PAPER

Rhodium-catalyzed asymmetric addition of arylboronic acids to cyclic *N*-sulfonyl ketimines towards the synthesis of α,α-diaryl-α-amino acid derivatives†
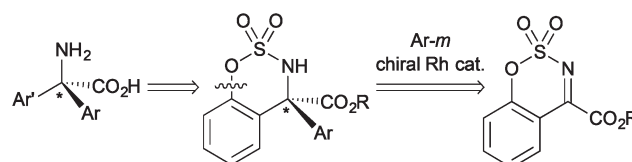
Ryosuke Takechi and Takahiro Nishimura*

Rhodium/chiral diene complex-catalyzed asymmetric addition of arylboronic acids to cyclic ketimines having an ester group proceeded to give the corresponding α-amino acid derivatives in high yields with high enantioselectivity. The cyclic amino acid derivative was transformed into a linear α,α-diaryl-substituted α-*N*-methylamino acid ester.

Introduction

Transition metal-catalyzed addition reaction of organometallic reagents to imines is one of the most powerful methods for the selective formation of a carbon–carbon bond, which provides an easy access to α-chiral amines.[1] Although many successful reports on the asymmetric alkylation or arylation to aldimines have been reported,[2] the addition to ketimines giving chiral α-*tert*-amines is still a challenging objective in organic chemistry.[1d,3] Pioneering studies of the transition metal-catalyzed asymmetric addition of organometallic reagents to ketimines have been attained by Kanai and Shibasaki (allylboronates, Cu),[3a] Charette (dialkylzinc, Cu),[3b] and Snapper and Hoveyda (dialkylzinc, Zr).[3c] The rhodium-catalyzed asymmetric addition of arylboron reagents to *N*-sulfonyl ketimines reported by Hayashi and co-workers is an another approach leading to chiral α-*tert*-amines.[4,5] On the other hand, cyclic *N*-sulfonyl and *N*-acyl ketimines are good substrates for the asymmetric addition to give chiral α-*tert*-amines with high enantioselectivity, because the geometry (*E* or *Z*) of the imine is fixed, and thus the enantioface of the C=N bond is selectively differentiated without an influence of the isomerization.[6,7] For example, the rhodium-catalyzed asymmetric arylation of diaryl-substituted cyclic ketimines has been reported by us in 2012[6a] and Xu in 2013.[7a] Asymmetric alkenylation and allylation were also reported by Lam and co-workers.[8] Recently, Pd-catalyzed asymmetric addition of aryl-

boronic acids to the same types of cyclic *N*-sulfonyl ketimines was reported.[9,10]

α,α-Disubstituted α-amino acids have been focused on as non-proteinogenic amino acids in medicinal chemistry, and the stereoselective synthesis giving α,α-dialkyl and α,α-alkyl-aryl substituted α-amino acid derivatives has been developed.[11] We were interested in the development of general synthetic methods for chiral α,α-diaryl-substituted amino acid derivatives in an enantioselective manner. Although it was reported that rhodium can catalyze the asymmetric addition of arylboronic acids to five-membered cyclic *N*-sulfonyl ketimines substituted with an ester group to give α,α-diaryl-substituted amino acid derivatives,[7a] the transformation of the cyclic structure to the linear α-amino acid derivatives has not been achieved probably due to the difficulty of cleavage of the cyclic structure. Our approach leading to chiral α,α-diaryl-α-amino acid derivatives is the asymmetric arylation of cyclic ketimines giving benzosulfamidates and the subsequent breaking the cyclic structure (Scheme 1). Here we report that the rhodium/chiral diene complex can catalyze the asymmetric addition of arylboronic acids to cyclic aromatic ketimines having an ester group to give the corresponding α-amino acid derivatives in high yields with high enantioselectivity.[12] The cyclic amino acid derivative was successfully transformed into a linear

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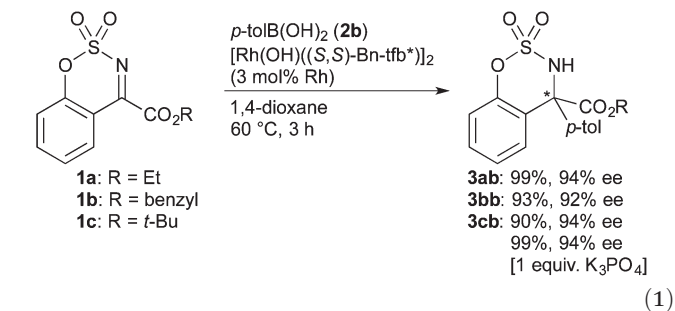Scheme 1   Synthetic strategy for diaryl-substituted α-amino acids.

α,α-diaryl-α-N-methylamino acid ester by reductive cleavage of a carbon–oxygen bond constituting the cyclic structure.

Results and discussion

Our initial studies were focused on the addition of phenylboronic acid to cyclic ketimine **1a** in the presence of rhodium complexes for the catalytic synthesis of sulfamidate **3aa** substituted with an ester group (Table 1). Treatment of **1a** with phenylboronic acid (**2a**, 3 equiv.) in the presence of [Rh(OH)(cod)]$_2$ (5 mol% of Rh) in 1,4-dioxane at 60 °C for 12 h gave **3aa** in 99% yield (entry 1). The use of [RhCl(cod)]$_2$ as a catalyst in the presence of K$_3$PO$_4$ was found to decrease the yield of **3aa** (67% yield, entry 2). We have recently developed chiral diene ligands base on a tetrafluorobenzobarrelene (tfb) framework,[13] which display high coordination ability to Rh(I) giving stable hydroxorhodium complexes. A ferrocenyl-substituted tfb-ligand (Fc-tfb*) displayed high enantioselectivity (93% ee), but the yield of **3aa** was low (34% yield, entry 3). Higher catalytic activity was observed with phenyl-substituted tfb (Ph-tfb*) and benzyl-substituted tfb (Bn-tfb*) giving **3aa** in 73% and 99% yield, respectively (entries 4 and 5), with high enantioselectivity (96% ee). The use of ligand **L1**,[14] which is effective in catalyzing the asymmetric addition of arylboronic acids to aldimines, gave **3aa** in 20% yield with 96% ee (entry 6). A hydroxorhodium complex coordinated with binap [Rh(OH)((S)-

