

α -Amino cyclic dithioketal mediated asymmetric synthesis of (*S*)-(-)- α -(*N*-*p*-toluenesulfonyl)aminopropiophenone (*N*-tosyl cathinone)

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Abstract

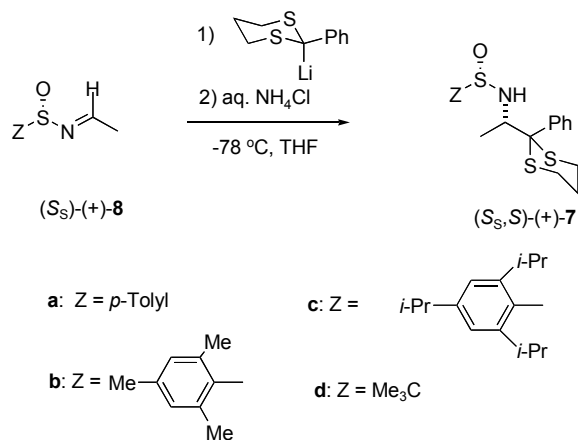
The asymmetric synthesis of *N*-tosyl cathinone, a high reactive α -amino ketone, via the addition of 2-lithio-2-phenyl-1,3-dithiane to a sulfinimine (*N*-sulfinyl imine), is described. It was found that the resistance of *N*-tosyl α -amino ketones to epimerization is related to the ability of this protecting group to stabilize anions at nitrogen.

Keywords: Sulfinimine (*N*-sulfinyl imine), asymmetric synthesis, 1,3-dithiane, cathinone, α -amino ketones, *N*-protection, epimerization

Introduction

Recently we described a new approach for the asymmetric synthesis of α -amino aldehydes and ketones which are valuable chiral building blocks widely used in asymmetric synthesis.^{1,2} This protocol involves addition of 2-lithio-1,3-dithianes to enantiopure sulfinimines (*N*-sulfinyl imines) (*S_S*)-**1** to give *N*-sulfinyl α -amino cyclic dithioketals **2a** ($R' = \text{alkyl, aryl}$)³ and acetals **2b** ($R' = \text{H}$)⁴ in good yield and high diastereoselectivity (Scheme 1). Removal of the thioketal group in **2a** was selectively accomplished using the Stork reagent bis(trifluoroacetoxy)iodobenzene [$\text{PhI}(\text{O}_2\text{CCF}_3)_2$], affording the *N*-sulfinyl α -amino ketones (*S_{S,S}*)-**4** without epimerization.³ Similar treatment of **2b** resulted in decomposition, but with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, **3**) they gave the *N*-tosyl α -amino aldehydes (*S*)-**5**, again without epimerization.⁴ We describe here the synthesis of (*S*)-(-)- α -(*N*-*p*-toluenesulfonyl)aminopropiophenone (*N*-tosyl cathinone), and as a result further define the scope and limitations of the asymmetric synthesis of α -amino ketones using α -amino cyclic dithioketals.

and co-workers reported that the presence of Lewis acids improved the stereoselectivity for 2-lithio-1,3-dithiane addition to sulfinimines.¹⁴ However, we observed just the opposite for $\text{BF}_3 \cdot \text{OEt}_2$ and MgBr_2 , which result in lower de's and yields (Table 1, entries 2 and 3).



Scheme 3. Synthesis of α -amino cyclic dithioketals.

Table 1. Addition of 2-lithio-2-phenyl-1,3-dithiane to sulfinamides at $-78\text{ }^\circ\text{C}$ in THF

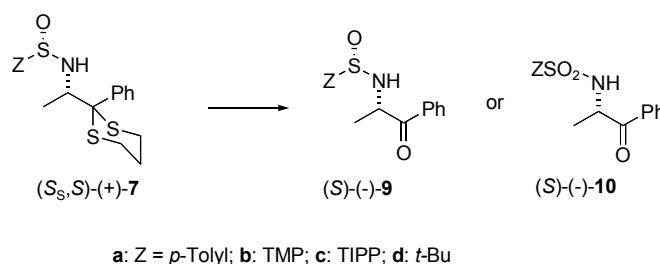
Entry	(S _S)- 8 (Z)	Lewis acid	% yield ^a [% de] ^b
1	8a (<i>p</i> -Tolyl)		7a , 68 ^c [71]
2	8a (<i>p</i> -Tolyl)	$\text{BF}_3 \cdot \text{OEt}_2$ ^d	7a , 55 ^c [48]
3	8a (<i>p</i> -Tolyl)	$\text{MgBr}_2 \cdot \text{OEt}_2$ ^d	7a , 47 ^c [59]
4	8b (TMP)		7b , 65 [58]
5	8c (TIPP)		7c , 80 [73]
6	8d (<i>t</i> -Bu)		7d , 30 [>98]
7	8d (<i>t</i> -Bu)		7d , 70 ^e [>98]

^aIsolated yield of major diastereoisomer. ^bDetermined by ^1H NMR on the crude reaction mixture. ^cCombined yield of inseparable diastereoisomers. ^dTwo equiv added. ^eTwo equiv of 2-lithio-2-phenyl-1,3-dithiane were added.

The inability to separate diastereoisomers is occasionally observed in the addition of carbanion species to sulfinimines and can often be overcome by changing the Z group linked to sulfinyl moiety.¹⁵ Diverse enantiopure *N*-sulfinyl imines can be prepared using the *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide chiral auxiliary introduced by Senanayake and co-workers.¹⁶ This research group also reported that the diastereoselectivity for Grignard addition to sulfinimines improves as the steric size of the *N*-sulfinyl moiety increases.^{16b} Importantly, we found that the reaction of (S_S)-**8b** and (S_S)-**8c**, showing in turn 2,4,6-trimethylphenyl (TMP) and 2,4,6-triisopropylphenyl (TIPP) groups linked to sulfur atom, resulted in separable mixtures of isomers affording (S_S,S)-**7b** and (S_S,S)-**7c** in 65 and 80 % isolated yields, respectively (Scheme 3 and

Table 1, entries 4 and 5). However, the effect of *Z*'s size on the stereoselectivity was unclear. Best results were observed for the *N*-*tert*-butanesulfinyl group where only a single diastereoisomer was obtained. However, the reaction was slow resulting in only 30% of (*S*_s,*S*)-(+)-**7d** after 0.5 h. With two equiv of 2-lithio-2-phenyl-1,3-dithiane the yield of (+)-**7d** improved to 70% (Table 1, entry 7).

