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PAPER

Highly diastereoselective Friedel–Crafts reaction of arenes with *N-tert*-butanesulfinylimino ester towards the efficient synthesis of α-arylglycines†

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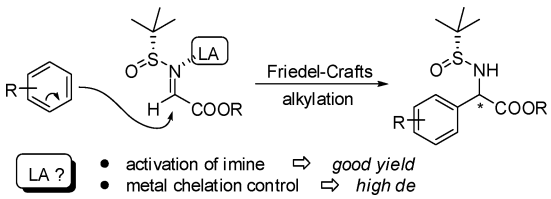
Lewis acid-catalyzed highly diastereoselective asymmetric Friedel–Crafts alkylation of arenes with a chiral *N-tert*-butanesulfinylimino ester is described. The reaction can be accomplished with ease in the presence of a catalytic amount of $In(OTf)_3$ at room temperature, providing a series of enantiomerically enriched α-arylglycines in good yields and with excellent diastereoselectivities (up to 99% de). Highly stereoselective double Friedel–Crafts alkylation to afford dialkylation product was also investigated.

Introduction

In recent years, optically active non-proteinogenic amino acids have attracted much attention, not only because of their significant biological activities, but also because they can be incorporated into the peptide chain for intriguing protein property studies as well as be used as fundamental building blocks for extensive applications in organic synthesis and new drug discovery.[1] Among them, α-arylglycines and their derivatives are key structural components of many biologically active natural products and pharmaceutical compounds.[2] Due to this importance, a great number of approaches have been developed to access these valuable compounds,[3–6] mainly including asymmetric catalysis,[4] enzymatic resolution[5] and chiral auxiliary-mediated induction.[6] While some of these methods can be highly stereoselective, many require special reagents/conditions,[6d–f,6n] or need to involve extra multi-transformations.[4p,6p] Further development of new methods that allow efficient synthesis of enantiomerically pure α-arylglycines from easily accessible precursors under mild and practical conditions has been certainly a desirable subject. In general, asymmetric Friedel–Crafts reaction of arenes with glyoxylate imines represents the simplest and most direct approach for the stereoselective preparation of α-arylglycines in terms of reagent availability. To our knowledge, despite the fact that the strategies of transition metal catalysis,[4r–t] organocatalysis,[4h,4n,6f] and Lewis acid-promoted induction[6e,6m] have been employed, the results are far from satisfactory, and achieving high stereoselectivity through Friedel–Crafts alkylation for synthesis of α-arylglycines remains a significant challenge. Herein, we report our efforts to address this issue by employing simple Lewis acid to catalyze the asymmetric Friedel–Crafts reaction of arenes with an *N-tert*-butanesulfinylimino ester to produce various enantioenriched α-arylglycines directly at room temperature.

N-tert-Butanesulfinyl imines have recently shown versatile application in the asymmetric synthesis of various chiral amines.[7,8] In our previous work, we demonstrated the successful use of *N-tert*-butanesulfinylimino ester as a chiral glycine cation equivalent for the asymmetric synthesis of synthetically useful diverse amino acids such as D-allylglycine,[8g] β-vinyl-α-arylalanines,[8j] α-(3-indolyl)glycines,[8l] and α-allenylglycines.[8m] In continuation of our interest in this area, we considered to prepare α-arylglycines especially α-phenylglycine analogues *via* asymmetric Friedel–Crafts alkylation of arenes with *N-tert*-butanesulfinylimino ester. It is worth noting that the same strategy has been examined to synthesize heteroaromatic glycine derivatives in the presence of stoichiometric amounts of TMSOTf, but the only example of anisole addition showed very low diastereoselectivity (1 : 2.6 dr ratio) even at −20 °C.[6m] Taking account of our earlier successes involving metal chelation,[8] we anticipated that a high reaction stereocontrol might be achieved with a proper transition-metal-based Lewis acid catalyst under mild conditions (Scheme 1).



Scheme 1 Synthetic strategies to chiral α-arylglycine derivatives.