binap)]$_2$[15] efficiently catalyzed the present reaction to give a 92% yield of **3aa**, but the enantioselectivity was modest (61% ee; entry 7). The reaction in the presence of [Rh(OH)((S,S)-Bn-tfb*)]$_2$ using 2 equiv. of phenylboronic acid (**2a**) proceeded as well to give **3aa** in 99% yield with 96% ee within 3 h (entry 8).

$$(1)$$

The addition of p-tolylboronic acid (**2b**) to ketimine **1** having ethyl (**1a**), benzyl (**1b**), and tert-butyl ester (**1c**) proceeded to give the corresponding sulfamidates **3ab–3cb** in high yields with high enantioselectivity (92–94% ee, eqn (1)). In the reaction of tert-butyl ester **1c**, the use of K$_3$PO$_4$ improved the yield of **3cb** to avoid the formation of a small amount of an arylated carboxylic acid observed in the absence of the base. We selected the tert-butyl esters as suitable substrates, which are tolerant to a basic condition and are readily transformed into carboxylic acids.
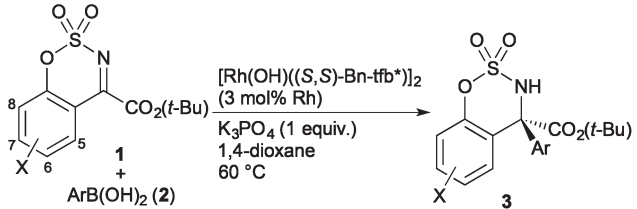
The results obtained for the reaction of ketimine **1** having a tert-butyl ester group with a variety of arylboronic acids **2** are summarized in Table 2. Aryl groups having electron-donating and -withdrawing substituents (**2a–2j**) were successfully introduced into ketimine **1c** with 86–96% ee (entries 1–10). The addition of p-tolylboronic acid (**2b**) to ketimines **1d–1h** possessing methyl, methoxy, and methylenedioxy proceeded to give the corresponding sulfamidates **3db–3hb** with high enantioselectivity (93–97% ee, entries 11–15). A slight decrease of the enantioselectivity was observed in the addition to ketimines **1i** and **1j** substituted with electron-withdrawing groups (F, Cl) at the 6-position (entries 16 and 17).[16]

The reductive cleavage of the O–S bond of benzosulfamidates by LiAlH$_4$ has been reported, where 2-(aminomethyl)-phenols are formed.[6a,9b] On the other hand, nickel-catalyzed cross-coupling of benzosulfamidates with phenylboronic acid was reported to give ortho-phenylated product involving the cleavage of the C–O bond.[8a,17] A nickel catalysis using alkyl-magnesium reagents was also reported by Du Bois and co-workers,[18] but the catalytic systems are not applicable to the benzosulfamidates having tetra-substituted α-carbon of the amino group. After screening and modifying the reported catalytic conditions[18] to cleave a C–O bond of the benzosulfamidate formed in the present arylation, it was found that the reductive cleavage of the C–O bond proceeds using diethylzinc as a reducing reagent to give a linear α,α-diaryl-α-amino acid derivative (eqn (2)). Thus, introduction of a methyl group on the nitrogen atom of **3cb** (94% ee) followed by reductive cleavage of the C–O bond by use of diethylzinc in the presence of NiCl$_2$(dippe) in N,N-dimethylacetamide (DMA) at 100 °C for

Table 1 Rhodium-catalyzed asymmetric arylation of cyclic ketimine **1a**[a]

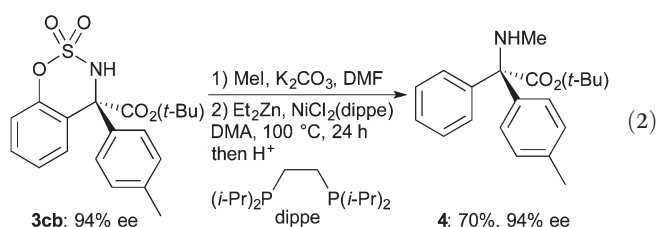| Entry	Rh catalyst	Yield[b] (%)	ee[c] (%)
1	[Rh(OH)(cod)]$_2$[d]	99	—
2	[RhCl(cod)]$_2$/K$_3$PO$_4$[d,e]	67	—
3	[Rh(OH)((S,S)-Fc-tfb*)]$_2$	34	93
4	[Rh(OH)((R,R)-Ph-tfb*)]$_2$	73	96
5	[Rh(OH)((S,S)-Bn-tfb*)]$_2$	99	96
6	[RhCl((R)-L1)]$_2$/K$_3$PO$_4$[d]	20	96
7	[Rh(OH)((S)-binap)]$_2$	92	61
8[f]	[Rh(OH)((S,S)-Bn-tfb*)]$_2$	99	96

[a] Reaction conditions: **1a** (0.10 mmol), PhB(OH)$_2$ (0.30 mmol), and Rh catalyst (3 mol% of Rh) in 1,4-dioxane (0.4 mL) at 60 °C for 12 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] 5 mol% of Rh was used. [e] K$_3$PO$_4$ (1 equiv.). [f] Performed with 2 equiv. of PhB(OH)$_2$ (**2a**, 0.20 mmol) for 3 h.

