 = 35.7 min (minor).

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-(furan-2-yl)ethan-1-one (**3an**):[10d] White solid; m.p. 184.5-185.3 °C; R_f = 0.26 (CH_2Cl_2); 95% *ee*, $[\alpha]^{25}_D$ = 51.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, Acetone-d_6) δ 7.88 (d, *J* = 1.1 Hz, 1H), 7.51-7.38 (m, 4H), 7.27 (td, *J* = 7.6, 1.1 Hz, 1H), 7.08 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.71 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.48 (dd, *J* = 9.6, 3.8 Hz, 1H), 4.04 (dd, *J* = 17.3, 9.6 Hz, 1H), 3.44 (dd, *J* = 17.3, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.5, 151.7, 150.8, 148.3, 129.5, 127.4, 125.3, 122.0, 119.5, 118.3, 112.7, 52.3, 42.5; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 15.2min (major, *S*), t_2 = 37.2 min (minor).

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-(thiophen-2-yl)ethan-1-one (**3ao**): White solid; m.p. 161.9-162.6 °C; R_f = 0.22 (CH_2Cl_2); 93% *ee*, $[\alpha]^{25}_D$ = -12.4 (*c* 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.07-7.99 (m, 2H), 7.52 (d, *J* = 6.5 Hz, 1H), 7.39 (t, *J* = 7.0 Hz, 1H), 7.28-7.26 (m, 2H), 7.12 (d, *J* = 7.9 Hz, 1H), 5.27 (d, *J* = 8.5 Hz, 1H), 3.94 (dd, *J* = 16.4, 10.4 Hz, 1H), 3.59-3.54 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 189.4, 150.8, 143.5, 135.6, 134.0, 129.5, 129.0, 127.5, 125.3, 122.0, 118.3, 52.7, 43.1; HRMS (ESI): m/z calculated for $C_{13}H_{11}NNaO_4S_2$ $[M+Na]^+$ 332.0027, found: 332.0018; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 11.4 min (major, *S*), t_2 = 40.9 min (minor).

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-1-(thiophen-3-yl)ethan-1-one (**3ap**): White solid; m.p. 138.8-139.6 °C; R_f = 0.33 (PE/EA, 3:1); 98% *ee*, $[\alpha]^{25}_D$ = -17.1 (*c* 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.57 (s, 1H), 7.66 (d, *J* = 0.5 Hz, 1H), 7.57-7.50 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.0 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 5.27 (d, *J* = 9.6 Hz, 1H), 3.88 (dd, *J* = 17.3, 10.3 Hz, 1H), 3.55 (dd, *J* = 16.8, 0.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.6, 150.8, 141.6, 134.5, 129.4, 127.7, 127.4, 126.5, 125.2, 122.2, 118.3, 52.5, 43.8; HRMS (ESI): m/z calculated for $C_{13}H_{12}NO_4S_2$ $[M+H]^+$ 310.0208, found: 310.0199; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 9.7 min (major, *S*), t_2 = 17.3 min (minor).

Transformation of Mannich product 3aa (Scheme 3)

(*S,E*)-4-(2-(hydroxyimino)-2-phenylethyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (**4**): A mixture of **3aa** (242.6 mg, 0.8 mmol), hydroxylamine hydrochloride (194.6 mg, 2.8 mmol) and KOAc (196.3 mg, 2.0 mmol) in 80% aqueous EtOH (15 mL) was heated gently to reflux for 3 hours. After the reaction mixture was cooled to room temperature, the solvent was removed in vacuo and the residue was purified by column chromatography to provide yellow solid (233.5 mg, 92% yield); m.p. 169.3-170.1 °C; R_f = 0.42 (PE/EA, 3:1); $[\alpha]^{25}_D$ = 66.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (br, 1H), 7.64-7.60 (m, 2H), 7.40-7.35 (m, 3H), 7.31-7.28 (m, 2H), 7.2-7.12 (m, 1H), 7.01-6.99 (m, 1H), 5.57 (s, 1H), 5.24-5.07 (m, 1H), 3.65 (dd, *J* = 13.7, 10.9 Hz, 1H), 3.43 (dd, *J* = 13.8, 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 150.8, 134.6, 130.0, 129.7, 128.9, 126.7, 126.5, 125.4, 121.6, 119.0, 55.1, 32.0; HRMS (ESI): m/z calculated for $C_{15}H_{14}N_2NaO_4S$ $[M+Na]^+$ 341.0572, found: 341.0565.

(*S*)-2-(2,2-dioxido-3,4-dihydrobenzo[*e*][1,2,3]oxathiazin-4-yl)-N-phenylacetamide (**5**): To a solution of ketoxime **4** (130.5 mg, 0.41 mmol) in dry MeCN (2 mL) under N_2, $AlCl_3$ (5.5 mg, 0.041 mmol) was added. Then the reaction mixture was heated to reflux for 1.5 hours. After completion of the reaction (TLC), it was quenched with H_2O (10 mL), extracted with ethyl acetate, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography to give the corresponding amide **5** as a white solid (122.6 mg, 94% yield); m.p. 194.2-195.2 °C; R_f = 0.31 (PE/EA, 3:1); 97% *ee*, $[\alpha]^{25}_D$ = -26.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.75 (s, 1H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.47-7.40 (m, 2H), 7.37-7.31 (m, 2H), 7.28-7.22 (m, 1H), 7.14-7.05 (m, 2H), 5.22 (s, 1H), 3.21-3.07 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.6, 150.7, 138.9, 129.4, 128.7, 127.1, 125.2, 123.3, 122.3, 119.1, 118.3, 53.2, 41.5; HRMS (ESI): m/z calculated for $C_{15}H_{14}N_2NaO_4S$ $[M+Na]^+$ 341.0572, found: 341.0561; HPLC (Chiralcel IC column, hexane/iPrOH = 70/30, 0.8 mL/min, 254 nm): t_1 = 6.7 min (major, *S*), t_2 = 8.3 min (minor).

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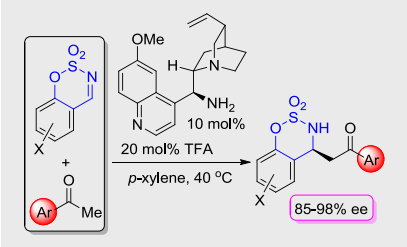

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Asymmetric Mannich Reaction of Aryl Methyl Ketones with Cyclic Imines Benzo[e][1,2,3]oxathiazine 2,2-Dioxides Catalyzed by Cinchona Alkaloid-based Primary Amines

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