Next, we explored the selective hydrolysis of the thioketal moiety in **7a-d** using DBDMH (**3**) and bis(trifluoroacetoxy)iodobenzene (Scheme 4). These results are summarized in Table 2. For *Z* = *p*-tolyl, earlier results had shown that **3** not only hydrolyzes the thioketal group but also oxidizes the *p*-toluenesulfinyl group to a tosyl group.⁴ Bis(trifluoroacetoxy)iodobenzene was more selective leaving the *p*-toluenesulfinyl group intact.³ In both examples there was no epimerization of the α -amino carbonyl compounds.



Scheme 4. Hydrolysis of *N*-sulfinyl α -amino dithioketals.

The results summarized in Table 2 reveal that hydrolysis with $\text{PhI}(\text{O}_2\text{CCF}_3)_2$ of **7a**, **7b**, and **7c**, where the *N*-sulfinyl *Z* group is aryl, gives the corresponding *N*-sulfinyl α -amino ketones **9** in good yield. However, the only compound which did not experience some racemization was **9a** where *Z* is *p*-tolyl (Table 2, entry 1), while **9b** and **9c** with the TMP and TIPP *N*-sulfinyl groups respectively exhibited some epimerization (Table 2, entries 3 and 5). For **7d** where the *Z* group is *tert*-butyl (*t*-Bu) complete racemization occurred (Table 2, entry 7). For **7a**, **7b**, and **7c** hydrolysis with **3** (DBDMH) afforded the corresponding sulfonamides **10a**, **10b**, and **10c** in moderate yields (Table 2, entries 2, 4, and 6). However, with **7d** decomposition was the result (Table 2, entry 8).

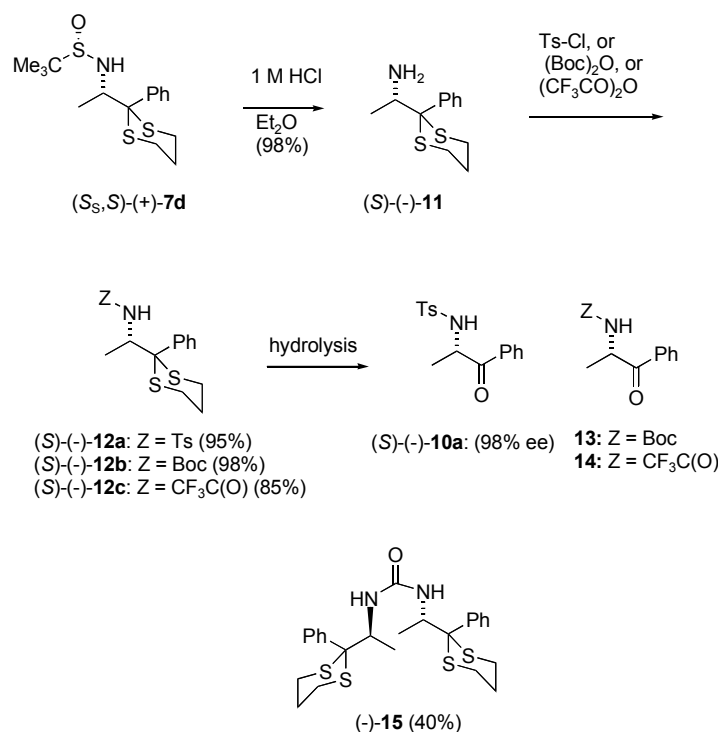
One of the advantages of preparing α -amino carbonyl compounds from sulfinimines and lithio-1,3-dithianes is that the *N*-sulfinyl group can be easily removed in the *N*-sulfinyl α -aminoalkyl 1,3-dithiane product. This means that the free amino group can be re-protected with a group more amenable to hydrolysis of the thioketal group, one that does not lead to epimerization. To explore this possibility (*S*_s,*S*)-(+)-**7d** (>98% de) was treated with 1 N HCl in ether to give (*S*)-(-)-2-(α -aminoethyl)-1,3-dithiane (**11**) in 98% yield (Scheme 5). The amino group was re-protected as the tosylate with TsCl to give (-)-**12a**, with $(\text{Boc})_2\text{O}$ to give (-)-**12b**, and with trifluoroacetic anhydride (TFAA) to give (-)-**12c**. In using *N,N*-dimethyl-4-aminopyridine (DMAP) to affect the *N*-Boc protection of (-)-**11** low yields of **12b** (ca 20%) resulted with the formation of urea (-)-**15** in 40% yield. Ureas, such as **15**, have been noted by

others.¹⁷ The formation of **15** was avoided by omitting the use of DMAP, so affording (*S*)-(-)-**12b** in 98% yield.