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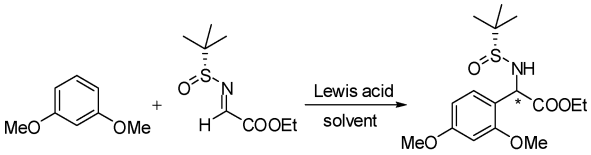
† Electronic supplementary information (ESI) available: Experimental details including copies of ^1H and ^{13}C NMR and HPLC spectra. See DOI: 10.1039/c1ob06450a

Table 1 Screening of reaction conditions for diastereoselective Friedel–Crafts reaction of 1,3-dimethoxybenzene **1a** with (*R*)-*N*-*tert*-butanesulfinylimino ester **2**[a]



Entry	Catalyst	mol (%)	**1a** (equiv)	*T*/°C	Time (h)	Solvent	Yield (%)[b]	de (%)[c]
1	$Cu(OTf)_2$	15	1.5	rt	12	CH_2Cl_2	23	97
2	$InBr_3$	15	1.5	rt	12	CH_2Cl_2	22	76
3	$Zn(OTf)_2$	15	1.5	rt	12	CH_2Cl_2	18	84
4	$FeCl_3$	15	1.5	rt	12	CH_2Cl_2	16	62
5	$AlCl_3$	15	1.5	rt	12	CH_2Cl_2	20	53
6	$AgNO_3$	15	1.5	rt	12	CH_2Cl_2	n.r.[d]	—
7	$In(OTf)_3$	15	1.5	rt	12	CH_2Cl_2	36	98
8	$In(OTf)_3$	15	1.5	50	12	CH_2Cl_2	16	92
9	$In(OTf)_3$	15	1.5	rt	12	toluene	38	94
10	$In(OTf)_3$	15	1.5	rt	12	$CHCl_3$	45	95
11	$In(OTf)_3$	15	1.5	rt	12	CH_3CN	12	43
12	$In(OTf)_3$	15	1.5	rt	12	THF	12	71
13	$In(OTf)_3$	15	1.1	rt	12	CH_2Cl_2	27	97
14	$In(OTf)_3$	15	2.0	rt	12	CH_2Cl_2	38	98
15	$In(OTf)_3$	20	1.5	rt	8	CH_2Cl_2	61	98
16	$In(OTf)_3$	30	1.5	rt	1	CH_2Cl_2	89	98

[a] The reaction was performed with 0.25 mmol of glyoxylate imine **2** and 0.375 mmol of 1,3-dimethoxybenzene **1a** in dry solvent (2.0 mL) at room temperature. [b] Yield of isolated and purified products. [c] The diastereoselectivity of the product was determined by measuring the enantiomeric excess of its acetyl derivative. [d] No reaction.

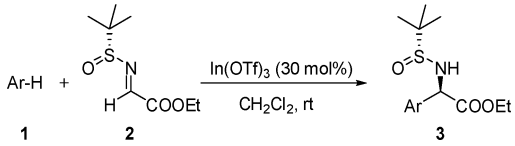
Results and discussion

Inspired by the previous findings on the synthesis of optically active α-(3-indolyl)glycines,[81] we began our survey by examining the reaction of 1,3-dimethoxybenzene **1a** with (*R*)-*N*-*tert*-butanesulfinylimino ester of ethyl glyoxylate (**2**) in the presence of 15 mol% of $Cu(OTf)_2$ in CH_2Cl_2 at ambient temperature.[9] The reaction proceeded slowly, affording the desired α-arylglycine **3a** as the sole product in 23% yield after 12h. Although the yield was not ideal, a very high diastereoselectivity (97% de) of the reaction was observed (Table 1, entry 1). To achieve better results, a series of transition-metal Lewis acids were carefully screened (entries 2–7). While $AgNO_3$ catalyst was ineffective, 15 mol% of $In(OTf)_3$[10] provided a clearly better yield over $Cu(OTf)_2$, along with the best de of 98% (entry 7). Unfortunately, elevating the reaction temperature to 50 °C did not result in further improvement, but caused lower yield and diminished diastereoselectivity (entry 8). The investigation of various solvents indicated that the use of CH_2Cl_2 as solvent was the best choice (entries 9–12). In addition, the optimal ratio of imino ester **2** to 1,3-dimethoxybenzene **1a** was determined to be 1 : 1.5 in terms of atom economy and efficiency (entries 7, 13 and 14). Gratifyingly, when the loading amount of catalyst was increased, the Friedel–Crafts reaction between **1a** and **2** was significantly promoted to gave **3a** in high yield (entries 15–16). It was found that the employment of 30 mol% of $In(OTf)_3$ was essential to achieve the reaction with both high yield and excellent diastereoselectivity (89% yield, 98% de) (entry 16). After these studies, the optimal conditions were determined to be performing the reaction with 1.5 equiv of alkylating arene using CH_2Cl_2 as solvent in the presence of 30 mol% of $In(OTf)_3$ at room temperature.