Table 2 Rhodium-catalyzed asymmetric arylation of ketimine 1^a

Entry	X	Ar	Yield^b (%)	ee^c (%)
1	H (1c)	Ph (2a)	98 (3ca)	96
2	H (1c)	4-MeC$_6$H$_4$ (2b)	99 (3cb)	94
3	H (1c)	4-MeOC$_6$H$_4$ (2c)	96 (3cc)	86
4	H (1c)	3,4-(OCH$_2$O)C$_6$H$_3$ (2d)	93 (3cd)	94
5	H (1c)	3,4,5-(MeO)$_3$C$_6$H$_2$ (2e)	94 (3ce)	86
6	H (1c)	4-FC$_6$H$_4$ (2f)	95 (3cf)	94
7	H (1c)	4-ClC$_6$H$_4$ (2g)	95 (3cg)	95
8	H (1c)	4-BrC$_6$H$_4$ (2h)	97 (3ch)	94
9	H (1c)	4-CF$_3$C$_6$H$_4$ (2i)	96 (3ci)	94
10	H (1c)	2-Naphthyl (2j)	96 (3cj)	95
11	8-Me (1d)	4-MeC$_6$H$_4$ (2b)	94 (3db)	94
12	7-Me (1e)	4-MeC$_6$H$_4$ (2b)	93 (3eb)	96
13	6-Me (1f)	4-MeC$_6$H$_4$ (2b)	95 (3fb)	93
14	6-MeO (1g)	4-MeC$_6$H$_4$ (2b)	99 (3gb)	93
15^d	5,6-(OCH$_2$O) (1h)	4-MeC$_6$H$_4$ (2b)	84 (3hb)	97
16	6-F (1i)	4-MeC$_6$H$_4$ (2b)	95 (3ib)	83
17	6-Cl (1j)	4-MeC$_6$H$_4$ (2b)	99 (3jb)	84

^{a} Reaction conditions: 1 (0.20 mmol), ArB(OH)$_2$ (0.40 mmol), [Rh(OH)-((S,S)-Bn-tfb*)]$_2$ (3 mol% of Rh) and K$_3$PO$_4$ (1 equiv.) in 1,4-dioxane (0.8 mL) at 60 °C. Reaction time: 3 h (entries 1 and 2), 6 h (entries 6, 11–17), 12 h (entries 3–5, 7–10). ^{b} Isolated yields. ^{c} Determined by chiral HPLC analysis. ^{d} Performed with 4 equiv. of 2b and 2 equiv. of K$_3$PO$_4$.

24 h gave α,α-diaryl-α-N-methylamino acid ester **4** in 70% yield in two steps without loss of the enantiomeric purity.

Conclusions

In summary, we have developed the asymmetric synthesis of α,α-diaryl-α-amino acid derivatives in the enantioselective addition of arylboronic acids to cyclic aromatic ketimines having an ester group catalyzed by a hydroxorhodium/chiral diene complex. The cyclic amino acid derivative was successfully transformed into a linear α,α-diaryl-α-N-methylamino acid ester by reductive cleavage of a carbon–oxygen bond constituting the cyclic structure.

Experimental

General remarks

All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen. NMR spectra were recorded on JEOL JNM ECA-600 spectrometer (600 MHz for ^{1}H, 150 MHz for ^{13}C). Chemical shifts are reported in δ (ppm) referenced to the residual peak of CDCl$_3$ (δ 7.26) for ^{1}H NMR, and CDCl$_3$ (δ 77.00) for ^{13}C NMR. The following abbreviations are used; s: singlet, d: doublet, t: triplet, m: multiplet. Optical rotations were measured on a JASCO P-2200 polarimeter. High-resolution mass spectra were obtained with a Bruker micrOTOF spectrometer. Flash column chromatography was performed with Silica Gel 60 N (spherical, neutral) (Cica-Reagent). Preparative thin-layer chromatography was performed with Silica Gel 60 PF$_{254}$ (Merck). Alumina (activated 200) for column chromatography was purchased from Nacalai Tesque.

1,4-Dioxane was purified by passing through a neutral alumina column under N$_2$. Rhodium complexes, [RhCl-(cod)]$_2$ [19] (CAS: 12092-47-6), [Rh(OH)(cod)]$_2$ [20] (CAS: 73468-85-6), [Rh(OH)((S)-binap)]$_2$ [15] (CAS: 805323-12-0 for (R)-complex), [Rh(OH)((S,S)-Bn-tfb*)]$_2$ [13b] (CAS: 1204591-09-2), [Rh(OH)((R,R)-Ph-tfb*)]$_2$ [21] (CAS: 1235989-05-5), and [Rh(OH)((S,S)-Fc-tfb*)]$_2$ [22] (CAS: 1204591-10-5) were prepared according to the reported procedures.

A diene ligand L1^{6a} (CAS: 1365284-85-0) were prepared according to the reported procedures. Ketimines were prepared as shown in the ESI.† All other chemicals were purchased from commercial suppliers and used as received.

General procedure for Table 1

A rhodium catalyst (0.0030 mmol of Rh), **1a** (25.5 mg, 0.10 mmol), and PhB(OH)$_2$ (36.6 mg, 0.30 mmol) were placed in a Schlenk tube under nitrogen. 1,4-Dioxane (0.4 mL) was added and the mixture was stirred at 60 °C for 12 h. The mixture was passed through a short column of silica gel with ethyl acetate as eluent. The solvent was removed on a rotary evaporator and the residue was subjected to preparative TLC on silica gel with hexane–ethyl acetate (3 : 1) to give **3aa**. The ee of **3aa** was determined by chiral HPLC (Daicel Chiralpak AD-H).