Table 2. Hydrolysis of thioketals **7** and **12**

Entry	Ketal 7 (<i>Z</i>) [% de or ee]	Reagents	Amino ketone, % yield ^a (% de ^b or ee ^c)
1	7a (<i>p</i> -Tolyl) [71]	PhI(O ₂ CCF ₃) ₂	9a , 60 (70)
2	7a (<i>p</i> -Tolyl) [71]	DMDBH	10a , 60 (70)
3	7b (TMP) [>98]	PhI(O ₂ CCF ₃) ₂	9b , 50 (66) ^b
4	7b (TMP) [>98]	DMDBH	10b , 30 (40)
5	7c (TIPP) [>98]	PhI(O ₂ CCF ₃) ₂	9c , 33 (60) ^b
6	7c (TIPP) [>98]	DMDBH	10c , 25
7	7d (<i>t</i> -Bu) [>98]	PhI(O ₂ CCF ₃) ₂	9d , 70 (0)
8	7d (<i>t</i> -Bu) [>98]	DMDBH	decomposition
9	12a (Ts) [98]	DMDBH	10a , 96 (>98) ^c
10	12b (Boc) [98]	DMDBH	13 , 78 (0)
11	12b (Boc) [98]	PhI(O ₂ CCF ₃) ₂	13 , 70 (0)
12	12b (Boc) [98]	HgCl ₂	13 , 28 (0)
13	12b (Boc) [98]	DMI	13 , 46 (0)
14	12c (CF ₃ CO)	DMDBH	14 , 60 (>96) ^d

^aIsolated yield. ^bDetermined by ¹H NMR on the crude reaction mixture. ^cDetermined by comparison of the rotation with literature values. See ref. 10. ^dDetermined using Eu(hfbc)₃ and ¹⁹F NMR as previously described. See ref. 20.



Scheme 5. Hydrolysis of *N*-protected α -amino cyclic dithioketals.

Hydrolysis of (-)-**12a** (Z = Ts) with **3** afforded (*S*)-(-)- α -(*N*-tosyl)aminopropiophenone (**10a**) in 96% yield and better than 98% ee (Table 2, entry 9).¹⁰ The synthesis of (*S*)-(-)-**10a** represents a formal asymmetric synthesis of (-)-cathinone (**6**). Interestingly, similar hydrolysis of the *N*-Boc (-)-**12b** with **3** or PhI(O₂CCF₃)₂ resulted in good yields of **13**, but the product was racemic (Table 2, entries 10 and 11). Hydrolysis with HgCl₂-CH₃CN-H₂O and Dess-Martin periodinane (DMI) also resulted in racemization (Table 2, entries 12 and 13).

From the above studies, it appears that only the tosyl and sulfinyl *N*-protecting groups are able to prevent racemization of the α -amino carbonyl moiety under the conditions employed for thioketal hydrolysis (Table 2, entries 1 and 2). Racemization results from the removal of the α -proton in the α -amino carbonyl compound forming the enol. Earlier we remarked on the superior protecting group abilities of the *N*-tosyl group for preventing racemization of α -amino carbonyl compounds because of its ability to stabilize anions at nitrogen.⁴ The lesser ability of the *N*-Boc group to stabilize anions at nitrogen is reflected in the epimerization (-)-**12b** under the hydrolysis conditions (Table 2, entries 10-13). In support of this argument there is the fact that hydrolysis of (-)-**12c**, which has the *N*-trifluoroacetyl protecting group, did not result in epimerization (Table 2, entry 14). The anion stabilizing effects of tosyl, Boc, and CF₃C(O) can be estimated from Hammett σ_p values of 0.72, 0.45, and 0.8 respectively.²¹ Since the σ_p for MeS(O) is 0.49, similar to Boc, this strongly suggests that the arenesulfinyl groups in **7a-c** are first oxidized by **3** to the corresponding arenesulfonyl groups prior to hydrolysis of the thioketal moiety.

Conclusions

In conclusion, a four step synthesis of (*S*)-(-)- α -(*N*-tosyl)aminopropiophenone (**10a**), with an overall yield of 62% is described involving the addition 2-lithio-2-phenyl-1,3-dithiane to a sulfinimine. This represents a highly efficient formal asymmetric synthesis of the alkaloid cathinone, a reactive α -amino ketone that is not stable without suitable *N*-protection. The highest diastereoselectivities were observed for addition of the 2-lithio-1,3-dithiane to the *tert*-butane-derived sulfinimine of acetaldehyde (+)-**8d**. However, hydrolysis of the thioketal moiety resulted in decomposition and it was avoided by its conversion into the corresponding *N*-tosyl derivative. These results further emphasize the superior protecting group ability of the *N*-tosyl group for α -amino carbonyl compounds. A variety of methods are now available for the facile cleavage of sulfonamides.²²

Experimental Section

General Procedures. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless otherwise noted. ¹H NMR and ¹³C NMR spectra were recorded at 400 and 100 MHz, respectively. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. Sulfinimines **8a**,¹³ **8b**, **8c**, and **8d** were prepared by condensing acetaldehyde with (*S_S*)-(+)-*p*-toluenesulfinamide,¹³ (*S_S*)-(+)-2,4,6-trimethylbenzenesulfinamide,^{16,18} (*S_S*)-(+)-2,4,6-triisopropylbenzenesulfinamide,¹⁶ and (*S_S*)-(+)-*tert*-butanesulfinamide.¹⁹

General procedure for synthesizing (*S_S*,*E*)-*N*-ethylidenesulfinamides. (*S_S*,*E*)-*N*-Ethylidene-2,4,6-trimethylbenzenesulfinamide (**8b**). Typical Procedure

In a 50 mL round bottom flask equipped with stirring bar and argon balloon 0.100 g (0.546 mmol) of (+)-2,4,6-trimethylbenzenesulfinamide, 0.185 mL (3.297 mmol) of acetaldehyde, and 0.570 mL (2.719 mmol) of Ti(OEt)₄ (Aldrich) in 10 mL of CH₂Cl₂ were placed. After stirring at rt for 1.5 h and monitoring by TLC, the reaction was quenched at 0 °C by addition of H₂O (10 mL). The turbid solution was filtered through Celite, and the filter cake was washed with CH₂Cl₂ (2 × 10 mL). The aqueous phase was washed with CH₂Cl₂ (10 mL), the combined organic portions were dried (Na₂SO₄) and concentrated. Flash chromatography (EtOAc/hexane, 3:7) afforded 0.100 g (88%) of a colourless oil; [α]_D²⁰ + 311.5 (*c* 0.32, CHCl₃); IR (NaCl) 2923, 2854, 1623, 1456, 1086; ¹H NMR (C₆D₆) δ 8.32 (q, *J* = 4.8 Hz, 1 H), 6.84 (s, 2 H), 2.45 (s, 6 H), 2.26 (s, 3 H), 2.24 (d, *J* = 4.8 Hz, 3 H); ¹³C NMR (C₆D₆) δ 164.5, 141.9, 138.5, 135.4, 131.1, 22.4, 21.3, 18.9; HRMS calculated for C₁₁H₁₆NOS (M+H) 210.0953. Found 210.0946.