Having identified the optimal reaction conditions, a wide range of electron-rich aromatic ring compounds were examined to investigate the reaction generality and substrate scope; the results are summarized in Table 2. To our delight, in all examples of diverse arenes, the reactions worked well. Generally, the phenyl arenes reacted exclusively at the expected electrophilic site giving the corresponding *N*-sulfinyl addition products in good to high yields (60–91%), regardless of the manner of substitution on the benzene ring. Among them, excellent diastereoselectivities (93–98% de) were achieved with the 1,3,5- and 1,2,4-trisubstituted benzene compounds (entries 2–6). In contrast, the 1,2,3-trisubstituted benzene substrates usually gave slightly lower yields and diastereoselectivities (entries 7–9). The naphthalene derivatives can be suitable substrates as well, providing the desired products with excellent diastereoselectivities (98–99% de) (entries 10–14). Notably, with 1-methoxynaphthalene and 1-naphthol as reactant, a regioselective ratio of 3 : 1 and 5 : 1 in favor of α-alkylation product was observed, respectively. In both cases, each regioisomer was isolated with great diastereoselectivity (97–99% de) (entries 10 and 12). The current system was also applicable to heteroaromatic substrates, which afforded α-heteroarylglycine derivatives in good yields with up to 90% de (entries 15 and 16).

Encouraged by the above results, we next turned our attention to explore more challenging stereoselective double Friedel–Crafts alkylation. As illustrated in Scheme 2, the reaction of dimethoxybenzene **1a** with (*R*)-*N*-*tert*-butanesulfinylimino ester **2** was examined. Initially, the desired dialkylation product **4** was only obtained in less than 5% yield under the standard conditions using 30 mol% $In(OTf)_3$ as Lewis acid catalyst even after prolonging the reaction time to 12 h. Interestingly, when the amount of $In(OTf)_3$ was increased to 1 equiv, the reaction was promoted and afforded

Table 2 Diastereoselective Friedel–Crafts reaction of arenes **1** with (*R*)-*N*-*tert*-butanesulfinylimino ester **2**[a]



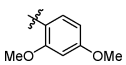
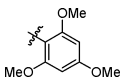
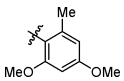
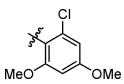
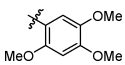
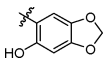
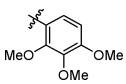
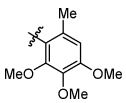
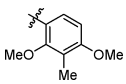
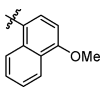
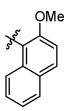
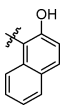
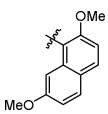
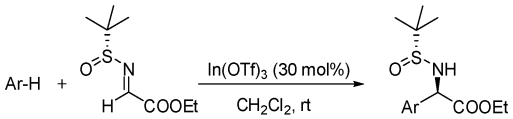
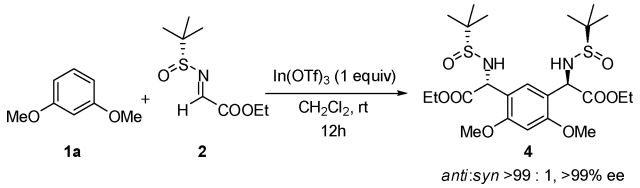
Entry	Product **3**	Ar	Time (h)	Yield (%)[b]	de (%)[c]
1	**3a**		1	89%	98%
2	**3b**		1	91%	97%
3	**3c**		8	84%	95%
4	**3d**		8	80%	98%
5	**3e**		1	86%	98%
6	**3f**		0.5	72%	93%
7	**3g**		8	60%	70%
8	**3h**		8	74%	73%
9	**3i**		8	72%	79%
10[d]	**3j**		8	66%[d]	>99%
11	**3k**		8	72%	>99%
12[e]	**3l**		1	74%[e]	98%
13	**3m**		1	70%	98%
14	**3n**		8	74%	98%
15	**3o**		1	90%	90%

Table 2 (*Contd.*)



