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Chiral lithium amido sulfide ligands for asymmetric addition reactions of alkyllithium reagents to aldehydes

Johan Granander, Richard Sott and Göran Hilmersson*

Department of Chemistry, Organic Chemistry, Göteborg University, S-412 96 Göteborg, Sweden

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Abstract—Six chiral amino sulfides have been synthesised from the amino acids phenylalanine, phenylglycine and valine. These amino sulfides were used as chiral ligands in the asymmetric addition of *n*-butyllithium and metyllithium to various aldehydes at low temperatures. The highest stereoselectivities were obtained with benzaldehyde, resulting in 1-phenyl-1-pentanol and 1-phenyl-1-ethanol in enantiomeric excesses of >98.5 and 95%, respectively. These stereoselectivities were significantly higher than those induced by the ether analogues.

1. Introduction

Synthesis using organometallic reagents is a highly versatile way to create new carbon–carbon bonds while at the same time introducing a stereogenic center. Extensive research has been directed toward the development of chiral ligands that bind non-covalently to the organometallic reagent to allow asymmetric synthesis.[1] Chiral lithium amides with an internal coordinating group, such as an amine or ether, have been shown to be effective ligands in the enantioselective addition of alkyllithium reagents to aldehydes[2] as well as the enantioselective deprotonation of epoxides.[3] Chiral amides containing a chelating sulfur atom have proven very successful in asymmetric reactions such as the addition of diethylzinc to aromatic aldehydes,[4] palladium-catalysed allylic substitutions,[5] and copper-catalysed conjugate addition of Grignard reagents to enones.[6] Sulfur is more polarizable than oxygen and nitrogen and exhibits a higher affinity for transition metals but it is not clear how it would coordinate to the smaller and harder lithium atom. To the best of our knowledge there has only been one report where a chiral lithium amide containing a sulfur atom has been used as a ligand.[4e] A lithium amide thiolate was used as a ligand in the asymmetric addition of diethylzinc to benzaldehyde yielding the corresponding alcohol in 76% enantiomeric excess (ee). However the acidity of the α-protons of sulfides is utilized in the generation of α-lithiated sulfides which are common nucleophiles in organic synthesis.[7] We have previously reported the selectivities and solution structures of a number of chiral lithium amides[2g–i,8] with internal coordinating oxygen and nitrogen atoms, used in the asymmetric addition of different organolithium compounds to aldehydes. In the work reported herein, we have developed a number of chiral amino sulfides from the amino acids phenylalanine, phenylglycine, and valine. These amino sulfides have been used in the asymmetric addition of methyllithium (MeLi) and *n*-butyllithium (*n*-BuLi) to various aldehydes at low temperatures and their asymmetric induction properties have been compared to those of their amino ether analogues.

2. Results and discussion

The amino sulfides **7a**–**f** were easily synthesised from the enantiomerically pure amino acids phenylalanine, phenylglycine and valine in good yields (Scheme 1). The amino acids **1** were reduced to the corresponding amino alcohols **2** using lithium aluminium hydride and the amino group transformed into an amide group using di-*tert*-butyl dicarbonate. This was necessary in order to avoid an internal substitution reaction when the hydroxyl group is changed into a sulfonyloxy group in the next step. The amido alcohols **3** were subsequently reacted with methanesulfonyl chloride resulting in the amido sulfonates **4**. The methylsulfonyloxy group was substituted by the appropriate thiolate anion, yielding the amido sulfides **5**. The *tert*-butyl carbonate group was removed using concentrated hydrochloric acid and

* Corresponding author. Fax: (+46) 31 7723840; e-mail: hilmers@organic.gu.se

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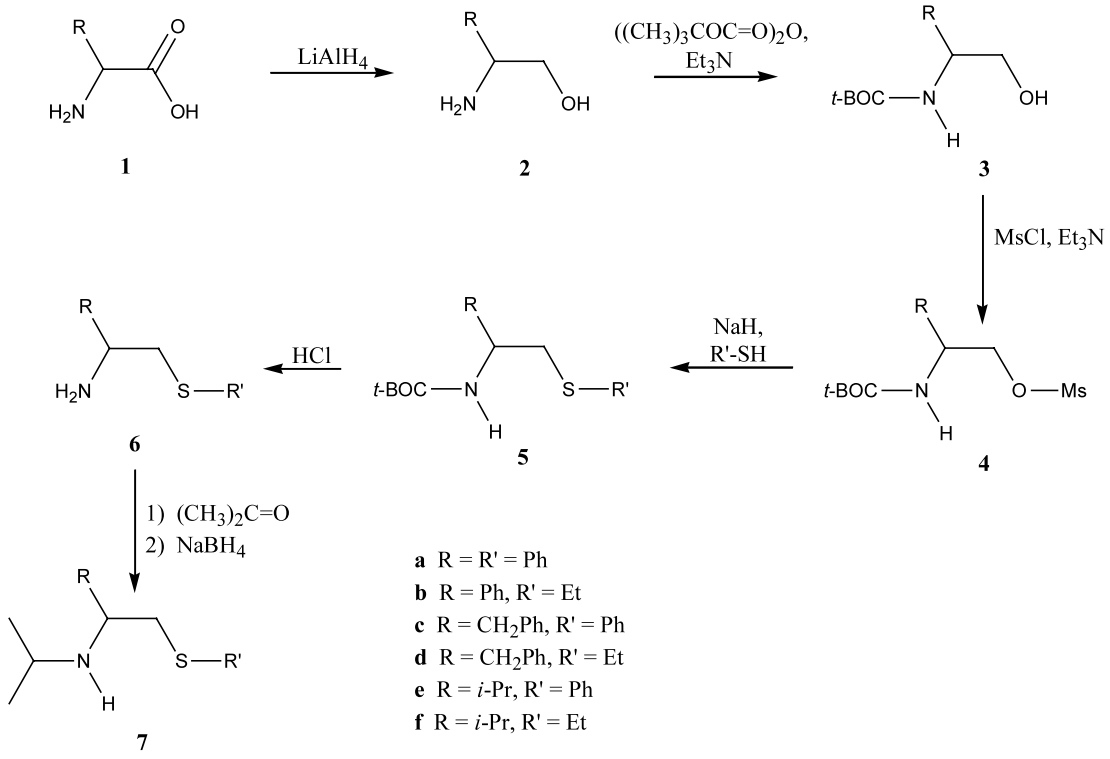


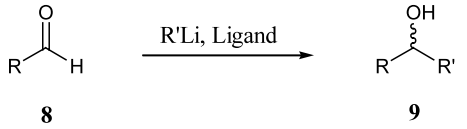
Scheme 1. Synthesis of the chiral amino sulfides.

the resulting primary amino sulfides **6** were condensed with acetone to afford the corresponding imines, which were subsequently reduced cleanly with sodium borohydride to the desired secondary amino sulfides **7**.