(*S_S*,*E*)-*N*-Ethylidene-2,4,6-triisopropylbenzenesulfinamide (8c**).** Flash chromatography (EtOAc/hexane, 3:7) afforded 62% yield of a white solid, mp 84.0 °C; [α]_D²⁰ +219.6 (*c* 0.97,

CHCl₃); IR (NaCl) 1459, 1068; ¹H NMR (CDCl₃) δ 8.33 (q, J = 5.2 Hz, 1 H), 7.05 (s, 2 H), 3.74 (m, 2 H), 2.85 (m, 1 H), 2.22 (d, J = 4.8 Hz, 3 H), 1.24 (d, J = 6.8 Hz, 6 H), 1.20 (d, J = 6.4 Hz, 6 H), 1.19 (d, J = 6.8 Hz, 6 H); ¹³C NMR (CDCl₃) δ 164.4, 153.1, 149.9, 123.3, 34.7, 28.1, 24.7, 24.2, 24.1, 22.9. HRMS calculated for C₁₇H₂₈NOS (M+H) 294.1892. Found 294.1894.

(S_S,E)-N-Ethylidene-2-methylpropane-2-sulfinamide (8d). Flash chromatography (EtOAc/hexane, 3:7) afforded 92% yield of a colourless oil; [α]_D²⁰ -94.8 (c 1.00, CHCl₃); IR (NaCl) 1626, 1081 cm⁻¹; ¹H NMR (CDCl₃) δ 7.94 (1H, q, J = 5.1 Hz), 2.34 (3H, d, J = 5.1 Hz), 1.09 (9H, s); ¹³C NMR (CDCl₃) δ 165.8, 56.3, 55.0, 22.1. HRMS calculated for C₆H₁₄NOS (M+H) 148.0796. Found 148.0791.

General procedure for addition of 2-lithio-2-phenyl-1,3-dithiane to sulfinimines. (S_S,S)-2-Phenyl-2-[[1-N-(p-toluenesulfinyl)amino]ethyl]-1,3-dithiane (7a) (major diastereoisomer)

In a 25 mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon 2-phenyl-1,3-dithiane (0.160 g, 0.815 mmol) was placed in THF (3 mL), the solution was cooled to -20 °C and BuLi (0.44 mL, 1.100 mmol, 2.5 M in hexanes) was added slowly. After 1.5 h, the solution was cooled to -78 °C and added via cannula to a solution of (S_S)-(-)-**8a** (0.100 g, 0.552 mmol) in THF (3 mL) maintained at -78 °C. The reaction mixture was stirred for 0.5 h and quenched at -78 °C by addition of sat. NH₄Cl solution (1 mL). EtOAc (5 mL) was added to the solution, the aqueous phase was washed with EtOAc (2×10 mL), and the combined organic phases were washed with brine (5 mL), dried (Na₂SO₄), and concentrated. Flash chromatography (EtOAc/hexane, 3:7) afforded 0.140 g (68%) of an oil as a mixture of inseparable diastereoisomers; ¹H NMR (CDCl₃) δ 7.94 (d, J = 7.6 Hz, 1.73 H), 7.86 (d, J = 7.6 Hz, 0.30 H), 7.71 (d, J = 8.0 Hz, 1.65 H), 7.58 (d, J = 8.0 Hz, 0.34 H), 7.38 (t, J = 7.2 Hz, 2 H), 7.29 (t, J = 7.6 Hz, 3 H), 4.63 (d, J = 6.0 Hz, 0.13 H), 4.04 (m, 0.83 H), 3.79 (d, J = 10.4 Hz, 0.82 H), 3.68 (m, 0.18 H), 2.69 (m, 4 H), 2.43 (s, 0.46 H), 2.42 (s, 2.65 H), 1.91 (m, 2 H), 1.31 (d, J = 6.8 Hz, 0.46 H), 1.21 (d, J = 6.8 Hz, 2.62 H). HRMS calculated for C₁₉H₂₄NOS₃ (M+H) 378.1020. Found 378.1027.

(S_S,S)-2-[[1-N-(2,4,6-Trimethylbenzenesulfinyl)amino]ethyl]-2-phenyl-1,3-dithiane (7b). Flash chromatography (EtOAc/hexane, 3:7) gave 54% yield of a colourless oil; [α]_D²⁰ +86.2 (c 0.98, CHCl₃); IR (NaCl) 3745, 2928, 1078; ¹H NMR (CDCl₃) δ 7.86 (d, J = 7.2 Hz, 2 H), 7.36 (t, J = 7.6 Hz, 3 H), 7.26 (t, J = 7.2 Hz, 1 H), 6.83 (s, 2 H), 4.06 (d, J = 10 Hz, 1 H), 3.95 (m, 1 H), 2.63 (m, 4 H), 2.53 (s, 6 H), 2.28 (s, 3 H), 1.87 (m, 2 H), 1.28 (d, J = 6.4 Hz, 3 H); ¹³C NMR (CDCl₃) δ 140.7, 139.3, 138.6, 136.6, 128.9, 127.7, 65.6, 62.5, 27.7, 25.2, 21.4, 19.9. HRMS calculated for C₂₁H₂₈NOS₃ (M+H) 406.1333. Found 406.1335.