Entry	Product **3**	Ar	Time (h)	Yield (%)[b]	de (%)[c]
16	**3p**		8	74%	79%

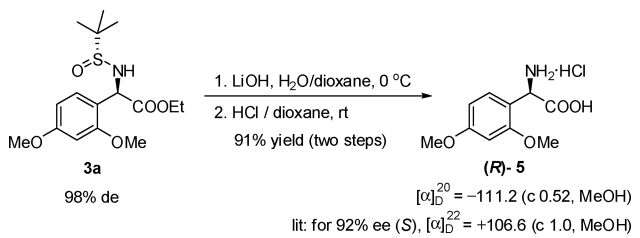
[a] Reactions were performed with 30 mol% of $In(OTf)_3$, 0.25 mmol of glyoxylate imine **2** and 0.375 mmol of arene **1** in 2.0 mL of dry CH_2Cl_2 at room temperature. [b] Yield of isolated and purified products. [c] The diastereoselectivity of the products was determined by measuring the enantiomeric excess of their acetyl or sulfonyl derivatives. [d] The regioisomer β-alkylation product **3j′** was obtained in 22% yield with >99% de. [e] The regioisomer β-alkylation product **3l′** was obtained in 15% yield with 97% de.



Scheme 2 Stereoselective double Friedel–Crafts alkylation.

4 in a significantly increased yield (43%) with an extremely high diastereo- and enantioselectivity (*anti* : *syn* > 99 : 1, >99% ee).

To realize the stereochemical outcome of the reaction, removal of the ethyl and *N*-sulfinyl groups was subsequently carried out. As exemplified by **3a**, the reactions proceeded smoothly under very mild conditions and yielded the free amino acid **5**. The absolute configuration of **3a** at α-stereogenic center was unambiguously determined to be *R* by comparison of the optical rotation of **5** with that of the known compound[4n] (Scheme 3). Assuming an analogous reaction mechanism, the same absolute configuration of the obtained α-arylglycines could be assigned.



Scheme 3 Removal of ethyl and *N*-sulfinyl groups.

To explain the observed diastereofacial selectivity of this asymmetric Friedel–Crafts alkylation, a plausible five-membered chelation transition state model as previously proposed[8l] is illustrated (Fig. 1), in which the activation of imino ester by the coordination of the Lewis acidic metal to both the imine nitrogen and carbonyl oxygen is considered. Since the uncoordinated *N*-sulfinyl group adopts an approximately synperiplanar configuration,[11] in the case of (*R*)-*N*-*tert*-butanesulfinyl imino ester, the bulky *tert*-butyl group is positioned at the *si*-face of imine molecule. As a result, the arene addition to the sterically unblocked *re*-face of the imine C=N

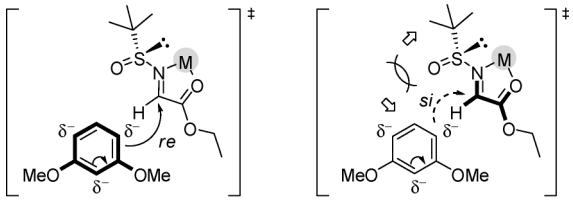


Fig. 1 Mechanistic proposals for stereocontrol.

bond would be preferred, thereby facilitating (*R*)-α-arylglycine product formation.

Conclusion

In summary, we have developed a highly diastereoselective synthesis of α-arylglycines *via* asymmetric Friedel–Crafts alkylation of arenes with a chiral *N*-*tert*-butanesulfinylimino ester. The reaction could be accomplished with ease in the presence of a catalytic amount of $In(OTf)_3$ at room temperature. It allows exceptionally mild, efficient and ready access to various enantiomerically enriched α-arylglycines. By this method, we have also successfully explored the potential of highly stereoselective double Friedel–Crafts alkylation to afford dialkylation product. Given the importance of α-arylglycines in medicinal chemistry and organic synthesis, application of this methodology is currently ongoing in our laboratory.

Experimental

General methods

Unless otherwise specified, all reactions were carried out in flame-dried glassware with magnetic stirring under an atmosphere of nitrogen. Solvents were dried and distilled by standard procedures. NMR spectra were recorded on Varian spectrometers (300 MHz for ^{1}H, and 100 MHz for ^{13}C). Chemical shifts are reported in δ (ppm) referenced to an internal $SiMe_4$ standard for ^{1}H NMR and chloroform-*d* (δ 77.16) for ^{13}C NMR. HPLC was performed on a JASCO 2000 instrument by using Daicel AS-H, AD-H and AD-3 column with 2-propanol/hexane as the eluent at 214 nm.