The amino sulfides were then used as chiral ligands in the addition of MeLi and *n*-BuLi to aldehydes (Scheme 2) to evaluate their ability to induce asymmetry in these reactions.

The ligand was dissolved in diethyl ether (Et_2O) or a 1:1 mixture of tetrahydrofuran (THF) and Et_2O and the solution was cooled to −78°C prior to the addition of the alkyllithium reagent. This was done to avoid the possibility of deprotonation of an α-proton of the sulfide by the base, which is known to proceed rapidly at room temperature. Ligands with a phenyl group attached to the sulfur atom are especially prone to undergo deprotonation. However, quenching experiments with CH_3OD performed at −78°C did not indicate any deprotonation of the α-proton of the sulfide. Benzaldehyde was added slowly as a solution in toluene. In some of the experiments the solution was further cooled to −116°C before benzaldehyde was added. The results of the asymmetric addition reactions of MeLi and *n*-BuLi to benzaldehyde are presented below (Table 1).

The lithium amido sulfides achieve moderate to excellent stereoselectivity in the asymmetric addition reactions. In the addition of MeLi to benzaldehyde the highest stereoselectivity, 95% ee (entry 2), was obtained with ligand **7a** in a Et_2O/THF mixture at −116°C. All ligands gave high stereoselectivity at −116°C in a mixture of Et_2O/THF, none lower than 71% ee, with conversions around 70%. At higher temperatures (−78°C) the stereoselectivity was slightly lower while the conversions were similar. However, changing the solvent to pure Et_2O drastically reduced both the stereoselectivities and the conversions. When *n*-BuLi was used as the organolithium reagent the stereoselectivity induced by the chiral amido sulfides was even higher. The highest stereoselectivity obtained, >98.5% ee (entry 14), was again with ligand **7a** in a Et_2O/THF mixture at −116°C, while ligands **7b**, **7e**, and **7f** induced high stereoselectivities (>90% ee) under the same reaction conditions. The conversions of the reactions were around 85%. The stereoselectivity of the reaction was reduced by some 10% when the reactions were performed at −78°C while the conversions were largely



a R = Ph, R' = Me
b R = Ph, R' = *n*-Bu
c R = *o*-Tolyl, R' = Me
d R = *o*-Tolyl, R' = *n*-Bu
e R = Cyclohexyl, R' = *n*-Bu

Scheme 2. Asymmetric addition of alkyllithium reagents to aldehydes.

Table 1. Asymmetric alkylation of benzaldehyde (1.0 equiv.) with MeLi or *n*-BuLi (14.5 equiv.) in the presence of the chiral amines **7a–f** (10.0 equiv.). The ees and conversions of the product alcohols, 1-phenyl-1-ethanol[a] **9a** and 1-phenyl-1-pentanol[b] **9b** were determined by chiral stationary phase GC analysis

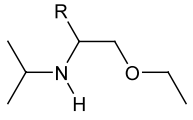
Entry	Ligand	Organolithium reagent	Temp. (°C)	Et_2O/THF		Et_2O	
				ee (%)	Conv. (%)	ee (%)	Conv. (%)
1	(*S*)-**7a**	MeLi	−78	88 (*R*)	65	–	–
2	(*R*)-**7a**	MeLi	−116	95 (*S*)	67	34 (*S*)	22
3	(*S*)-**7b**	MeLi	−78	85 (*R*)	69	–	–
4	(*S*)-**7b**	MeLi	−116	84 (*R*)	62	12 (*R*)	22
5	(*S*)-**7c**	MeLi	−78	66 (*R*)	70	–	–
6	(*S*)-**7c**	MeLi	−116	71 (*R*)	74	29 (*R*)	59
7	(*S*)-**7d**	MeLi	−78	75 (*R*)	72	–	–
8	(*S*)-**7d**	MeLi	−116	83 (*R*)	86	25 (*R*)	53
9	(*R*)-**7e**	MeLi	−78	78 (*S*)	69	–	–
10	(*R*)-**7e**	MeLi	−116	92 (*S*)	77	2 (*S*)	32
11	(*S*)-**7f**	MeLi	−78	78 (*R*)	78	–	–
12	(*S*)-**7f**	MeLi	−116	92 (*R*)	89	27 (*R*)	56
13	(*S*)-**7a**	*n*-BuLi	−78	90 (*R*)	79	79 (*R*)	80
14	(*R*)-**7a**	*n*-BuLi	−116	>98.5 (*S*)	82	97 (*S*)	82
15	(*S*)-**7b**	*n*-BuLi	−78	85 (*R*)	82	61 (*R*)	83
16	(*S*)-**7b**	*n*-BuLi	−116	94 (*R*)	84	83 (*R*)	90
17	(*S*)-**7c**	*n*-BuLi	−78	57 (*R*)	81	46 (*R*)	75
18	(*S*)-**7c**	*n*-BuLi	−116	68 (*R*)	87	70 (*R*)	87
19	(*S*)-**7d**	*n*-BuLi	−78	68 (*R*)	87	25 (*R*)	83
20	(*S*)-**7d**	*n*-BuLi	−116	81 (*R*)	92	58 (*R*)	88
21	(*R*)-**7e**	*n*-BuLi	−78	84 (*S*)	74	41 (*S*)	46
22	(*S*)-**7e**	*n*-BuLi	−116	97 (*R*)	80	87 (*R*)	70
23	(*S*)-**7f**	*n*-BuLi	−78	82 (*R*)	90	32 (*R*)	87
24	(*S*)-**7f**	*n*-BuLi	−116	91 (*R*)	72	71 (*R*)	91