(S_S,S)-2-Phenyl-2-[[1-N-(2,4,6-triisopropylbenzenesulfinyl)amino]ethyl]-1,3-dithiane (7c). Flash chromatography (EtOAc/hexane, 1:9) gave 48% yield of a colourless oil; [α]_D²⁰ +52.7 (c 0.59, CHCl₃); IR (NaCl) 3720, 2918, 1084 cm⁻¹; ¹H NMR (CDCl₃) δ 7.86 (m, 2 H), 7.34 (m, 2 H), 7.26 (m, 1 H), 7.05 (s, 2 H), 4.21 (d, J = 9.6 Hz, 1 H), 3.94 (m, 3 H), 2.88 (m, 1 H), 2.63 (m, 4 H), 1.87 (m, 2 H), 1.30 (d, J = 6.4 Hz,), 1.25 (t, J = 6.8 Hz, 12 H), 1.21 (d, J = 7.2 Hz, 6 H); ¹³C NMR (CDCl₃) δ 151.6, 147.4, 139.0, 138.1, 130.4, 128.9, 127.6, 123.0, 65.1, 62.7, 34.4, 28.6,

27.6, 27.5, 25.0, 24.7, 24.3, 23.9, 19.8. HRMS calculated for $C_{27}H_{39}NNaOS_3$ (M+Na) 512.2091. Found 512.2099.

(*S,S*)-2-{[1-*N*-(2-Methylpropane-2-sulfinyl)amino]ethyl}-2-phenyl-1,3-dithiane (7d). In a 25 mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic bar, rubber septum, and argon balloon 2-phenyl-1,3-dithiane (0.260 g, 1.324 mmol) in THF (4 mL) was placed, the solution was cooled to $-20\text{ }^{\circ}\text{C}$ and BuLi (0.71 mL, 1.775 mmol, 2.5 M in hexanes) was added slowly. After 1.5 h, the resulting solution was cooled to $-78\text{ }^{\circ}\text{C}$ and added via cannula to a solution of (*S*_S)-(-)-**8a** (0.100 g, 0.552 mmol) in THF (3 mL) maintained at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 0.5 h and quenched at $-78\text{ }^{\circ}\text{C}$ by addition of sat. NH_4Cl solution (1 mL). EtOAc (5 mL) was added to the solution, the aqueous phase was washed with EtOAc (2 \times 10 mL), and the combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc/hexane, 3:7) gave 0.130 g (68%) of a colourless oil; $[\alpha]_D^{20} +36.0$ (*c* 0.53, CHCl_3); IR (NaCl) 3220, 2903, 1443, 1069 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.89 (m, 2 H), 7.34 (m, 2 H), 7.23 (m, 1 H), 3.74 (m, 1 H), 2.81 (d, *J* = 10.8 Hz, 1 H), 2.56 (m, 4 H), 1.83 (m, 2 H), 1.18 (d, *J* = 7.2 Hz, 3 H), 1.16 (s, 9 H); ^{13}C NMR (CDCl_3) δ 137.9, 130.8, 128.9, 127.9, 65.7, 62.8, 57.5, 27.8, 27.7, 25.3, 23.2, 19.6. HRMS calculated for $C_{16}H_{26}NOS_3$ (M+H) 344.1176. Found 344.1178.

General procedure for hydrolysis of *N*-sulfinyl α -aminoethyl 1,3-dithianes using bis(trifluoroacetoxy)iodobenzene [$\text{PhI}(\text{O}_2\text{CCF}_3)_2$]. (*S,S*)-2-[*N*-(2,4,6-Trimethylbenzenesulfinyl)amino]-1-phenylpropan-1-one (9b)

In a 25 mL, oven-dried, one-necked, round-bottomed flask equipped with a magnetic stirring bar, (+)-**7b** (0.040 g, 0.099 mmol) was placed in acetonitrile/ H_2O (9:1, 6 mL). The solution was cooled to $-20\text{ }^{\circ}\text{C}$ using CCl_4/CO_2 and bis(trifluoroacetoxy)iodobenzene (0.086 g, 0.267 mmol) was added in one portion. After 20 min, the reaction was quenched by addition of sat. aqueous NaHCO_3 (2 mL), followed by addition of 1,3-dithiane (0.0624 g, 0.2 mmol). The solution was diluted with EtOAc (5 mL), the aqueous phase was extracted with EtOAc (2 \times 5 mL), and the combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc/hexane, 3:7) afforded 0.012 g (50%) of a colourless oil, as 4.8:1 mixture of diastereoisomers; $[\alpha]_D^{20} +80.3$ (*c* 0.38, CHCl_3); IR (NaCl) 3745, 2927, 1684, 1086 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.95 (m, 2 H), 7.61 (m, 1 H), 7.49 (m, 2 H), 6.84 (s, 2 H), 5.08 (m, 2 H), 2.56 (s, 6 H), 2.27 (s, 3 H), 1.44 (d, *J* = 6.8 Hz, 3 H). HRMS calculated for $C_{18}H_{21}NNaO_2S$ (M+Na) 338.1191. Found 338.1187.