General procedure for eqn (1)

[Rh(OH)((S,S)-Bn-tfb*)]$_2$ (1.6 mg, 0.0030 mmol of Rh), **1a,b or c** (0.10 mmol), and p-tolylboronic acid (24.4 mg, 0.20 mmol) were placed in a Schlenk tube under nitrogen. 1,4-Dioxane (0.4 mL) was added and the mixture was stirred at 60 °C for 3 h. The mixture was passed through a short column of silica gel with ethyl acetate as eluent. The solvent was removed on a rotary evaporator and the residue was subjected to preparative TLC on silica gel with hexane–ethyl acetate (3 : 1) to give **3**. The ee of **3** was determined by chiral HPLC.

General procedure for Table 2, entries 1–10

[Rh(OH)((S,S)-Bn-tfb*)]$_2$ (3.2 mg, 0.0060 mmol of Rh), **1c** (56.6 mg, 0.20 mmol), and arylboronic acids **2** (0.40 mmol)

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were placed in a Schlenk tube under nitrogen. 1,4-Dioxane (0.8 mL) was added and the mixture was stirred at 60 °C. The mixture was passed through a short column of silica gel with ethyl acetate as eluent. The solvent was removed on a rotary evaporator and the residue was subjected to preparative TLC on silica gel with hexane–ethyl acetate (3 : 1) to give **3**.

General procedure for Table 2, entries 11–17

[Rh(OH)((*S*,*S*)-Bn-tfb*)]₂ (3.2 mg, 0.0060 mmol of Rh), **1** (0.20 mmol), and *p*-tolylboronic acid (**2b**, 48.8 mg, 0.40 mmol) were placed in a Schlenk tube under nitrogen. 1,4-Dioxane (0.8 mL) was added and the mixture was stirred at 60 °C for 3 h. The mixture was passed through a short column of silica gel with ethyl acetate as eluent. The solvent was removed on a rotary evaporator and the residue was subjected to preparative TLC on silica gel with hexane–ethyl acetate (3 : 1) to give **3**.

Ethyl 4-phenyl-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine-4-carboxylate 2,2-dioxide (3aa). The ee was measured by HPLC (Chiralpak AD-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min⁻¹, 254 nm, t_1 = 14.9 min (*R*), t_2 = 18.9 min (*S*)); $[\alpha]_D^{20}$ −45 (*c* 0.82, CHCl₃) for 96% ee (*S*). ¹H NMR (CDCl₃) δ 1.28 (t, *J* = 7.1 Hz, 3H), 4.32–4.41 (m, 2H), 6.45 (s, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.21–7.26 (m, 3H), 7.34–7.38 (m, 3H), 7.43 (td, *J* = 8.1, 1.4 Hz, 1H), 7.51 (dd, *J* = 8.1, 1.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 13.8, 64.1, 76.8, 118.9, 119.7, 124.9, 127.5, 128.5, 128.9, 130.5, 130.8, 139.3, 151.1, 170.0. HRMS (ESI) calcd for C₁₆H₁₅NNaO₅S (M + Na)⁺ 356.0563, found 356.0564.

Ethyl 4-(*p*-tolyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine-4-carboxylate 2,2-dioxide (3ab). The ee was measured by HPLC (Chiralpak AD-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min⁻¹, 254 nm, t_1 = 16.5 min (*R*), t_2 = 21.7 min (*S*)); $[\alpha]_D^{20}$ −40 (*c* 0.69, CHCl₃) for 94% ee (*S*). ¹H NMR (CDCl₃) δ 1.28 (t, *J* = 6.8 Hz, 3H), 2.35 (s, 3H), 4.32–4.41 (m, 2H), 6.41 (s, 1H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.22 (td, *J* = 8.1, 1.4 Hz, 1H), 7.42 (td, *J* = 8.1, 2.0 Hz, 1H), 7.50 (dd, *J* = 8.1, 1.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 13.8, 21.1, 64.0, 71.0, 119.2, 119.6, 124.8, 127.5, 129.2, 130.5, 130.7, 134.0, 136.5, 138.9, 151.0, 170.1. HRMS (ESI) calcd for C₁₇H₁₇NNaO₅S (M + Na)⁺ 370.0720, found 370.0714.

Benzyl 4-(*p*-tolyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine-4-carboxylate 2,2-dioxide (3bb). The ee was measured by HPLC (Chiralpak AD-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min⁻¹, 254 nm, t_1 = 21.0 min (*R*), t_2 = 27.7 min (*S*)); $[\alpha]_D^{20}$ −41 (*c* 0.88, CHCl₃) for 92% ee (*S*). ¹H NMR (CDCl₃) δ 2.34 (s, 3H), 5.29 (d, *J* = 12.2 Hz, 1H), 5.32 (d, *J* = 12.2 Hz, 1H), 6.35 (s, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 2H), 7.23–7.27 (m, 2H), 7.31–7.36 (m, 3H), 7.38–7.43 (m, 2H); ¹³C NMR (CDCl₃) δ 21.1, 69.4, 71.1, 119.2, 119.5, 124.8, 127.4, 128.57, 128.63, 128.9, 129.2, 130.67, 130.69, 134.0, 136.3, 139.0, 150.9, 169.9. HRMS (ESI) calcd for C₂₂H₁₉NNaO₅S (M + Na)⁺ 432.0876, found 432.0867.

