Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 2021–2027

Highly enantioselective 1,2-additions of various organolithium reagents to aldehydes

Johan Granander, Jonas Eriksson and Göran Hilmersson*

Department of Chemistry, Organic Chemistry, Göteborg University, SE-41296 Göteborg, Sweden

Received 8 June 2006; accepted 7 July 2006

Abstract—Several asymmetric 1,2-additions of various organolithium reagents (methyllithium, *n*-butyllithium, phenyllithium, lithioacetonitrile, lithium *n*-propylacetylide, lithium phenylacetylide) to aldehydes are shown to result in decent to excellent enantiomeric excesses (65–98%) when performed in the presence of a chiral lithium amido sulfide. The chiral lithium amido sulfides invariably exhibited higher levels of enantioselectivity in all the reactions tested, compared to the structurally similar chiral lithium amido ethers and the chiral lithium amide without a chelating group.

1. Introduction

The asymmetric formation of new carbon–carbon bonds is an area of organic synthesis currently experiencing intense research. The nucleophilic 1,2-addition of an organometallic reagent to a prochiral carbonyl substrate is frequently used to create a new carbon–carbon bond and introduce a new stereogenic centre.[1–3] Organozinc reagents have proven particularly suited for this reaction due to their low reactivity in the absence of a coordinating ligand and several highly enantioselective and catalytic reactions have been reported. However, the higher intrinsic reactivity of organolithium reagents and the wider selection of reagents available, directly and indirectly, make them an invaluable alternative. The asymmetric 1,2-addition of alkyllithiums to aldehydes produces optically active secondary alcohols which can be used as chiral building blocks in further asymmetric synthesis. Since the seminal work by Nozaki in 1968, asymmetry has been induced in the 1,2-addition reaction of alkyllithium reagents to aldehydes using chiral amines,[4–6] chiral lithium alkoxides[7–9] and chiral lithium amides.[10–16] In contrast to the number of reports on asymmetric 1,2-additions of alkyllithiums, only a handful of studies have been devoted to the enantioselective 1,2-addition of functionalized organolithium reagents.[17–19] The 1,2-addition of lithiated nitriles to aldehydes, for example, yields synthetically versatile β-hydroxy nitriles. These compounds can potentially be used as precursors in the synthesis of novel chiral γ-hydroxy amines and β-hydroxy carboxylic acids. The success in the asymmetric 1,2-addition of lithium cyclopropylacetylide to a trifluoromethyl ketone, yielding a precursor to efivarenz, shows that functionalized organolithium reagents also can play a valuable role in the development of enantiopure pharmaceuticals. The asymmetric 1,2-addition of lithium cyclopropylacetylide has been studied in great detail and has resulted in enantiomeric excesses of 99% and excellent conversions.[20–22]

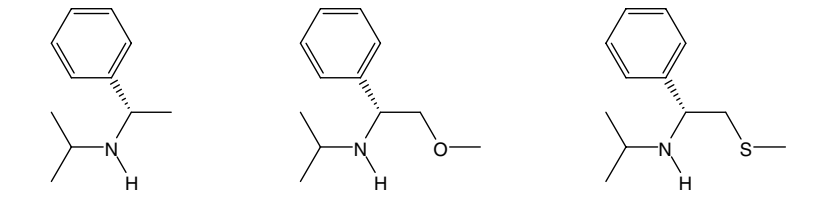
Recently, we reported on the excellent enantioselectivity in the 1,2-addition of *n*-butyllithium and methyllithium to aldehydes induced by a novel chiral lithium amido sulfide.[23] Herein, we report on the efficiency of the lithium amido sulfide as a ligand in the asymmetric 1,2-addition of alkyllithiums and functionalized organolithium reagents (phenyllithium, lithioacetonitrile, lithium phenylacetylide and lithium *n*-propylacetylide) to aldehydes. A comparison of the enantioselectivity in the 1,2-addition reaction between chiral lithium amides, formed from amines **1**–**6**, is also reported.