[a] Absolute configuration determined by preparing an authentic sample of (*S*)-**9a**.
[b] Absolute configuration determined by comparing the specific rotation with the literature value.[2b]

unaffected. The stereoselectivity was generally lower in Et_2O, but ligand **7a** still gave 97% ee at −116°C. The conversions were largely unaffected by the change of solvents. In all reactions the product obtained had the opposite configuration to the ligand itself. A relatively large excess of both the ligand and the alkyllithium reagent, compared to the aldehyde substrate, was used to ensure a high conversion and that only alkyllithium reagent coordinated to the ligand would react with the substrate. No attempt to systematically determine the optimum ratios between ligand/reagent/substrate was made but earlier studies show that both more substrate and less ligand can be used without deteriorating either the conversion or stereoselectivities of the reactions.[2h]

In previous studies by our group several chiral amino ethers have been synthesised and used as ligands in the asymmetric addition of *n*-BuLi to benzaldehyde. Three of the previously studied amines,[2i] **10a–c**, are the ether analogues of the amino sulfides with an ethyl group attached to the sulfur atom (Scheme 3). The asymmetric induction properties of the sulfide and ether analogues in the addition of *n*-BuLi to benzaldehyde at −116°C are presented below (Table 2).

It is clear that the amido sulfides are superior to their oxygen analogues in this reaction. These results came as a bit of a surprise since we expected that the sulfur would coordinate more weakly to the lithium atom than oxygen and thus make a less rigid chelate yielding a lower stereoselectivity. Perhaps a strong chelate complex is not as important, as previously argued when comparing lithium amides of amino ethers and



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a R = Ph
b R = CH_2Ph
c R = *i*-Pr

Scheme 3. The chiral amino ethers **10a–c**.

Table 2. Asymmetric alkylation of benzaldehyde (1.0 equiv.) with *n*-BuLi (14.5 equiv.) in the presence of the chiral amines **7b**, **7d**, **7f**, and **10a–c** (10.0 equiv.) at −116°C. The ees of the product 1-phenyl-1-pentanol[a] **9b** were determined by chiral stationary phase GC analysis

Entry	Ligand	Et_2O/THF ee (%)	Et_2O ee (%)
1	(*S*)-**7b**	94 (*R*)	83 (*R*)
2[b]	(*S*)-**10a**	79 (*R*)	60 (*R*)
3	(*S*)-**7d**	81 (*R*)	58 (*R*)
4[b]	(*S*)-**10b**	69 (*R*)	41 (*R*)
5	(*S*)-**7f**	91 (*R*)	16 (*R*)
6[b]	(*S*)-**10c**	74 (*R*)	44 (*R*)

[a] Absolute configuration determined by comparing the specific rotation with the literature value.[2b]
[b] Ref. 2i.

diamines, to achieve a high degree of stereoselectivity. It is also interesting to note that both kinds of amides yield the product with configuration opposite to that of the ligand, indicating that the two transition states are similar.

The amido sulfides were also tested as chiral inducers in other addition reactions. The most successful ligand, **7a**, was used in the addition of MeLi and *n*-BuLi to *o*-tolualdehyde **8c** and cyclohexanecarboxaldehyde **8e** at various temperatures and Et_2O/THF as solvent mixture (Table 3).

The results show that ligand **7a** gives very good to excellent stereoselectivities in all of the addition reactions tested with stereoselectivities exceeding 86% throughout the study, even at −78°C. In general, however, the ligand is slightly more effective with *n*-BuLi than with MeLi. Ligand **7a** was also used in the addition of MeLi to cyclohexanecarboxaldehyde but baseline separation of the product enantiomers could not be achieved on the chiral GC. Analysis of the chromatogram for the reaction performed at −116°C showed only one peak, while at −78°C a small peak overlapping with a much larger peak was discernible, indicating that the higher temperature reaction also occurred with high stereoselectivity.

It is difficult to explain the higher stereoselectivity of the sulfides compared to that of the ethers. However, there is a significant structural difference between a chelate with oxygen and a chelate with sulfur. The Li–S bond (∼2.5 Å)[9] is considerably longer than the Li–O bond (∼2.0 Å)[10] which affects the geometry of the chelate. This small, structural difference may at least partially explain the enhancement of the stereoselectivity in the alkylation reactions with the sulfides compared to those with the ethers.

3. Conclusion

In conclusion, six novel chiral amino sulfides have been synthesised and characterised. The amido sulfides have been used in the asymmetric addition of MeLi and *n*-BuLi to different aldehydes. The addition products 1-phenyl-1-ethanol, 1-phenyl-1-pentanol, 1-(*o*-tolyl)-1-ethanol, 1-(*o*-tolyl)-1-pentanol and 1-cyclohexyl-1-pentanol were obtained in 95, >98.5, 87, 96 and 93% ee, respectively, at −116°C using ligand **7a**. The selectivities were only affected slightly by carrying out the reaction at −78°C. These results represent the most successful additions of alkyllithium reagents to aldehydes, in terms of stereoselectivity, reported. In comparison with their ether analogues they give far better selectivity. NMR studies of the lithium amido sulfide complexes in solution will be reported separately. These studies indicate that the species present in these reactions are the same as those present in the reactions mediated by lithium amido ethers.