tert-Butyl 4-(*p*-tolyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine-4-carboxylate 2,2-dioxide (3cb). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min⁻¹, 254 nm, t_1 = 14.0 min (*S*), t_2 = 22.4 min (*R*)); $[\alpha]_D^{20}$ −30 (*c* 0.61, CHCl₃) for 94% ee (*S*). ¹H NMR (CDCl₃) δ 1.47 (s, 9H), 2.35 (s, 3H), 6.41 (s, 1H), 7.10–7.16 (m, 5H), 7.21 (td, *J* = 7.5, 1.4 Hz, 1H), 7.41 (td, *J* = 7.8, 2.1 Hz, 1H), 7.49 (dd, *J* = 7.5, 2.1 Hz, 1H); ¹³C NMR (CDCl₃) δ 21.1, 27.6, 71.1, 85.7, 119.5, 124.6, 127.4, 129.1, 130.5, 130.6, 137.0, 138.5, 151.0, 168.8. HRMS (ESI) calcd for C₁₉H₂₁NNaO₅S (M + Na)⁺ 398.1033, found 398.1024.

tert-Butyl 4-phenyl-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine-4-carboxylate 2,2-dioxide (3ca). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min⁻¹, 254 nm, t_1 = 13.9 min (*S*), t_2 = 21.7 min (*R*)); $[\alpha]_D^{20}$ −29 (*c* 1.13, CHCl₃) for 96% ee (*S*). ¹H NMR (CDCl₃) δ 1.46 (s, 9H), 6.45 (s, 1H), 7.13 (dd, *J* = 8.9 Hz, 1H), 7.02–7.29 (m, 3H), 7.32–7.39 (m, 3H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H); ¹³C NMR (CDCl₃) δ 27.6, 71.2, 85.8, 119.2, 119.6, 124.6, 127.5, 128.4, 128.6, 130.5, 130.6, 139.9, 151.1, 168.7. HRMS (ESI) calcd for C₁₈H₁₉NNaO₅S (M + Na)⁺ 384.0876, found 384.0870.

tert-Butyl 4-(4-methoxyphenyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine-4-carboxylate 2,2-dioxide (3cc). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min⁻¹, 254 nm, t_1 = 16.0 min (*S*), t_2 = 24.1 min (*S*)); $[\alpha]_D^{20}$ −26 (*c* 1.06, CHCl₃) for 86% ee (*S*). ¹H NMR (CDCl₃) δ 1.47 (s, 9H), 3.80 (s, 3H), 6.41 (s, 1H), 6.85 (d, *J* = 8.9 Hz, 2H), 7.12 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.15 (d, *J* = 8.9 Hz, 2H), 7.21 (td, *J* = 8.1, 1.4 Hz, 1H), 7.41 (td, *J* = 8.1, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.1, 1.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 27.6, 55.2, 71.0, 85.7, 113.7, 119.57, 119.63, 124.6, 128.8, 130.5, 130.6, 132.0, 151.0, 159.6, 168.8. HRMS (ESI) calcd for C₁₉H₂₁NNaO₆S (M + Na)⁺ 414.0982, found 414.0979.

tert-Butyl 4-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydrobenzo[*e*]-[1,2,3]oxathiazine-4-carboxylate 2,2-dioxide (3cd). The ee was measured by HPLC (Chiralpak AD-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min⁻¹, 254 nm, t_1 = 20.1 min (*S*), t_2 = 28.4 min (*R*)); $[\alpha]_D^{20}$ −33 (*c* 0.94, CHCl₃) for 94% ee (*S*). ¹H NMR (CDCl₃) δ 1.47 (s, 9H), 5.97 (d, *J* = 1.4 Hz, 1H), 5.98 (d, *J* = 1.4 Hz, 1H), 6.42 (s, 1H), 6.68–6.75 (m, 3H), 7.11 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.22 (td, *J* = 7.5, 1.4 Hz, 1H), 7.42 (td, *J* = 7.8, 1.4 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 27.6, 71.0, 85.9, 101.5, 107.8, 108.1, 119.2, 119.6, 121.4, 124.7, 130.3, 130.7, 133.7, 147.80, 147.83, 151.0, 168.6. HRMS (ESI) calcd for C₁₉H₁₉NNaO₇S (M + Na)⁺ 428.0774, found 428.0768.

tert-Butyl 4-(3,4,5-trimethoxyphenyl)-3,4-dihydrobenzo[*e*]-[1,2,3]oxathiazine-4-carboxylate 2,2-dioxide (3ce). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min⁻¹, 254 nm, t_1 = 13.7 min (*S*), t_2 = 28.6 min (*R*)); $[\alpha]_D^{20}$ −9 (*c* 0.94, CHCl₃) for 85% ee (*S*). ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 3.75 (s, 6H), 3.85 (s, 3H), 6.40 (s, 1H), 6.48 (s, 2H), 7.12 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.21 (td, *J* = 8.1, 1.4 Hz, 1H), 7.41 (td, *J* = 7.8, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.1, 1.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 27.6, 56.1, 60.8, 71.3, 85.7, 119.5, 119.6, 124.6, 130.7, 130.8, 135.2, 138.2, 150.8, 153.0, 168.5. HRMS (ESI) calcd for C₂₁H₂₅NNaO₈S (M + Na)⁺ 474.1193, found 474.1187.

tert-Butyl 4-(4-fluorophenyl)-3,4-dihydrobenzo[*e*][1,2,3]-oxathiazine-4-carboxylate 2,2-dioxide (3cf). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol =

80 : 20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 11.9 min (S), t_2 = 17.1 min (R)); $[\alpha]_D^{20}$ −53 (c 1.09, CHCl$_3$) for 94% ee (S). ^{1}H NMR (CDCl$_3$) δ 1.46 (s, 9H), 6.50 (s, 1H), 7.02 (t, J = 8.5 Hz, 2H), 7.14 (dd, J = 8.1, 1.4 Hz, 1H), 7.19–7.26 (m, 3H), 7.44 (dt, J = 7.8, 1.4 Hz, 1H), 7.53 (dd, J = 8.1, 2.1 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 27.6, 70.6, 86.2, 105.0, 115.3 (d, J_{F-C} = 21 Hz), 118.7, 119.9, 124.8, 129.5 (d, J_{F-C} = 9 Hz), 129.9, 130.9, 135.7, 151.2, 162.5 (d, J_{F-C} = 247 Hz), 168.5. HRMS (ESI) calcd for C$_{18}$H$_{18}$FNNaO$_5$S (M + Na)$^+$ 402.0782, found 402.0776.

tert-Butyl 4-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,2,3]-oxathiazine-4-carboxylate 2,2-dioxide (3cg). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 11.3 min (S), t_2 = 14.6 min (R)); $[\alpha]_D^{20}$ −48 (c 1.18, CHCl$_3$) for 95% ee (S). ^{1}H NMR (CDCl$_3$) δ 1.45 (s, 9H), 6.53 (s, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 8.6 Hz, 2H), 7.25 (td, J = 7.8, 1.4 Hz, 1H), 7.31 (d, J = 8.6 Hz, 2H), 7.45 (dd, J = 7.8, 1.4 Hz, 1H), 7.54 (dd, J = 7.8, 1.4 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 27.6, 70.6, 86.3, 118.3, 119.9, 124.8, 128.5, 128.9, 129.9, 131.0, 134.6, 138.4, 151.2, 168.3. HRMS (ESI) calcd for C$_{18}$H$_{18}$ClNNaO$_5$S (M + Na)$^+$ 418.0486, found 418.0481.

tert-Butyl 4-(4-bromophenyl)-3,4-dihydrobenzo[e][1,2,3]-oxathiazine-4-carboxylate 2,2-dioxide (3ch). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 13.9 min (S), t_2 = 18.1 min (R)); $[\alpha]_D^{20}$ −38 (c 0.70, CHCl$_3$) for 94% ee (S). ^{1}H NMR (CDCl$_3$) δ 1.45 (s, 9H), 6.51 (s, 1H), 7.10 (d, J = 8.9 Hz, 2H), 7.17 (dd, J = 8.1, 1.4 Hz, 1H), 7.25 (td, J = 8.1, 1.4 Hz, 1H), 7.45 (td, J = 8.1, 1.4 Hz, 1H), 7.47 (d, J = 8.9 Hz, 2H), 7.53 (dd, J = 8.1, 1.4 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 27.6, 70.7, 86.4, 118.3, 119.9, 122.9, 124.8, 129.2, 129.8, 131.0, 131.5, 138.9, 151.2, 168.2. HRMS (ESI) calcd for C$_{18}$H$_{18}$BrNNaO$_5$S (M + Na)$^+$ 461.9981, found 461.9980.

tert-Butyl 4-(4-(trifluoromethyl)phenyl)-3,4-dihydrobenzo[e]-[1,2,3]oxathiazine-4-carboxylate 2,2-dioxide (3ci). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 9.8 min (S), t_2 = 11.4 min (R)); $[\alpha]_D^{20}$ −60 (c 0.65, CHCl$_3$) for 94% ee (S). ^{1}H NMR (CDCl$_3$) δ 1.45 (s, 9H), 6.58 (s, 1H), 7.16 (dd, J = 8.2, 1.4 Hz, 1H), 7.28 (td, J = 8.2, 1.4 Hz, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.48 (td, J = 8.1, 1.4 Hz, 1H), 7.56 (dd, J = 8.1, 1.4 Hz, 1H), 7.60 (d, J = 8.1 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 27.6, 70.7, 86.7, 117.9, 120.1, 123.8 (q, J_{F-C} = 273 Hz), 124.9, 125.3 (q, J_{F-C} = 3 Hz), 128.0, 129.7, 130.7 (q, J_{F-C} = 31 Hz), 131.2, 143.6, 151.4, 168.0. HRMS (ESI) calcd for C$_{19}$H$_{18}$F$_3$NNaO$_5$S (M + Na)$^+$ 452.0750, found 452.0744.

tert-Butyl 4-(naphthalen-2-yl)-3,4-dihydrobenzo[e][1,2,3]-oxathiazine-4-carboxylate 2,2-dioxide (3cj). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 16.4 min (S), t_2 = 22.6 min (R)); $[\alpha]_D^{20}$ −26 (c 1.05, CHCl$_3$) for 95% ee (S). ^{1}H NMR (CDCl$_3$) δ 1.47 (s, 9H), 6.54 (s, 1H), 7.18 (dd, J = 8.2, 1.4 Hz, 1H), 7.26 (td, J = 7.8, 1.4 Hz, 1H), 7.38 (dd, J = 8.9, 2.0 Hz, 1H), 7.44–7.54 (m, 3H), 7.59 (dd, J = 8.1, 1.4 Hz, 1H), 7.63 (d, J = 1.4 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.84 (t, J = 8.9 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 27.6, 71.4, 86.0, 118.9, 119.8, 124.7, 124.8,

126.5, 126.9, 127.1, 127.6, 128.5, 128.6, 130.5, 130.8, 132.6, 133.0, 137.0, 151.2, 168.7. HRMS (ESI) calcd for C$_{22}$H$_{21}$NNaO$_5$S (M + Na)$^+$ 434.1033, found 434.1025.