2. Results and discussion

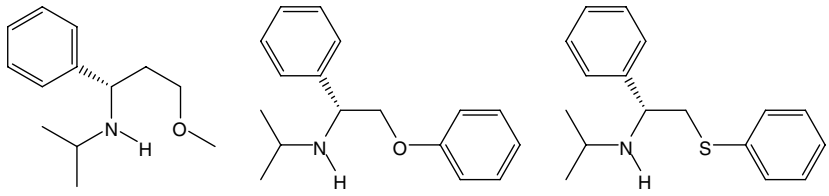
Chiral amines, (*S*)-**1**, (*R*)-**2**, (*S*)-**4** and (*R*)-**6**, were prepared from (*S*)-phenylethylamine or (*R*)-phenylglycine according to previously published methods.[14,23–25] The novel chiral

* Corresponding author. Tel.: +46 31 772904; fax: +46 31 7723840; e-mail: hilmers@chem.gu.se

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.07.009



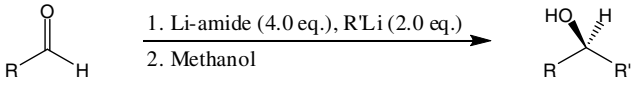
(*S*)-**1** (*R*)-**2** (*R*)-**3**



(*S*)-**4** (*R*)-**5** (*R*)-**6**

amino sulfide (*R*)-**3** was synthesized in a fashion similar to the preparation of (*R*)-**6**. The key step of the preparation of (*R*)-**5** was the copper(II)-catalyzed etherification of the corresponding *tert*-butoxycarbonyl amido alcohol using potassium trifluorophenylborate according to the method reported by Batey.[26]

The amines were lithiated and used as chiral inducers in the 1,2-addition of methyllithium, *n*-butyllithium and phenyllithium to benzaldehyde and cyclohexanecarboxaldehyde, respectively, in diethyl ether (Et_2O)/tetrahydrofuran (THF) mixtures at −116 °C (Scheme 1). The product compositions were analyzed using chiral stationary phase gas chromatography and the conversions and enantiomeric excesses of the reactions are given in Table 1.



Scheme 1. Asymmetric 1,2-addition of alkyl- or phenyllithium to aldehydes mediated by chiral lithium amides.

Lithium amido sulfide Li-**6** is the most efficient ligand, yielding impressive enantiomeric excesses of 96%, 98% and 96% in the additions of methyllithium, *n*-butyllithium and phenyllithium, respectively. The chiral lithium amide without an internal chelating group, Li-**1**, is evidently a poor ligand in the reactions studied. The inability to form a rigid chelate appears to have a very detrimental effect on the enantioselectivity of the reaction. The conversions using Li-**1** are generally lower than when using the other amides, possibly because the lesser steric bulk makes the lithium amide able to add to the substrate aldehyde itself. The lithium amido ethers, Li-**2**, Li-**4** and Li-**5** all produce good selectivities with enantiomeric excesses ranging from 75% to 96%. Aryl ether Li-**5** is the most effective of the lithium amido ethers at inducing chirality in the addition of alkyllithiums, while being the least effective ligand for phenyllithium additions. When comparing the lithium amido sulfides with the structurally analogues lithium amido ethers, Li-**3** versus Li-**2** and Li-**6** versus Li-**5**, it becomes evident that the lithium amido sulfides are more efficient at inducing asymmetry in the reaction.