General procedure for hydrolysis of *N*-sulfinyl α -aminoethyl 1,3-dithianes using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, 3). 4-Methyl-*N*-[(1*S*)-1-methyl-2-oxo-2-phenylethyl]benzenesulfonamide (10a)

In a 10 mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic bar, rubber septum, and argon balloon crude (+)-**7a** (de 71%, 0.063 g, 0.167 mmol) in acetone (1 mL) was placed at rt and the mixture was added to a solution of 1,3-dibromo-5,5-dimethylhydantoin

(**3**, DBDMH) (0.143 g, 0.500 mmol) in 95% aqueous acetone (3 mL) at 0 °C in a 25 mL round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon. The solution was stirred at 0 °C for 15 min, shaken with a mixture of sat. aqueous sodium sulfite (5 mL), and 1:1 hexane/CH₂Cl₂ (20 mL) in a separatory funnel. The organic phase was washed with sat. aqueous NaHCO₃ (1 x 5 mL), H₂O (5 mL), brine (5 mL), dried, and concentrated. Flash chromatography (EtOAc/hexane, 3:7) afforded 0.025 g (49%) of a colourless oil; $[\alpha]_D^{20}$ -46.4 (*c* 0.62, CHCl₃) {lit.¹⁰ $[\alpha]_D^{20}$ -62.6 (*c* 1.0, CHCl₃)}, 70% ee. Spectral values were in agreement with literature values.¹⁰

2,4,6-Trimethyl-N-[(1S)-1-methyl-2-oxo-2-phenylethyl]benzenesulfonamide (10b). Flash chromatography (EtOAc/hexane, 3:7) gave 30% yield of a colourless oil, $[\alpha]_D^{20}$ -7.1 (*c* 0.40, CHCl₃); IR (NaCl) 3301, 1685, 1337, 1160 cm⁻¹; ¹H NMR (CDCl₃) δ 7.74 (d, *J* = 8 Hz, 2 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 6.83 (s, 2 H), 5.85 (d, *J* = 8 Hz, 1 H), 4.89 (m, 1 H), 2.64 (s, 6 H), 2.20 (s, 3 H), 1.36 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 198.6, 142.6, 139.2, 134.5, 134.3, 133.8, 132.3, 129.1, 128.7, 53.1, 23.2, 21.2. HRMS calculated for C₁₈H₂₂NO₃S (M+H) 332.1320. Found 332.1319.

2,4,6-Tris(1-methylethyl)-N-[(1S)-1-methyl-2-oxo-2-phenylethyl]benzenesulfonamide (10c). Flash chromatography (EtOAc/hexane, 1:9) gave 25% yield of a colourless oil, $[\alpha]_D^{20}$ -25.0 (*c* 0.10, CHCl₃); IR (NaCl) 1692, 1456, 1323, 1139 cm⁻¹; ¹H NMR (CDCl₃) δ 7.82 (m, 2 H), 7.58 (m, 1 H), 7.45 (m, 2 H), 7.11 (s, 2 H), 5.76 (d, *J* = 7.2 Hz, 1 H), 5.04 (m, 1 H), 4.15 (m, 2 H), 2.84 (m, 1 H), 1.38 (d, *J* = 7.2 Hz, 3 H), 1.28 (d, *J* = 6.8 Hz, 6 H), 1.23 (d, *J* = 7.2 Hz, 6 H), 1.20 (d, *J* = 6.8 Hz, 6 H); ¹³C NMR (CDCl₃) δ 198.2, 152.9, 150.2, 134.1, 133.6, 133.2, 129.0, 128.7, 123.8, 52.9, 34.2, 30.0, 25.0, 24.9, 23.6, 23.5, 21.2. HRMS calculated for C₂₄H₃₄NO₃S (M+H) 416.2259. Found 416.2277.

(S)-α-Methyl-2-phenyl-1,3-dithiane-2-methanamine (11). In a 25 mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon (+)-**7d** (0.110 g, 0.320 mmol) was placed in MeOH (17 mL). HCl (1.25 mL, 1.0 M in Et₂O) was added at rt, the solution stirred for 1 h, the mixture was diluted with H₂O (10 mL), and enough NaOH (1 M in H₂O) was added until pH 9 was attained. The reaction mixture was extracted with CH₂Cl₂ (2 x 10 mL), the combined organic phases were dried (Na₂SO₄), and concentrated. Flash chromatography (EtOAc/hexane, 1:1) gave 0.070 g (94%) of a white solid, mp 55-56 °C; $[\alpha]_D^{20}$ -11.7 (*c* 0.92, CHCl₃); IR (NaCl) 3373, 2902, 1441, 1069 cm⁻¹; ¹H NMR (CDCl₃) δ 7.87 (m, 2 H), 7.34 (m, 2 H), 7.22 (m, 1 H), 3.16 (q, *J* = 6.4 Hz, 12.8 Hz, 1 H), 2.61 (m, 4 H), 1.83 (m, 2 H), 1.37 (bs, 2 H), 0.97 (d, *J* = 6.4 Hz, 3 H); ¹³C NMR (CDCl₃) δ 139.3, 130.5, 128.8, 127.5, 57.8, 27.8, 27.6, 25.6, 18.4. HRMS calculated for C₁₂H₁₈NS₂ (M+H) 240.0881. Found 240.0880.

(S)-2-Phenyl-2-[1-N-(*p*-toluenesulfonyl)amino]ethyl]-1,3-dithiane (12a). In a 25 mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic bar, rubber septum, and argon balloon (-)-**11** (0.060 g, 0.251 mmol) was placed together with triethylamine (0.07 mL, 0.502 mmol), and DMAP (0.031 g 0.251) in CH₂Cl₂ (5.5 mL). The solution was cooled to 0 °C and after 5 min TsCl (0.072 g, 0.378 mmol) was added. The reaction mixture was warmed to rt,

stirred for 8 h, and quenched by addition of H₂O (5 mL) at 0 °C. The solution was diluted with CH₂Cl₂ (5 mL), the phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. Flash chromatography (EtOAc/hexane, 1:1) afforded 0.094 g (95%) of a colourless oil; $[\alpha]_D^{20}$ -62.5 (*c* 1.20, CHCl₃); IR (NaCl) 3279, 2906, 1597, 1412, 1336, 1160 cm⁻¹; ¹H NMR (CDCl₃) δ 7.78 (m, 2 H), 7.65 (m, 2 H), 7.29 (m, 2 H), 7.20 (m, 3 H), 4.72 (d, *J* = 8 Hz, 1 H), 3.62 (m, 1 H), 2.50 (m, 4 H), 2.34 (s, 3 H), 1.77 (m, 2 H), 0.94 (d, *J* = 6.4 Hz, 3 H); ¹³C NMR (CDCl₃) δ 143.6, 138.5, 138.0, 130.3, 129.8, 129.1, 128.0, 127.7, 64.7, 59.0, 27.7, 27.6, 25.0, 21.9, 17.8. HRMS calculated for C₁₉H₂₄NO₂S₃ (M+H) 394.0969. Found 394.0971.