4. Experimental

4.1. General

NMR spectra were recorded on a Varian 400 MHz spectrometer using $CDCl_3$ as solvent. Optical rotations were measured using a Perkin–Elmer 341 LC polarimeter. IR spectra were recorded on a Perkin–Elmer 1600 Series FTIR spectrometer. Melting points were determined using a Büchi Melting Point B-545 and are uncorrected. HRMS (FAB) spectra were recorded on a VG ZabSpec using a beam of Cs atoms as ionization source and glycerol was used to dissolve the sample. GC analyses were carried out using a Varian Star 3400 CX gas chromatograph equipped with a chiral stationary phase column (CP-Chirasil-DEX CB, 25 m, 0.32

Table 3. Asymmetric alkylation of aldehydes **8a**, **8c**, and **8e** (1.0 equiv.) with MeLi or *n*-BuLi (14.5 equiv.) in the presence of the chiral amine **7a** (10.0 equiv.) in a Et_2O/THF solvent mixture. The ees and conversions of the products **9a**[a], **9b**[b], **9c**[c], **9d**[d], and **9e**[d] were determined by chiral stationary phase GC analysis

Entry	Ligand	Organolithium reagent	Aldehyde	Temp. (°C)	ee (%)	Conv. (%)
1	(*S*)-**7a**	MeLi	**8a**	−78	88 (*R*)	65
2	(*R*)-**7a**	MeLi	**8a**	−116	95 (*S*)	67
3	(*S*)-**7a**	*n*-BuLi	**8a**	−78	90 (*R*)	79
4	(*R*)-**7a**	*n*-BuLi	**8a**	−116	>98.5 (*S*)	82
5	(*S*)-**7a**	MeLi	**8c**	−78	91 (*R*)	69
6	(*S*)-**7a**	MeLi	**8c**	−116	87 (*R*)	73
7	(*S*)-**7a**	*n*-BuLi	**8c**	−78	95	87
8	(*S*)-**7a**	*n*-BuLi	**8c**	−116	96	88
9	(*S*)-**7a**	*n*-BuLi	**8e**	−78	86	88
10	(*S*)-**7a**	*n*-BuLi	**8e**	−116	93	74

[a] Absolute configuration determined by preparing an authentic sample of (*S*)-**9a**.
[b] Absolute configuration determined by comparing the specific rotation with the literature value.[2b]
[c] Absolute configuration determined by preparing an authentic sample of (*S*)-**9c**.
[d] Absolute configuration not yet determined.

mm) from Chrompack. Analyses were done using He (1.5 mL min^{-1}) as carrier gas (injector 225°C, detector 250°C). Dried solvents were distilled from sodium/benzophenone.

4.2. Synthesis

The starting materials, the chiral amino acids, **1**, were purchased from Sigma-Aldrich and their reduction to the corresponding amino alcohols,[2i,11] **2**, protection as *t*-BOC-amido alcohols,[12] **3**, and conversion to methanesulfonates,[12d,13] **4**, were made according to literature procedures.

4.2.1. (*S*)-*N*-*t*-BOC-2-Amino-2-phenyl-1-thiophenylethane, (*S*)-5a. Thiophenol (7.51 g, 6.97 mL, 68.2 mmol, 1.1 equiv.) was added slowly to an ice cooled suspension of sodium hydride (60% in mineral oil, 2.73 g, 68.2 mmol, 1.1 equiv.) in dry THF (150 mL). The mixture was allowed to slowly reach room temperature and after one hour a solution of crude (*S*)-**4a** (19.55 g, 62.0 mmol, 1.0 equiv.) in dry THF (150 mL) was added slowly over 30 min. The mixture was stirred at room temperature over night (12 h). Water (100 mL) was added, the mixture concentrated under reduced pressure and the residue extracted with CH_2Cl_2 (3×100 mL). The combined organic extract was dried over Na_2SO_4 and the solvent evaporated under reduced pressure yielding a clear yellow oil which slowly crystallized (20.43 g, 100%). The crude product was recrystallized from ethyl acetate:hexane yielding white needle-shaped crystals. Spectral data were consistent with those reported in the literature.[14]

4.2.2. (*S*)-*N*-*t*-BOC-2-Amino-2-phenyl-1-thioethylethane, (*S*)-5b. Preparation identical to that of (*S*)-**5a** except that ethanethiol was used instead of thiophenol. Yield 96% of the crude product as a white solid which was recrystallized from hexane yielding white needle-shaped crystals. Mp = 93–94°C; $[\alpha]_D^{20} = +44.9$ (*c* 1.01, CH_2Cl_2); ν_{max} (KBr) 3384, 2974, 1680, 1522, 1176, 731, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, $J = 7.4$ Hz, 3H, SCH_2CH_3), 1.43 (s, 9H, $(CH_3)_3CO$), 2.44 (q, $J = 7.4$ Hz, 2H, SCH_2CH_3), 2.93 (d, $J = 6.0$ Hz, 2H, $PhCHCH_2$), 4.84 (s (br), 1H, $PhCHCH_2$), 5.18 (s (br), 1H, CONHC), 7.26–7.37 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9 (SCH_2CH_3), 26.6 (SCH_2CH_3), 28.5 ($(CH_3)_3C$), 38.5 ($PhCHCH_2$), 54.1 ($PhCHCH_2$), 79.9 ($(CH_3)_3C$), 126.5 (*o*-Ph), 127.7 (*p*-Ph), 128.8 (*m*-Ph), 141.6 (*i*-Ph), 155.4 (OCONH); HRMS (FAB): MH^+, found 282.1527. $C_{15}H_{24}NO_2S$ requires 282.1528.

4.2.3. (*S*)-*N*-*t*-BOC-2-Amino-3-phenyl-1-thiophenylpropane, (*S*)-5c. Preparation identical to that of (*S*)-**5a**. Yield 100% as a white solid which was recrystallized from ethyl acetate:hexane yielding white needle-shaped crystals. Mp = 86°C; $[\alpha]_D^{20} = +21.9$ (*c* 1.05, CH_2Cl_2); ν_{max} (KBr) 3372, 2974, 1693, 1680, 1526, 1173, 737, 702, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H, $C(CH_3)_3$), 2.92 (d, $J = 6.8$ Hz, 2H, $PhCH_2$), 3.04 (d, $J = 5.6$ Hz, 2H, CH_2SPh), 4.06 (s (br), 1H, $CH(NHCO_2)$), 4.67 (s (br), 1H, CONH), 7.17–7.37 (m, 10H, Ar); ^{13}C (100 MHz, $CDCl_3$) δ 28.5 ($C(CH_3)_3$), 38.0 (PhCH), 39.7 ($CHCH_2S$), 51.5 ($CHCH_2$), 79.6 ($C(CH_3)_3$), 126.5 (Ar), 126.8 (Ar), 128.7 (Ar), 129.2 (Ar), 129.6 (Ar), 129.8 (Ar), 136.3 (Ar), 137.7 (Ar), 155.3 (C=O); HRMS (FAB): MH^+, found 344.1682. $C_{20}H_{26}NO_2S$ requires 344.1684.[14,15]