Table 1. Enantiomeric excesses and conversions of the 1,2-addition of alkyl- and phenyllithium reagents (0.30 mmol) to aldehydes (0.05 mmol) mediated by chiral amines (0.20 mmol) in Et_2O/THF (2.0 mL) at −116 °C

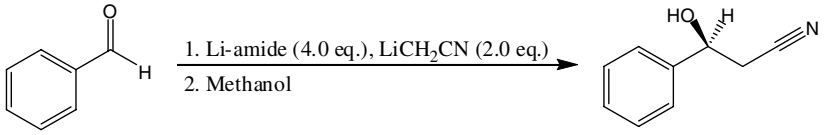
Entry	Amine	R	R′	Conv. (%)	ee (%)
1	(*S*)-**1**	Ph	CH_3	37	21 (*S*)[a]
2	(*R*)-**2**	Ph	CH_3	89	79 (*S*)[a]
3	(*R*)-**3**	Ph	CH_3	64	82 (*S*)[a]
4	(*S*)-**4**	Ph	CH_3	65	75 (*S*)[a]
5	(*R*)-**5**	Ph	CH_3	96	94 (*S*)[a]
6	(*R*)-**6**	Ph	CH_3	70	96 (*S*)[a]
7	(*S*)-**1**	Ph	$(CH_2)_3CH_3$	73	28 (*S*)[b]
8	(*R*)-**2**	Ph	$(CH_2)_3CH_3$	93	80 (*S*)[b]
9	(*R*)-**3**	Ph	$(CH_2)_3CH_3$	85	88 (*S*)[b]
10	(*S*)-**4**	Ph	$(CH_2)_3CH_3$	84	79 (*S*)[b]
11	(*R*)-**5**	Ph	$(CH_2)_3CH_3$	96	96 (*S*)[b]
12	(*R*)-**6**	Ph	$(CH_2)_3CH_3$	82	98 (*S*)[b]
13	(*S*)-**1**	*c*-C_6H_{11}	Ph	76	1 (*R*)[c]
14	(*R*)-**2**	*c*-C_6H_{11}	Ph	92	82 (*R*)[c]
15	(*R*)-**3**	*c*-C_6H_{11}	Ph	89	95 (*R*)[c]
16	(*S*)-**4**	*c*-C_6H_{11}	Ph	80	92 (*R*)[c]
17	(*R*)-**5**	*c*-C_6H_{11}	Ph	89	80 (*R*)[c]
18	(*R*)-**6**	*c*-C_6H_{11}	Ph	80	96 (*R*)[c]

[a] Absolute configuration determined by comparison with authentic (*S*)-1-phenyl-1-ethanol.[23]

[b] Absolute configuration determined by comparison of the specific rotation with the literature values.[27]

[c] Absolute configuration determined by comparison of the specific rotation with the literature values.[28]

The 1,2-addition of lithioacetonitrile to benzaldehyde yields 3-hydroxy-3-phenylpropionitrile, a potential precursor of fluoxetine. Previous studies of this reaction have revealed a wide variety of different mixed complexes between chiral lithium amides and lithioacetonitrile in solution.[18,29] Asymmetric 1,2-addition reactions using chiral β-amino ethers, have previously resulted in an enantiomeric excess of 55%, when using Li-**2** as the chiral inducer. Inspired by the efficiency of Li-**6** in the addition of alkyl- and phenyllithium, the 1,2-addition of lithioacetonitrile to benzaldehyde was re-examined using the new ligands. Lithioacetonitrile was generated in situ in the reaction vessel by adding acetonitrile to a mixture of the chiral amine and *n*-butyllithium at −78 °C. The reaction was subsequently cooled further to −116 °C, and benzaldehyde was added



Scheme 2. Asymmetric 1,2-addition of lithioacetonitrile to benzaldehyde yielding 3-hydroxy-3-phenylpropionitrile.

(Scheme 2). The products were analyzed using chiral stationary phase gas chromatography and the conversions and enantiomeric excesses of the reactions are given in Table 2.