General procedure for $In(OTf)_3$-catalyzed Friedel–Crafts reaction of arenes 1 with (*R*)-*N*-*tert*-butanesulfinylimino ester 2

Under a nitrogen atmosphere, $In(OTf)_3$ (0.075 mmol, 30 mol%) was placed into a glass reaction vessel, glyoxylate imine **2** (0.25 mmol) in 2 mL of dry CH_2Cl_2 and arene **1** (0.375 mmol) were added successively. The mixture was stirred at room temperature and monitored by TLC. When the reaction was over, a saturated aq. NH_4Cl solution was added and the mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash chromatography to afford the corresponding α-arylglycine product **3**.

General procedure for determination of the diastereoselectivity/enantiomeric excess

The diastereoselectivities of the α-arylglycine products were measured as enantiomeric excess for their acetate or *N*-sulfonylate derivatives after the removal or oxidation of the sulfinyl group by chiral HPLC analysis. α-Arylglycines **3e** and **4** were converted to the corresponding *N*-sulfonylate, all others were converted to their acetate. The HPLC reference compound was a mixture of related products consisting of *R* and *S* enantiomers.

(*R*)-Ethyl 2-(2,4-dimethoxyphenyl)-2((*R*)-1,1-dimethylethylsulfinamido)acetate (3a)

89% yield, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (s, 9H), 1.18 (t, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 4.13–4.20 (m, 2H), 4.51 (d, J = 4.2 Hz, 1H), 5.19 (d, J = 4.2 Hz, 1H), 6.43–6.45 (m, 2H), 7.10 (d, J = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.14, 22.51, 55.39, 55.55, 55.82, 56.00, 61.85, 98.94, 104.22, 118.74, 130.12, 158.21, 161.03, 172.03; ESI-MS (*m*/*z*, %) 344 $[M + H]^+$; ESI-HRMS calcd for $C_{16}H_{25}NNaO_5S$ $[M + Na^+]$ 366.1351, found 366.1351.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(2,4,6-trimethoxyphenyl)acetate (3b)

91% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.17 (t, 3H), 3.77 (s, 6H), 3.80 (s, 3H), 4.09–4.22 (m, 2H), 4.58 (d, J = 5.1 Hz, 1H), 5.49 (d, J = 5.1 Hz, 1H), 6.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.27, 22.44, 51.35, 55.39, 55.76, 55.85, 61.59, 90.68, 107.92, 158.83, 161.38, 172.55; ESI-MS (*m*/*z*, %) 374 $[M + H]^+$; ESI-HRMS calcd for $C_{17}H_{27}NNaO_6S$ $[M + Na^+]$ 396.1457, found 396.1454.

(*R*)-Ethyl 2-(2,4-dimethoxy-6-methylphenyl)-2-((*R*)-1,1-dimethylethylsulfinamido)acetate (3c)

84% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (s, 9H), 1.16 (t, 3H), 2.36 (s, 3H), 3.73 (s, 3H), 3.78 (s, 3H), 4.09–4.21 (m, 2H), 4.63 (d, J = 3.0 Hz, 1H), 5.33 (d, J = 3.9 Hz, 1H), 6.29 (d, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.24, 20.24, 22.50, 53.44, 55.26. 55.63, 55.71, 61.79, 96.58, 107.05, 117.52, 139.22, 158.74, 160.17, 172.34; ESI-MS (*m*/*z*, %) 358 $[M + H]^+$; ESI-HRMS calcd for $C_{17}H_{28}NO_5S$ $[M + H^+]$ 358.1688, found 358.1697.

(*R*)-Ethyl 2-(2-chloro-4,6-dimethoxyphenyl)-2-((*R*)-1,1-dimethylethylsulfinamido)acetate (3d)

80% yield, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 9H), 1.18 (t, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 4.09–4.23 (m, 2H), 4.59 (d, J = 4.2 Hz, 1H), 5.60 (d, J = 4.2 Hz, 1H), 6.34 (d, J = 2.1 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.22, 22.44, 55.65, 55.91, 56.01, 62.07, 97.93, 106.12, 117.96, 135.60, 159.09, 160.55, 171.42; ESI-MS (*m*/*z*, %) 378 $[M + H]^+$; ESI-HRMS calcd for $C_{16}H_{24}ClNNaO_5S$ $[M + Na^+]$ 400.0961, found 400.0945.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(2,4,5-trimethoxyphenyl)acetate (3e)

86% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (s, 9H), 1.17 (t, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H),