4.2.4. (*S*)-*N*-*t*-BOC-2-Amino-3-phenyl-1-thioethylpropane, (*S*)-5d. Preparation identical to that of (*S*)-**5a** except that ethanethiol was used instead of thiophenol. Yield 97% as a slightly yellowish solid. The crude product was recrystallized from hexane yielding white needle-shaped crystals. Spectral data consistent with those reported in the literature.[16]

4.2.5. (*S*)-*N*-*t*-BOC-2-Amino-3-methyl-1-thiophenylbutane, (*S*)-5e. Preparation identical to that of (*S*)-**5a**. Yield 81% as a yellow oil. Spectral data consistent with those reported in the literature.[5e,14]

4.2.6. (*S*)-*N*-*t*-BOC-2-Amino-3-methyl-1-thioethylbutane, (*S*)-5f. Preparation identical to that of (*S*)-**5a** except that ethanethiol was used instead of thiophenol. Yield 70% as a yellow oil. Mp = 65°C; $[\alpha]_D^{20} = +19.3$ (*c* 1.09, CH_2Cl_2); ν_{max} (KBr) 3318, 2977, 1639, 1538, 1452, 1367, 1304, 1251, 1176, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, $J = 7.3$ Hz, 3H, $C(CH_3)_3$), 0.95 (d, $J = 7.3$ Hz, 3H, $C(CH_3)_3$), 1.3 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 1.45 (s, 9H, $C(CH_3)_3$), 1.90 (m, 1H, $(CH_3)_2CH$), 2.55 (q, $J = 7.5$ Hz, 2H (SCH_2CH_3), 2.70 (m, 1H, SCH_2CH), 3.6 (m, 1H, $CH(NHCO_2)$), 4.6 (m, 1H, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0 ($CH(CH_3)_2$), 17.9 ($CH(CH_3)_2$), 19.8 (CH_2CH_3), 26.7 ($CH(CH_3)_2$), 28.6 ($C(CH_3)_3$), 30.9 (CH_2CH_3), 35.0 ($CHCH_2S$), 55.1 ($CHCH_2$); HRMS (FAB): MH^+, found 248.1661. $C_{12}H_{26}NO_2S$ requires 248.1684.

4.2.7. (*S*)-2-Amino-2-phenyl-1-thiophenyl-ethane, (*S*)-6a. Crude (*S*)-**5a** (20.43 g, 62.0 mmol, 1.0 equiv.) was dissolved in ethyl acetate (400 mL) and concentrated hydrochloric acid (62.8 g, 53.2 mL, 0.62 mol, 10 equiv.) added slowly. The mixture was stirred at room temperature for 2 h. Water (200 mL) was added and the aqueous layer separated. The organic layer was extracted with aqueous hydrochloric acid (3×50 mL, 10%). The combined aqueous extract was basified with aqueous sodium hydroxide (800 mL, 5 M) and extracted with CH_2Cl_2 (4×100 mL). The combined organic extract was dried over Na_2SO_4 and the solvent evaporated under reduced pressure yielding a clear, slightly yellowish oil which quickly crystallized (8.92 g, 63%). Spectral data consistent with those reported in the literature.[5e,17]

4.2.8. (*S*)-2-Amino-2-phenyl-1-thioethyl-ethane, (*S*)-6b. Preparation identical to that of (*S*)-**6a**. Yield 63% as a clear, slightly yellowish oil. $[\alpha]_D^{20} = +29.7$ (*c* 1.33, CH_2Cl_2); ν_{max} (thin film) 3364, 3288, 2966, 1604, 1452, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, $J = 7.4$ Hz, 3H, SCH_2CH_3), 2.54 (q, $J = 7.4$ Hz, 2H, SCH_2CH_3), 2.67 (dd, $J = 9.4$, 13.4 Hz, 1H, $PhCHCH_2$), 2.90 (dd, $J = 4.2$, 13.4 Hz, 1H, $PhCHCH_2$), 4.10 (dd, $J = 4.2$, 13.4 Hz, 1H, $PhCHCH_2$), 7.20–7.40 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1 (SCH_2CH_3), 26.5 (SCH_2CH_3), 42.0 ($PhCHCH_2$), 55.2 ($PhCHCH_2$), 126.6 (*o*-Ph), 127.6 (*p*-Ph), 128.7 (*m*-Ph), 144.9 (*i*-Ph); HRMS (FAB): MH^+, found 182.0993. $C_{10}H_{16}NS$ requires 182.1003.

4.2.9. (*S*)-2-Amino-3-phenyl-1-thiophenyl-propane, (*S*)-6c. Preparation identical to that of (*S*)-**6a**. Yield 53% as a clear, slightly yellowish oil. Spectral data consistent with those reported in the literature.[17]

4.2.10. (*S*)-2-Amino-3-phenyl-1-thioethyl-propane, (*S*)-6d. Preparation identical to that of (*S*)-**6a**. Yield 97% as a clear, slightly yellowish oil. Spectral data consistent with those reported in the literature.[16]

4.2.11. (*S*)-2-Amino-3-methyl-1-thiophenyl-butane, (*S*)-6e. Preparation identical to that of (*S*)-**6a** except that ethanol saturated with HCl was used instead of conc. HCl. Yield 95% as a yellow oil. Spectral data consistent with those reported in the literature.[5e,17]

4.2.12. (*S*)-2-Amino-3-methyl-1-thioethyl-butane, (*S*)-6f. Preparation identical to that of (*S*)-**6a** except that ethanol saturated with HCl was used instead of conc. HCl. Yield 95% as a yellow oil. $[\alpha]_D^{20}=+78.4$ (*c* 1.02, CH_2Cl_2); ν_{max} (thin film) 3367, 2959, 1463, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, $J=7.1$ Hz, 3H, $C(CH_3)_3$), 0.91 (d, $J=7.1$ Hz, 3H, $C(CH_3)_3$), 1.23 (t, $J=7.5$ Hz, 3H, CH_2CH_3), 1.65 (m, 1H, $(CH_3)_2CH$), 2.30 (m, 1H, SCH_2CH), 2.50 (q, $J=7.5$ Hz, 2H (SCH_2CH_3), 2.62 (m, 1H, CHNH), 2.72 (m, 1H, SCH_2CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0 ($CH(CH_3)_2$), 17.8 ($CH(CH_3)_2$), 19.4 (CH_2CH_3), 26.2 ($NCH(CH_3)_2$), 33.1 (CH_2CH_3), 38.0 ($CHCH_2S$), 55.7 ($CHCH_2$)); HRMS (FAB): MH^+, found 148.1130. $C_7H_{18}NS$ requires 148.1160.