(S)-2-([1-*N*-(*tert*-Butoxycarbonyl)amino]ethyl)-2-phenyl-1,3-dithiane (12b). In a 10 mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic bar, rubber septum, and argon balloon (-)-**11** (0.035 g, 0.146 mmol) was placed in CCl₄ (2 mL), and triethylamine (0.025 mL, 0.179 mmol) was added at 0 °C. After 5 min (Boc)₂O (0.048 g, 0.220 mmol) was added, warmed to rt, and stirred for 8 h. At this time the reaction mixture was quenched by addition of H₂O (2 mL) at 0 °C. The solution was diluted with CH₂Cl₂ (5 mL), the phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 5 mL). The combined organic phases were washed with brine (5 mL), dried (Na₂SO₄), and concentrated. Flash chromatography (EtOAc/hexane, 1:9) afforded 0.05 g (100%) of a colourless oil; $[\alpha]_D^{20}$ -6.0 (*c* 1.00, CHCl₃); IR (NaCl) 3427, 2976, 1715, 1492, 1163 cm⁻¹; ¹H NMR (CDCl₃) δ 7.96 (m, 2 H), 7.40 (t, *J* = 7.6 Hz, 2 H), 7.28 (t, *J* = 7.2 Hz, 1 H), 4.86 (d, *J* = 9.2 Hz, 1 H), 4.17 (m, 1 H), 2.66 (m, 4 H), 1.90 (m, 2 H), 1.42 (s, 9 H), 1.05 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (CDCl₃) δ 155.5, 139.5, 130.3, 128.9, 127.7, 79.7, 55.6, 27.7, 27.6, 25.3, 17.0. HRMS calculated for C₁₇H₂₆NO₂S₂ (M+H) 340.1395. Found 340.1405.

(S)-2-([1-*N*-(Trifluoroacetyl)amino]ethyl)-2-phenyl-1,3-dithiane (12c). In a 10 mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic bar, rubber septum, and argon balloon (-)-**11** (0.060 g, 0.251 mmol) was placed in CH₂Cl₂ (3.5 mL), and triethylamine (0.04 mL, 0.287 mmol) was added at 0 °C. After 5 min (CF₃CO)₂O (0.052 mL, 0.374 mmol) was added, the reaction mixture was warmed to rt, and stirred for 8 h. At this time the reaction was quenched by addition of H₂O (5 mL) at 0 °C, diluted with CH₂Cl₂ (5 mL). The aqueous phase was extracted with CH₂Cl₂ (2 x 5 mL), the combined organic phases were washed with brine (5 mL), dried (Na₂SO₄), and concentrated. Flash chromatography (EtOAc/hexane, 1:1) afforded 0.070 g (83%) of a colourless oil; $[\alpha]_D^{20}$ -6.4 (*c* 1.10, CHCl₃); IR (NaCl) 1722, 1530, 1206, 1165 cm⁻¹; ¹H NMR (CDCl₃) δ 7.94 (m, 2 H), 7.42 (m, 2 H), 7.31 (m, 1 H), 6.78 (d, *J* = 8 Hz, 1 H), 4.40 (m, 1 H), 2.82-2.53 (m, 4 H), 1.92 (m, 2 H), 1.09 (d, *J* = 6.8 Hz); ¹³C NMR (CDCl₃) δ 156.5 (q, *J* = 36.4 Hz), 138.2, 129.7, 129.0, 128.0, 115.8 (q, *J* = -286.3 Hz), 63.8, 54.9, 27.3, 27.2, 15.4; ¹⁹F NMR (CDCl₃) δ -75.89 (CFCl₃ reference). HRMS calculated for C₁₄H₁₆F₃NNaOS₂ (M+Na) 358.0523. Found 358.0528.

4-Methyl-*N*-[(1S)-1-methyl-2-oxo-2-phenylethyl]benzenesulfonamide (10a) from (-)-12a. In a 25 mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic bar, rubber septum, and argon balloon **3** (0.180 g, 0.630 mmol) was placed in aqueous acetone (7 mL, 5%

H₂O) at 0 °C, and (-)-**12a** (0.100 g, 0.254 mmol) in acetone (1.5 mL) was added at this temperature. After stirring for 10 min, the reaction was quenched by shaking with sat. aqueous sodium sulfite (10 mL) and 1:1 hexane/CH₂Cl₂ (10 mL) in a separatory funnel. The organic phase was washed with aqueous sat. NaHCO₃ (10 mL), H₂O (10 mL), brine (10 mL), dried (Na₂SO₄), and concentrated. Flash chromatography (EtOAc/hexane, 3:7) gave 0.070 g (91%) of a white solid, mp 115° C [lit.¹⁰ mp 115-116 °C]; $[\alpha]_D^{20}$ -61.2 (*c* 0.90 CHCl₃) {lit.¹⁰ $[\alpha]_D^{20}$ -62.6 (*c* 1.0, CHCl₃)}; IR (NaCl) 3277, 1685, 1339, 1163 cm⁻¹; ¹H NMR (CDCl₃) δ 7.77-7.75 (m, 2 H), 7.70-7.67 (m, 2 H), 7.60-7.56 (m, 1 H), 7.46-7.42 (m, 2 H), 7.17-7.15 (m, 2 H), 5.82 (d, *J* = 8 Hz, 1 H), 4.93 (m, 1 H), 2.31 (s, 3 H), 1.39 (d, *J* = 7.2 Hz, 3 H); ¹³C NMR (CDCl₃) δ 198.4, 143.8, 137.5, 134.4, 133.8, 130.0, 129.2, 128.8, 127.4, 53.7, 21.8, 21.4. HRMS calculated for C₁₆H₁₈NO₃S (M+H) 304.1007. Found 304.1008.