4.11–4.21 (m, 2H), 4.51 (d, J = 3.3 Hz, 1H), 5.30 (d, J = 3.9 Hz, 1H), 6.51 (s, 1H), 6.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.15, 22.56, 55.13, 55.85, 56.09, 56.57, 56.93, 61.97, 97.96, 112.45, 117.52, 143.19, 149.81, 151.89, 171.98; ESI-MS (m/z, %) 396 [M + Na]$^+$; ESI-HRMS calcd for $C_{17}H_{27}NNaO_6S$ [M + Na$^+$] 396.1457, found 396.1455.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(2-hydroxy-4,5-dimethoxyphenyl)acetate (3f)

72% yield, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, 3H), 1.25 (s, 9H), 4.10–4.28 (m, 2H), 4.52 (d, J = 1.5 Hz, 1H), 5.21 (d, J = 2.7 Hz, 1H), 5.89 (s, 2H), 6.46 (s, 1H), 6.62 (s, 1H), 7.90 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.16, 22.71, 55.87, 56.30, 62.49, 99.56, 101.35, 108.15, 113.68, 141.28, 148.77, 150.90, 171.63; ESI-MS (m/z, %) 344 [M + H]$^+$; ESI-HRMS calcd for $C_{15}H_{21}NNaO_6S$ [M + Na+] 366.0987, found 366.0963.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(2,3,4-trimethoxyphenyl)acetate (3g)

60% yield, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (s, 9H), 1.18 (t, 3H), 3.84 (s, 6H), 3.88 (s, 3H), 4.11–4.24 (m, 2H), 4.59 (d, J = 3.9 Hz, 1H), 5.18 (d, J = 3.6 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.13, 22.61, 55.75, 55.84, 55.98, 60.77, 61.14, 62.06, 106.98, 123.75, 123.90, 142.15, 151.91, 154.07, 171.84; ESI-MS (m/z, %) 374 [M + H]$^+$; ESI-HRMS calcd for $C_{17}H_{27}NNaO_6S$ [M + Na$^+$] 396.1457, found 396.1467.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(2,3,4-trimethoxy-6-methylphenyl)acetate (3h)

74% yield, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (s, 9H), 1.18 (t, 3H), 2.34 (s, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.08–4.22 (m, 2H), 4.73 (d, J = 1.2 Hz, 1H), 5.29 (d, J = 2.7 Hz, 1H), 6.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.22, 19.97, 22.61, 53.61, 55.76, 55.82, 60.70, 60.98, 61.99, 109.11, 122.28, 132.79, 139.91, 152.28, 153.17, 172.08; ESI-MS (m/z, %) 388 [M + H]$^+$; ESI-HRMS calcd for $C_{18}H_{30}NO_6S$ [M + H$^+$] 388.1794, found 388.1791.

(*R*)-Ethyl 2-(2,4-dimethoxy-3-methylphenyl)-2-((*R*)-1,1-dimethylethylsulfinamido)acetate (3i)

72% yield, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16–1.18 (m, 12H), 2.15 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 4.09–4.23 (m, 2H), 4.59 (d, J = 3.0 Hz, 1H), 5.27 (d, J = 3.9 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.56, 14.15, 22.67, 55.09, 55.66, 55.84, 61.55, 62.10, 106.18, 119.99, 123.10, 126.58, 157.46, 159.03, 172.15; ESI-MS (m/z, %) 380 [M + Na]$^+$; ESI-HRMS calcd for $C_{17}H_{27}N_1NaO_5S$ [M + Na$^+$] 380.1508, found 380.1506.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(4-methoxynaphthalen-1-yl)acetate (3j)

66% yield, white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, 3H), 1.13 (s, 9H), 4.01 (s, 3H), 4.08–4.21 (m, 2H), 4.66 (s, 1H), 5.50 (s, 1H), 6.76 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.47–7.51 (m, 2H), 7.98 (d, J = 7.8 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.08, 22.63, 55.63, 55.79, 59.32, 62.33, 102.97, 122.79, 123.90, 124.34, 125.33, 126.33, 126.95, 128.62, 131.90, 156.24, 172.41; ESI-MS (m/z, %) 364 [M + H]$^+$; ESI-HRMS calcd for $C_{19}H_{25}NNaO_4S$ [M + Na$^+$] 386.1402, found 386.1411.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(1-methoxynaphthalen-2-yl)acetate (3j′)

22% yield, white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (t, 3H), 1.21 (s, 9H), 4.00 (s, 3H), 4.07–4.21 (m, 2H), 5.73 (d, J = 3.9 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 7.47–7.61 (m, 3H), 8.18 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.12, 22.65, 55.68, 56.46, 56.74, 61.88, 103.27, 122.85, 123.40, 125.06, 125.51, 126.11, 127.19, 127.46, 131.78, 156.21, 172.01; ESI-MS (m/z, %) 364 [M + H]$^+$; ESI-HRMS calcd for $C_{19}H_{25}NNaO_4S$ [M + Na$^+$] 386.1402, found 386.1390.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(2-methoxynaphthalen-1-yl)acetate (3k)