4.2.13. (*S*)-*N*-Isopropyl-2-amino-2-phenyl-1-thiophenyl-ethane, (*S*)-7a. Acetone (11.3 g, 14.3 mL, 0.19 mol, 5.0 equiv.) and crude (*S*)-**6a** (8.92 g, 38.9 mmol, 1.0 equiv.) were dissolved in dry benzene (300 mL) and the mixture refluxed over night (14 h) with a Dean–Stark trap to collect the water formed. The mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was dissolved in dry ethanol (250 mL), $NaBH_4$ (2.94 g, 77.8 mmol, 2.0 equiv.) added and the mixture stirred at room temperature for 8 h. Water (100 mL) was added and the mixture concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (3×100 mL), the combined extracts dried over Na_2SO_4, and the solvent evaporated under reduced pressure yielding a white solid (10.61 g, 100%). Mp 59–60°C; $[\alpha]_D^{20}=+7.8$ (*c* 1.03, CH_2Cl_2); ν_{max} (KBr) 3289, 2961, 1577, 1480, 1086, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, $J=6.1$ Hz, 6H, $(CH_3)_2CHN$), 2.52 (sept., $J=6.1$ Hz, 1H, $(CH_3)_2CHN$), 2.97 (dd, $J=9.2$, 13.2 Hz, 1H, $PhCHCH_2$), 3.15 (dd, $J=4.6$, 13.2 Hz, 1H, $PhCHCH_2$), 3.77 (dd, $J=4.6$, 9.2 Hz, 1H, $PhCHCH_2$), 7.11–7.32 (m, 10H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.29 ($(CH_3)_2CHN$), 24.54 ($(CH_3)_2CHN$), 42.89 ($PhCHCH_2$), 46.24 ($(CH_3)_2CHN$), 126.55 (*p*-Ar), 127.31 (Ar), 127.59 (*p*-Ar), 128.69 (Ar), 129.15 (Ar), 130.13 (Ar), 135.91 (*i*-ArS), 143.59 (*i*-Ar); HRMS (FAB): MH^+, found 272.1430. $C_{17}H_{22}NS$ requires 272.1473.

4.2.14. (*S*)-*N*-Isopropyl-2-amino-2-phenyl-1-thioethyl-ethane, (*S*)-7b. Preparation identical to that of (*S*)-**7a**. The product was purified by Kugelrohr distillation (80°C, 0.040 mbar) followed by column chromatography (aluminium oxide, dichloromethane) yielding a clear, colourless oil. Yield 61%. $[\alpha]_D^{20}=+90.0$ (*c* 1.12, CH_2Cl_2); ν_{max} (thin film) 3296, 2960, 1600, 1452, 1167, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, $J=6.2$ Hz, 3H, $(CH_3)_2CHN$), 1.10 (d, $J=6.2$ Hz, 3H, $(CH_3)_2CH$), 1.25 (t, $J=7.4$ Hz, 3H, SCH_2CH_3), 2.52 (q, $J=7.4$, 2H, SCH_2CH_3), 2.64 (sept., $J=6.2$ Hz, 1H, $(CH_3)_2CH$), 2.68 (dd, $J=9.0$, 13.1 Hz, 1H, $PhCHCH_2$), 2.84 (dd, $J=4.5$, 13.1 Hz, 1H, $PhCHCH_2$), 3.81 (dd, $J=4.5$, 9.0 Hz, 1H, $PhCHCH_2$), 7.25–7.40 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0 (SCH_2CH_3), 22.2 ($(CH_3)_2CHN$), 24.5 ($(CH_3)_2CHN$), 26.3 (SCH_2CH_3), 40.7 ($PhCHCH_2$), 46.1 ($(CH_3)_2CHN$), 59.3 ($PhCHCH_2$), 127.3 (*o*-Ph), 127.4 (*p*-Ph), 128.6 (*m*-Ph), 143.9 (*i*-Ph); HRMS (FAB): MH^+, found 224.1487. $C_{13}H_{22}NS$ requires 224.1473.

4.2.15. (*S*)-*N*-Isopropyl-2-amino-3-phenyl-1-thiophenyl-propane, (*S*)-7c. Preparation identical to that of (*S*)-**7a**. The crude product was purified by column chromatography (aluminium oxide, dichloromethane) yielding a clear, colourless oil. Yield 73%. $[\alpha]_D^{20}=+5.3$ (*c* 1.22, CH_2Cl_2); ν_{max} (thin film) 3312, 2961, 1583, 1480, 1173, 738, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, $J=6.4$ Hz, 3H, $NCH(CH_3)_2$), 1.00 (d, $J=6.4$ Hz, 3H, $NCH(CH_3)_2$), 2.86 (d, $J=6.4$ Hz, 2H, $PhCH_2$), 2.88 (sept., $J=6.4$ Hz, 1H, $NCH(CH_3)_2$), 2.92 (dd, $J=5.6$, 12.9 Hz, 1H, CH_2SPh), 3.03 (dd, $J=5.4$, 12.9 Hz, 1H, CH_2SPh), 3.06 (m, 1H, $CHCH_2$), 7.17–7.35 (m, 10H, Ar); ^{13}C (100 MHz, $CDCl_3$) δ 23.4 ($NCH(CH_3)_2$), 23.5 ($NCH(CH_3)_2$, 38.3 ($PhCH_2$), 40.6 ($CHCH_2$), 46.0 ($NCH(CH_3)_2$, 55.6 ($CHCH_2$), 126.1 (Ar), 126.5 (Ar), 128.6 (Ar), 129.0 (Ar), 129.4 (Ar), 129.6 (Ar), 136.7 (Ar), 138.9 (Ar); HRMS (FAB): MH^+, found 286.1625. $C_{18}H_{24}NS$ requires 286.1629.