1,1-Dimethylethyl *N*-[(1*S*)-1-methyl-2-oxo-2-phenylethyl]carbamate (13). In a 10 mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic bar, rubber septum, and argon balloon DMDBH (**3**) (0.105 g, 0.367 mmol) was placed in aqueous acetone (4 mL, 5% H₂O) at 0 °C, and (-)-**12b** (0.050 g, 0.147 mmol) in acetone (1 mL) was added at this temperature. After stirring for 10 min, the reaction was quenched by shaking with sat. aqueous sodium sulfite (5 mL) and 1:1 hexane/CH₂Cl₂ (10 mL) in a separatory funnel. The organic phase was washed with aqueous sat. sodium bicarbonate (5 mL), H₂O (5 mL), brine (5 mL), dried (Na₂SO₄), and concentrated. Flash chromatography (EtOAc/hexane, 3:7) gave 0.028 g (76%) of a white solid, mp 70 °C [lit.⁸ 70-72 °C]; $[\alpha]_D^{20}$ 0.0 (*c* 1.41, CHCl₃) {lit.⁸ $[\alpha]_D^{20}$ -6.7 (*c* 1.0, CHCl₃)}; IR (NaCl) 3352, 1714, 1685, 1497, 1166 cm⁻¹; ¹H NMR (CDCl₃) δ 7.97 (d, *J* = 7.2 Hz, 2 H), 7.47-7.63 (m, 3 H), 5.57 (d, *J* = 6.3 Hz, 1 H), 5.29 (m, 1 H), 1.46 (s, 9 H), 1.40 (d, *J* = 7.2 Hz, 3 H); ¹³C NMR (CDCl₃) δ 199.9, 155.4, 134.4, 133.8, 129.0, 128.8, 79.6, 50.9, 28.1, 19.6. Spectral properties were consistent with literature values.⁸

2,2,2-Trifluoro-*N*-[(1*S*)-1-methyl-2-oxo-2-phenylethyl]acetamide (14). In a 25 mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic bar, rubber septum, and argon balloon **3** (0.075 g, 0.262 mmol) was placed in aqueous acetone (2 mL, 5% H₂O) at 0 °C, and (-)-**12c** (0.035 g, 0.104 mmol) in acetone (1 mL) was added at this temperature. After stirring for 10 min, the reaction was quenched by shaking with sat. aqueous sodium sulfite (5 mL) and 1:1 hexane/CH₂Cl₂ (5 mL) in a separatory funnel. The organic phase was washed with aqueous sat. sodium bicarbonate (5 mL), H₂O (5 mL), brine (5 mL), dried (Na₂SO₄), and concentrated. Flash chromatography (EtOAc/hexane, 3:7) gave 0.014 g (55%) of a colourless oil, $[\alpha]_D^{20}$ -8.6 (*c* 0.17, CHCl₃); IR (NaCl) 3277, 1685, 1339, 1163 cm⁻¹; ¹H NMR (CDCl₃) δ 7.98 (m, 2 H), 7.66 (m, 1 H), 7.60 (bs, 1 H), 7.54 (m, 2 H), 5.53 (m, 1 H), 1.53 (d, *J* = 7.2 Hz, 3 H); ¹³C NMR (CDCl₃) δ 197.2, 156.7 (q, *J* = 37.3 Hz), 134.8, 133.2, 129.3, 129.0, 115.9 (q, *J* = -285.7 Hz), 51.0, 19.5. ¹⁹F NMR (CDCl₃) δ -75.56 (CFCl₃ reference). HRMS calculated for C₁₁H₁₁F₃NO₂ (M+H) 246.0742. Found 246.0737.

***N,N'*-Bis[(*S*)-1-(2-phenyl-1,3-dithian-2-yl)ethyl]urea (15).** In a 25 mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon (-)-**11** (0.147 g, 0.614 mmol) was placed in CH₂Cl₂ (14 mL). Triethylamine (0.26 mL,

1.865 mmol) was added followed by DMAP (0.074 g 0.614 mmol) at 0 °C, and after 5 min (Boc)₂O (0.072 g, 0.330 mmol) was added. The mixture was warmed to rt, stirred for 4 h, and quenched by addition of H₂O (5 mL) at 0 °C. At this time the solution was diluted with CH₂Cl₂ (5 mL), the aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL), and the combined organic phases were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. Flash chromatography (EtOAc/hexane, 1:1) afforded 0.062 g (40%) of a white solid, mp 201 °C; $[\alpha]_D^{20}$ -42.2 (*c* 0.18, CHCl₃); IR (NaCl) 3297,2923,1620,1554 ¹H NMR (CDCl₃) δ 7.96 (m, 4 H), 7.40 (m, 4 H), 7.28 (m, 2H), 4.66 (bs, 2 H), 4.34 (m, 2 H), 2.78-2.5 (m, 8 H), 1.90 (m, 4 H), 1.04 (d, J = 7.2 Hz, 6 H); ¹³C NMR (CDCl₃) δ 156.7, 139.9, 130.4, 128.9, 127.6, 66.1, 55.3, 27.8, 27.6, 25.4, 17.2. HRMS calculated for C₂₅H₃₃N₂OS₄ (M+H) 505.1476. Found 505.1472.

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