tert-Butyl 8-methyl-4-(p-tolyl)-3,4-dihydrobenzo[e][1,2,3]-oxathiazine-4-carboxylate 2,2-dioxide (3db). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 12.5 min (S), t_2 = 20.2 min (R)); $[\alpha]_D^{20}$ −12 (c 0.57, CHCl$_3$) for 94% ee (S). ^{1}H NMR (CDCl$_3$) δ 1.46 (s, 9H), 2.31 (s, 3H), 2.34 (s, 3H), 6.39 (s, 1H), 7.09 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 8.9 Hz, 2H), 7.14 (d, J = 8.9 Hz, 2H), 7.26 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 15.8, 21.1, 27.6, 71.2, 85.5, 119.5, 123.9, 127.5, 127.9, 128.8, 129.0, 131.9, 137.1, 138.4, 149.5, 168.9. HRMS (ESI) calcd for C$_{20}$H$_{23}$NNaO$_5$S (M + Na)$^+$ 412.1189, found 412.1186.

tert-Butyl 7-methyl-4-(p-tolyl)-3,4-dihydrobenzo[e][1,2,3]-oxathiazine-4-carboxylate 2,2-dioxide (3eb). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 13.7 min (S), t_2 = 20.4 min (R)); $[\alpha]_D^{20}$ −15 (c 0.70, CHCl$_3$) for 96% ee (S). ^{1}H NMR (CDCl$_3$) δ 1.46 (s, 9H), 2.34 (s, 3H), 2.38 (s, 3H), 6.39 (s, 1H), 6.92 (s, 1H), 7.01 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 8.9 Hz, 2H), 7.13 (d, J = 8.9 Hz, 2H), 7.36 (d, J = 8.2 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 21.0, 21.1, 27.6, 70.9, 85.5, 116.3, 119.7, 125.6, 127.4, 129.1, 130.2, 137.2, 138.4, 141.3, 150.9, 168.9. HRMS (ESI) calcd for C$_{20}$H$_{23}$NNaO$_5$S (M + Na)$^+$ 412.1189, found 412.1182.

tert-Butyl 6-methyl-4-(p-tolyl)-3,4-dihydrobenzo[e][1,2,3]-oxathiazine-4-carboxylate 2,2-dioxide (3fb). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 13.7 min (S), t_2 = 20.5 min (R)); $[\alpha]_D^{20}$ −20 (c 1.03, CHCl$_3$) for 93% ee (S). ^{1}H NMR (CDCl$_3$) δ 1.47 (s, 9H), 2.32 (s, 3H), 2.35 (s, 3H), 6.39 (s, 1H), 7.00 (d, J = 8.9 Hz, 1H), 7.13 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 7.20 (dd, J = 8.9, 1.4 Hz, 1H), 7.28 (d, J = 1.4 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 20.9, 21.1, 27.6, 71.1, 85.5, 119.0, 119.1, 127.4, 129.1, 130.7, 131.2, 134.3, 137.0, 138.5, 148.9, 168.8. HRMS (ESI) calcd for C$_{20}$H$_{23}$NNaO$_5$S (M + Na)$^+$ 412.1189, found 412.1185.

tert-Butyl 6-methoxy-4-(p-tolyl)-3,4-dihydrobenzo[e][1,2,3]-oxathiazine-4-carboxylate 2,2-dioxide (3gb). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 18.5 min (S), t_2 = 34.7 min (R)); $[\alpha]_D^{20}$ −47 (c 1.10, CHCl$_3$) for 93% ee (S). ^{1}H NMR (CDCl$_3$) δ 1.48 (s, 9H), 2.34 (s, 3H), 3.75 (s, 3H), 6.35 (s, 1H), 6.95 (dd, J = 8.8, 2.7 Hz, 1H), 7.02 (d, J = 2.7 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 7.12 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 21.1, 27.7, 55.7, 71.1, 85.6, 115.0, 116.3, 120.1, 120.3, 127.4, 129.1, 136.9, 138.5, 144.9, 155.9, 168.7. HRMS (ESI) calcd for C$_{20}$H$_{23}$NNaO$_6$S (M + Na)$^+$ 428.1138, found 428.1135.

tert-Butyl 9-(p-tolyl)-8,9-dihydro-[1,3]dioxolo[4',5':5,6]benzo-[1,2-e][1,2,3]oxathiazine-9-carboxylate 7,7-dioxide (3hb). The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80 : 20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 17.4 min (S), t_2 = 49.1 min (R)); $[\alpha]_D^{20}$ +34 (c 1.04, CHCl$_3$) for 97% ee (S). ^{1}H NMR (CDCl$_3$) δ 1.51 (s, 9H), 2.35 (s, 3H), 5.74 (d, J = 1.4 Hz, 1H), 5.85

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(d, J = 1.4 Hz, 1H), 5.86 (s, 1H), 6.62 (d, J = 8.6 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 7.14 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 21.1, 27.7, 70.1, 84.9, 101.8, 106.8, 109.0, 111.2, 127.3, 129.1, 134.7, 138.9, 145.0, 145.2, 146.1, 167.8. HRMS (ESI) calcd for C$_{20}$H$_{21}$NNaO$_7$S (M + Na)$^+$ 442.0931, found 442.0940.

***tert*-Butyl 6-fluoro-4-(*p*-tolyl)-3,4-dihydrobenzo[*e*][1,2,3]-oxathiazine-4-carboxylate 2,2-dioxide (3ib).** The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80:20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 15.4 min (*S*), t_2 = 26.1 min (*R*)); [α]$_D^{20}$ −8 (*c* 0.80, CHCl$_3$) for 88% ee (*S*). ^{1}H NMR (CDCl$_3$) δ 1.48 (s, 9H), 2.36 (s, 3H), 6.37 (s, 1H), 7.05–7.15 (m, 4H), 7.16 (d, J = 8.2 Hz, 2H), 7.21 (dd, J = 8.2, 2.7 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 21.1, 27.6, 71.0, 86.1, 117.2 (d, J_{F-C} = 27 Hz), 117.8 (d, J_{F-C} = 23 Hz), 120.9 (d, J_{F-C} = 9 Hz), 121.2 (d, J_{F-C} = 7 Hz), 127.2, 129.3, 136.5, 138.9, 146.9, 158.6 (d, J_{F-C} = 245 Hz), 168.3. HRMS (ESI) calcd for C$_{19}$H$_{20}$FNNaO$_5$S (M + Na)$^+$ 416.0938, found 416.0936.