4.2.16. (*S*)-*N*-Isopropyl-2-amino-3-phenyl-1-thioethyl-propane, (*S*)-7d. Preparation identical to that of (*S*)-**7a**. The crude product was purified by distillation under reduced pressure yielding a clear, colourless oil. The product was further purified by column chromatography (aluminium oxide, dichloromethane) yielding a clear, colourless oil. Yield 35%. Bp = 93°C, 0.10 mbar; $[\alpha]_D^{20}=+18.9$ (*c* 1.14, CH_2Cl_2); ν_{max} (thin film) 3298, 2961, 1600, 1452, 1173, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, $J=6.3$ Hz, 3H, $NCH(CH_3)_2$), 1.07 (d, $J=6.3$ Hz, 3H, $NCH(CH_3)_2$), 1.22 (t, $J=7.4$ Hz, 3H, SCH_2CH_3), 2.49 (dd, $J=6.2$, 12.9 Hz, 1H, $CHCH_2S$), 2.51 (q, $J=6.3$ Hz, 2H, SCH_2CH_3), 2.61 (dd, $J=8.4$ Hz, 1H, $CHCH_2S$), 2.77 (dd, $J=7.4$, 13.5 Hz, 1H, $PhCH_2$), 2.82 (dd, $J=6.0$, 13.5 Hz, 1H, $PhCH_2$), 2.92 (sept., $J=6.3$ Hz, 1H, $NCH(CH_3)_2$), 3.02 (dddd, $J=6.0$, 6.2, 7.4, 8.4 Hz, 1H, $CHCH_2$), 7.20–7.32 (m, 5H, Ar); ^{13}C (100 MHz, $CDCl_3$) δ 15.1 (SCH_2CH_3), 23.4 ($NCH(CH_3)_2$), 23.5 ($NCH(CH_3)_2$), 26.8 (SCH_2CH_3), 36.6 ($CHCH_2S$), 40.7 ($PhCH_2$), 45.9 ($NCH(CH_3)_2$), 55.8 ($CHCH_2$), 126.4 (Ar), 128.6 (Ar), 129.5 (Ar), 139.1 (Ar); HRMS (FAB): MH^+, found 238.1629. $C_{14}H_{24}NS$ requires 238.1629.

4.2.17. (*S*)-*N*-Isopropyl-2-amino-3-methyl-1-thiophenylbutane, (*S*)-7e. Preparation identical to that of (*S*)-**7a** except that chloroform was used as solvent and a reversed Dean–Stark trap was used to collect the water formed. Yield 82%. $[\alpha]_D^{20}=+30.0$ (*c* 0.96, CH_2Cl_2); ν_{max} (thin film) 3324, 2929, 1480, 1236, 737, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, $J=6.8$ Hz, 3H, $CH(CH_3)_2$), 1.01 (d, $J=6.4$ Hz, 3H, $NCH(CH_3)_2$), 1.94 (m, 1H, $CH(CH_3)_2$), 2.59 (dd, 1H, $CHCH_2S$), 2.82 (m, 1H, $NCH(CH_3)_2$), 2.60 (dd, $J=4.1$ Hz, 1H, $CHCH_2S$), 2.83 (dd, $J=6.2$ Hz, 1H, $CHCH_2S$), 2.88 (dd, $J=6.8$ Hz, 1H, $CHCH_2S$), 3.01 (dd, $J=5.2$ Hz, 1H, $CHCH_2S$), 7.15–7.37 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, (2C, $CH(CH_3)_2$), 23.6 ($(CH_3)_2CHN$), 23.7 ($(CH_3)_2CHN$), 30.3 ($(CH_3)_2CHN$), 36.6 (CH_2CH), 46.5 ($(CH_3)_2CHCH$), 59.1 ($CHCH_2$), 126.0 (Ar), 129.0 (Ar), 129.5 (Ar), 137.2 (Ar); HRMS (FAB): MH^+, found 238.1675. $C_{14}H_{24}NS$ requires 238.1629.

4.2.18. (*S*)-*N*-Isopropyl-2-amino-3-methyl-1-thioethylbutane, (*S*)-7f. Preparation identical to that of (*S*)-**7a** except that chloroform was used as solvent and a reversed Dean–Stark trap was used to collect the water formed. Yield 60%. $[\alpha]_D^{20}=+38.5$ (*c* 0.96, CH_2Cl_2); ν_{max} (thin film) 3297, 2958, 1462, 1173, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, $J=6.9$ Hz, 3H, $CH(CH_3)_2$), 1.03 (d, $J=7.2$ Hz, 3H, $NCH(CH_3)_2$), 1.25 (t, $J=7.4$ Hz, 3H, SCH_2CH_3), 1.87 (m, 1H, $CH(CH_3)_2$), 2.46 (m, 1H $CHCH_2S$), 2.52 (q, $J=7.2$ Hz, 2H, SCH_2CH_3), 2.60 (dd, $J=4.1$ Hz, 1H, $CHCH_2S$), 2.83 (dd, $J=6.2$ Hz, 1H, $NCH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0 (CH_3CH_2), 18.2 ($(CH_3)_2CH$), 18.4 ($(CH_3)_2CH$), 23.6 ($(CH_3)_2CHN$), 23.8 ($(CH_3)_2CHN$), 26.7 ($(CH_3)_2CH$), 30.2 ($(CH_3)_2CH$), 34.3 (CH_2CH), 46.6 ($(CH_3)_2CHN$), 59.3 ($CHCH_2$); HRMS (FAB): MH^+, found 190.1627. $C_{10}H_{24}NS$ requires 190.1629.