72% yield, white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06–1.10 (m, 12H), 3.98 (s, 3H), 4.11–4.18 (m, 2H), 4.76 (s, 1H), 6.10 (s, 1H), 7.28–7.36 (m, 2H), 7.46 (dd, J = 8.4 Hz, 7.2 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.14, 22.51, 52.18, 55.69, 57.17, 62.12, 113.67, 118.42, 123.34, 123.76, 127.09, 128.75, 129.47, 130.90, 132.31, 155.83, 172.77; ESI-MS (m/z, %) 364 [M + H]$^+$; ESI-HRMS calcd for $C_{19}H_{26}NO_4S$ [M + H$^+$] 364.1582, found 364.1578.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(4-hydroxynaphthalen-1-yl)acetate (3l)

74% yield, yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, 3H), 1.18 (s, 9H), 4.09–4.18 (m, 2H), 4.77 (d, J = 2.1 Hz, 1H), 5.49 (d, J = 2.1 Hz 1H), 6.78 (d, J = 7.8 Hz 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.43–7.46 (m, 2H), 7.92–7.96 (m, 1H), 8.18 (s, 1H), 8.28–8.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.04, 22.74, 56.03, 59.76, 62.42, 107.83, 122.59, 123.16, 123.86, 124.93, 125.69, 126.80, 129.66, 132.14, 153.98, 172.40; ESI-MS (m/z, %) 350 [M + H]$^+$; ESI-HRMS calcd for $C_{18}H_{23}NNaO_4S$ [M + Na$^+$] 372.1246, found 372.1244.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(1-hydroxynaphthalen-2-yl)acetate (3l′)

15% yield, yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, 3H), 1.28 (s, 9H), 4.11–4.29 (m, 2H), 4.59 (s, 1H), 5.36 (d, J = 2.7 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.45–7.52 (m, 2H), 7.76–7.79 (m, 1H), 8.26–8.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.11, 22.68, 56.53, 57.25, 62.76, 114.46, 120.34, 122.67, 125.57, 126.79, 127.07, 127.51, 134.83, 151.71, 171.29; ESI–MS (m/z, %) 372 [M + Na]$^+$; ESI-HRMS calcd for $C_{18}H_{23}NNaO_4S$ [M + Na$^+$] 372.1246, found 372.1253.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(2-hydroxynaphthalen-1-yl)acetate (3m)

70% yield, yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (t, 3H), 1.21 (s, 9H), 4.05–4.18 (m, 2H), 4.82 (s, 1H), 6.22 (s, 1H),7.17 (d, J = 8.7 Hz, 1H), 7.26 (dd, J = 6.6 Hz, 8.4 Hz, 1H), 7.39 (dd,

J = 8.4 Hz, 7.2 Hz, 1H), 7.67–7.74 (dd, J = 8.7 Hz, 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 1H), 9.55 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.07, 22.72, 52.00, 55.76, 62.32, 112.46, 118.40, 122.77, 122.90, 126.69, 128.74, 128.95, 130.81, 132.61, 155.18, 173.00; ESI-MS (m/z, %) 372 [M + Na]$^+$; ESI-HRMS calcd for $C_{18}H_{23}NNaO_4S$ [M + Na$^+$] 372.1246, found 372.1246.

(*R*)-Ethyl 2-(2,7-dimethoxynaphthalen-1-yl)-2-((*R*)-1,1-dimethylethylsulfinamido)acetate (3n)

74% yield, white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05–1.24 (m, 12H), 3.86 (s, 3H), 3.95 (s, 3H), 4.10–4.17 (m, 2H), 4.71 (s, 1H), 6.06 (s, 1H), 6.96–7.00 (dd, J = 1.5 Hz, 8.7 Hz, 1H), 7.11 (d, J = 8.7 Hz, 1H), 7.25 (d, J = 1.5 Hz, 1H), 7.64 (d, J = 9.3 Hz, 1H), 7.74 (d, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.16, 14.29, 22.55, 52.14, 55.33, 55.57, 57.00, 62.09, 101.66, 110.87, 116.61, 124.82, 130.20, 130.53, 133.79, 156.50, 158.59, 172.88; ESI-MS (m/z, %) 416 [M + Na]$^+$; ESI-HRMS calcd for $C_{20}H_{27}NNaO_5S$ [M + Na$^+$] 416.1508, found 416.1516.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(5-methylfuran-2-yl)acetate (3o)

90% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (s, 9H), 1.25 (t, 3H), 2.25 (s, 3H), 4.19–4.28 (m, 2H), 4.41 (d, J = 4.8 Hz, 1H), 5.03 (d, J = 5.4 Hz, 1H), 5.91 (s, 1H), 6.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.07, 14.13, 22.57, 55.36, 56.23, 62.52, 106.53, 109.86, 147.66, 153.04, 169.70; ESI-MS (m/z, %) 310 [M + Na]$^+$; ESI-HRMS calcd for $C_{13}H_{21}NNaO_4S$ [M + Na$^+$] 310.1089, found 310.1094.

(*R*)-Ethyl 2-((*R*)-1,1-dimethylethylsulfinamido)-2-(5-methylthiophen-2-yl)acetate (3p)

74% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (m, 12H), 2.44 (s, 3H), 4.18–4.28 (m, 2H), 4.57 (d, J = 4.8 Hz, 1H), 5.20 (d, J = 4.8 Hz, 1H), 6.60–6.61 (m, 1H), 6.84 (d, J = 3.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.14, 15.54, 22.73, 56.35, 56.95, 62.60, 125.18, 126.38, 137.78, 140.82, 170.57; ESI-MS (m/z, %) 326 [M + Na]$^+$; ESI-HRMS calcd for $C_{13}H_{21}NNaO_3S_2$ [M + Na$^+$] 326.0860, found: 326.0862.

(2*R*,2′*R*,26*R*)-Diethyl-2,2′-(4,6-dimethoxy-1,3-phenylene)bis(2-((*R*)-1,1-dimethylethylsulfinamido)acetate) (4)

43% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14–1.20 (m, 24H), 3.85 (s, 6H), 4.08–4.21 (m, 4H), 4.51 (d, J = 4.2 Hz, 2H), 5.29 (d, J = 4.2 Hz, 2H), 6.44 (s, 1H), 7.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.17, 22.58, 55.00, 55.87, 55.90, 61.94, 95.56, 118.29, 129.81, 158.38, 171.73; ESI-MS (m/z, %) 549 [M + H]$^+$; ESI-HRMS calcd for $C_{24}H_{40}N_2NaO_8S_2$ [M + Na$^+$] 571.2124, found 571.2133.

The synthesis of (*R*)-2-(chloroamino)-2-(2,4-dimethoxyphenyl)-acetic acid ((*R*)-5)

To a round bottomed flask containing LiOH (37.8 mg, 0.9 mmol, 10 equiv) was added distilled H_2O (5.0 mL), and the resulting solution was cooled to 0 °C. A solution of **3a** (30.0 mg, 0.09 mmol, 1.0 equiv) in dioxane (5.0 mL) was cannulated into the reaction flask. The resulting solution was stirred at 0 °C for 3 h. The reaction mixture was then concentrated to remove the dioxane, and the remaining material was diluted with distilled H_2O (3 mL) and EtOAc (3 mL) and placed in a separatory funnel. 1 N $NaHSO_4$ (2 mL) was added and the aqueous layer was extracted with EtOAc (5 × 4 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was isolated with no further purification as a white solid. Subsequently, the crude product was treated with 5 mL solution of dry HCl in 1,4-dioxane at room temperature for 1 h. The reaction mixture was concentrated *in vacuo*, and the amine hydrochloride was precipitated with dry diethyl ether. The precipitate was collected by filtration and washed with diethyl ether to yield the (*R*)-**5** (20 mg, 91% yield) as a white solid.

(*R*)-2-(Chloroamino)-2-(2,4-dimethoxyphenyl)acetic acid ((*R*)-5)

91% yield, white solid. $[\alpha]_D^{20}$ −111.2 (*c* 0.5, MeOH); The absolute configuration was determined to be (*R*) according to literature [lit[4n] $[\alpha]_D^{22}$ = +106.6 (*c* 1.0 MeOH)]. ^{1}H NMR (300 MHz, CD_3OD): δ 3.83 (s, 3H), 3.88 (s, 3H), 5.10 (s, 1H), 6.58–6.61 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.64 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 53.75, 56.06, 56.24, 99.73, 106.42, 114.21, 132.48, 159.90, 164.16, 171.17.

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