***tert*-Butyl 6-chloro-4-(*p*-tolyl)-3,4-dihydrobenzo[*e*][1,2,3]-oxathiazine-4-carboxylate 2,2-dioxide (3jb).** The ee was measured by HPLC (Chiralpak AS-H, hexane–2-propanol = 80:20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 14.1 min (*S*), t_2 = 26.9 min (*R*)); [α]$_D^{20}$ −19 (*c* 1.03, CHCl$_3$) for 84% ee (*S*). ^{1}H NMR (CDCl$_3$) δ 1.48 (s, 9H), 2.36 (s, 3H), 6.39 (s, 1H), 7.06 (d, J = 8.9 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.38 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (d, J = 2.7 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 21.1, 27.6, 70.9, 86.2, 120.8, 121.1, 127.2, 129.4, 129.9, 130.56, 130.60, 136.4, 138.9, 149.5, 168.2. HRMS (ESI) calcd for C$_{19}$H$_{20}$ClNNaO$_5$S (M + Na)$^+$ 432.0643, found 432.0641.

Transformations of 3cb

***tert*-Butyl 3-methyl-4-(*p*-tolyl)-3,4-dihydrobenzo[*e*][1,2,3]-oxathiazine-4-carboxylate 2,2-dioxide (3cb′).** To a solution of **3cb** (450 mg, 1.20 mmol, 94% ee) and K$_2$CO$_3$ (663 mg, 4.8 mmol) in DMF (2.4 mL) was added dropwise MeI (0.15 mL, 2.4 mmol), and the mixture was stirred at room temperature for 36 h. H$_2$O was added to the mixture and it was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated on a rotary evaporator. The residue was subjected to flash column chromatography on silica gel with hexane–ethyl acetate (10:1) to give **3cb′** (467 mg, 1.19 mmol, 99% yield). The ee was measured by HPLC (Chiralpak AD-H, hexane–2-propanol = 80:20, flow 0.5 mL min^{-1}, 254 nm, t_1 = 10.7 min (*R*), t_2 = 11.5 min (*S*)); [α]$_D^{20}$ +117 (*c* 1.01, CHCl$_3$) for 94% ee (*S*). ^{1}H NMR (CDCl$_3$) δ 1.56 (s, 9H), 2.36 (s, 3H), 2.91 (s, 3H), 6.93 (dd, J = 8.1, 1.4 Hz, 1H), 7.02 (dd, J = 8.1, 1.4 Hz, 1H), 7.03 (td, J = 8.1, 1.4 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.27 (td, J = 8.1, 1.4 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 21.1, 27.9, 34.0, 75.7, 84.3, 117.9, 124.1, 124.4, 128.5, 129.5, 129.6, 133.3, 136.0, 139.1, 148.9, 168.8. HRMS (ESI) calcd for C$_{20}$H$_{23}$NNaO$_5$S (M + Na)$^+$ 412.1189, found 412.1180.

***tert*-Butyl 2-(methylamino)-2-phenyl-2-(*p*-tolyl)acetate (4).** To a mixture of **3cb′** (38.9 mg, 0.10 mmol, 94% ee) and NiCl$_2$-(dippe)^{23} in *N,N*-dimethylacetamide (DMA) was added Et$_2$Zn

(1.0 M in toluene solution, 0.20 mL, 0.20 mmol) at room temperature, and the mixture was stirred at 100 °C for 24 h. Saturated NH$_4$Cl (aq., *ca.* 0.1 mL) and 0.5 M HCl (aq., *ca.* 0.5 mL) at room temperature was added to the mixture and it was stirred at room temperature for 10 min. The mixture was extracted with ethyl acetate. To the aqueous layer was added 0.5 M HCl (aq., *ca.* 2.0 mL) and mixture was stirred at room temperature for 30 min. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with H$_2$O, saturated NH$_4$Cl (aq.), dried over Na$_2$SO$_4$, filtered, and concentrated on a rotary evaporator. The residue was subjected to preparative TLC on silica gel with hexane–ethyl acetate (10:1) to give **4** (21.8 mg, 0.070 mmol, 70% yield). The ee was measured by HPLC (Chiralpak AD-H × 2, hexane–2-propanol = 90:10, flow 0.5 mL min^{-1}, 254 nm, t_1 = 17.3 min (*S*), t_2 = 18.1 min (*R*)); [α]$_D^{20}$ −1 (*c* 1.02, CHCl$_3$) for 94% ee (*R*). ^{1}H NMR (CDCl$_3$) δ 1.39 (s, 9H), 2.13 (s, 3H), 2.33 (s, 3H), 7.11 (d, J = 8.1 Hz, 2H), 7.22–7.26 (m, 1H), 7.28–7.32 (m, 4H), 8.14 (d, J = 8.1 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 21.0, 27.8, 30.6, 73.2, 81.8, 127.0, 127.6, 128.4, 128.5, 128.6, 136.6, 138.5, 141.6, 172.7. HRMS (ESI) calcd for C$_{20}$H$_{25}$NNaO$_2$ (M + Na)$^+$ 334.1778, found 334.1774.

Acknowledgements

Notes and references

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