4.2.19. (±)-1-Phenyl-1-ethanol, 9a. MeLi (0.92 mL, 1.6 M in Et_2O, 1.48 mmol, 1.5 equiv.) was added to dry THF (20 mL) and the resulting mixture cooled to −78°C over a Et_2O/dry ice cooling bath. Compound **8a** (0.104 g, 0.98 mmol, 1.0 equiv.) was added slowly and the mixture was stirred for 2 h while its temperature slowly reached room temperature. Methanol (5.0 mL) was added to quench the excess MeLi reagent and the mixture was concentrated in vacuo. The residue was dissolved in diluted hydrochloric acid (5.0 mL, 5%) and the resulting mixture was extracted with dichloromethane (3×5 mL). The combined organic extract was dried over Na_2SO_4 and the solvent removed under reduced pressure. The resulting crude product, a clear, yellowish oil, was purified using column chromatography (silica, ethyl acetate:hexane 20:80) yielding the product as a clear colourless oil (0.090 g, 75%). Spectral properties consistent with those reported in the literature.[18] Retention times on chiral stationary phase GC: 100°C, 14.3 (*R*) and 16.3 (*S*) min.

4.2.20. (±)-1-Phenyl-1-pentanol, 9b. Preparation identical to that of (*rac*)-**9a** except that *n*-BuLi was used instead of MeLi. Yield 76% as a clear, colourless oil. Spectral properties consistent with those reported in the literature.[2h] Retention times on chiral stationary phase GC: 100°C for 5 min then temperature was raised to 125°C, 14.7 (*S*) and 15.4 (*R*) min.

4.2.21. (±)-1-(*o*-Tolyl)-1-ethanol, 9c. Preparation identical to that of (±)-**9a** except that **8c** was used instead of **8a**. Yield 66% as a clear, slightly yellowish oil. Spectral properties consistent with those reported in the literature.[19] Retention times on chiral stationary phase GC: 100°C for 6 min then temperature was raised to 120°C, 15.0 (*R*) and 18.1 (*S*) min.

4.2.22. (±)-1-(*o*-Tolyl)-1-pentanol, 9d. Preparation identical to that of (±)-**9a** except that *n*-BuLi was used instead of MeLi and **8c** was used instead of **8a**. Yield 89% as a clear, colourless oil. Spectral properties consistent with those reported in the literature.[2d–f] Retention times on chiral stationary phase GC: 125°C for 6 min then temperature was raised to 125°C, 27.5 and 28.9 min.

4.2.23. (±)-1-Cyclohexyl-1-pentanol, 9e. Preparation identical to that of (±)-**9a** except that *n*-BuLi was used instead of MeLi and **8e** was used instead of **8a**. Yield 59% as a clear, colourless oil. Spectral properties consistent with those reported in the literature.[2h] Retention times on chiral stationary phase GC: 100°C for 5 min then temperature was raised to 125°C, 16.1 and 16.6 min.

4.2.24. (*S*)-1-Phenyl-1-ethanol, (*S*)-9a. Dimethylzinc (2.28 mL, 2.0 M in toluene, 4.56 mmol, 1.1 equiv.) was added slowly to an ice cooled suspension of sodium hydride (60% dispersion in mineral oil, 0.183 g, 4.56 mmol, 1.1 equiv.) in dry THF (15 mL). The mixture was stirred at this temperature for 1 h. (*R*)-Styrene oxide (0.50 g, 0.48 mL, 4.2 mmol, 1.0 equiv.) dissolved in dry THF (5 mL) was added slowly. The mixture was allowed to reach room temperature and was stirred over night (22 h). The mixture was concentrated in vacuo and the residue dissolved in saturated aqueous NH_4Cl (50 mL) and extracted with dichloromethane (3×50 mL). The combined organic extract was dried over Na_2SO_4 and the solvent removed in vacuo yielding the crude product. The crude product was purified using column chromatography (silica, ethyl acetate:hexane 1:3) yielding the pure product as a clear, colourless oil (0.305 g, 59%). $[\alpha]_D^{20}=-56.0$ (*c* 1.22, $CHCl_3$). Other spectral properties identical to the racemic material.

4.2.25. (*S*)-1-(*o*-Tolyl)-1-ethanol, (*S*)-9c. (*S*)-**9a** (0.42 g, 3.4 mmol, 1.0 equiv.) was dissolved in dry Et_2O (15 mL) and cooled to −78°C over a dry ice/acetone cooling bath. *t*-Butyllithium (4.0 mL, 1.7 M in pentane, 6.8 mmol, 2.0 equiv.) was added slowly and the mixture stirred for 2 h after which it was allowed to slowly reach room temperature over a period of 2 h. The orange solution was cooled to −78°C again and methyl iodide added slowly. The mixture was stirred at this temperature for 2 h after which it was allowed to slowly reach room temperature and was stirred further over night (17 h). Methanol (2.0 mL) was added to quench any remaining *t*-butyllithium. Aqueous HCl (20 mL,

5%) was added and the mixture extracted with Et_2O (3×20 mL). The organic extract was dried over Na_2SO_4 and the solvent removed under reduced pressure. The resulting yellowed oil was purified using column chromatography (silica, ethyl acetate:hexane 1:3) yielding a clear slightly yellowish oil (0.399 g). The oil consisted of 70% of the desired product and 30% of the starting material.

4.3. General procedure for the alkylation of aldehydes

Inside a glovebox: dry solvent, either Et_2O (2.0 mL) or a mixture of THF (1.0 mL) and Et_2O (1.0 mL), and the amino sulfide (0.22 mmol, 10.0 equiv.) were added to a reaction vessel, which was sealed with a septum. The vessel was taken out of the glovebox, fitted with a nitrogen inlet, and cooled to −78°C over a Et_2O/dry ice cooling bath. The alkyllithium solution (0.32 mmol, 14.5 equiv.), either MeLi (1.6 M in Et_2O) or *n*-BuLi (2.5 M in hexanes), was added slowly using a gas-tight syringe. The mixture was stirred for 30 min and was in some experiments cooled to −116°C over a Et_2O /liquid nitrogen cooling bath before the aldehyde solution (6.25 vol% in toluene, 0.022 mmol, 1.0 equiv.) was added slowly and the mixture stirred for 15 min before being quenched with methanol (1.0 mL). The mixture was allowed to reach room temperature and was acidified by adding diluted hydrochloric acid (5%, 1.0 mL). The mixture was extracted with Et_2O (2.5 mL) and the organic phase dried over Na_2SO_4 and analysed using chiral GC.

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