Table 2. Enantiomeric excesses and conversions of the 1,2-addition of acetonitrile (0.11 mmol) to benzaldehyde (0.05 mmol) mediated by chiral amines (0.20 mmol) and *n*-butyllithium (0.30 mmol) in Et_2O/THF (2.0 mL) at −116 °C

Entry	Amine	Conv. (%)	ee (%)[a]
1	(*S*)-**1**	81	12 (*S*)
2	(*R*)-**2**	97	55 (*S*)
3	(*R*)-**3**	60	31 (*S*)
4	(*S*)-**4**	82	15 (*S*)
5	(*R*)-**5**	90	5 (*S*)
6	(*R*)-**6**	88	75 (*S*)

[a] Absolute configuration determined by comparison with authentic (*S*)-3-hydroxy-3-phenylpropionitrile.[30]

The lithium amide without an internally chelating group, Li-**1**, again only yielded a very low level of enantioselectivity but pleasingly the lithium amido sulfide Li-**6** provided the β-hydroxy nitrile product in an enantiomeric excess of 75%. Though still far from being stereospecific it still is a vast improvement compared to previous attempts. Rather surprisingly the structurally analogues lithium amido aryl ether, Li-**5**, yields an almost racemic product.

The chiral lithium amides were employed as chiral inducers in the asymmetric 1,2-addition of lithium acetylides to benzaldehyde. Extraordinary results were obtained in the addition of lithium acetylides to trifluoromethyl ketones using the lithium alkoxide of an ephedrine analogue. Applying the same ligands in the addition of lithium acetylides to aldehydes resulted in less satisfactory selectivities unless exceptionally bulky lithium acetylides were used.[22,31] The lithium acetylides were generated in situ through the reaction between the acetylene and *n*-butyllithium at −78 °C. Benzaldehyde was added to the mixture at −116 °C yielding alkynyl alcohols (Scheme 3). The results of the reactions are given in Table 3.

While the addition of lithium *n*-propylacetylide to benzaldehyde did not give any spectacular results, it should be noted that the lithium amide without a chelating group,

Table 3. Enantiomeric excesses and conversions of the 1,2-addition of acetylenes (0.11 mmol) to aldehydes (0.05 mmol) mediated by chiral amines (0.20 mmol) and *n*-butyllithium (0.30 mmol) in Et_2O/THF (2.0 mL) at −116 °C

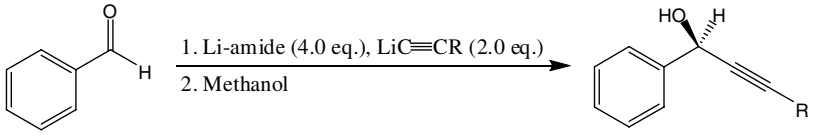
Entry	Amine	R	Conv. (%)	ee (%)
1	(*S*)-**1**	$(CH_2)_2CH_3$	48	66 (–)[a]
2	(*R*)-**2**	$(CH_2)_2CH_3$	66	66 (–)[a]
3	(*R*)-**3**	$(CH_2)_2CH_3$	40	69 (–)[a]
4	(*S*)-**4**	$(CH_2)_2CH_3$	47	39 (–)[a]
5	(*R*)-**5**	$(CH_2)_2CH_3$	79	57 (–)[a]
6	(*R*)-**6**	$(CH_2)_2CH_3$	34	65 (–)[a]
7	(*S*)-**1**	Ph	31	84 (*S*)[b]
8	(*R*)-**2**	Ph	91	88 (*S*)[b]
9	(*R*)-**3**	Ph	67	90 (*S*)[b]
10	(*S*)-**4**	Ph	78	83 (*S*)[b]
11	(*R*)-**5**	Ph	92	82 (*S*)[b]
12	(*R*)-**6**	Ph	42	91 (*S*)[b]

[a] Absolute configuration not determined.
[b] Absolute configuration determined by comparison of the specific rotation with the literature values.[32]

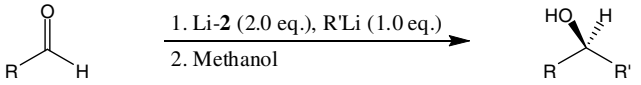
Li-**1**, actually offers an enantioselectivity of 66%, a value similar to the usually more efficient amides with coordinating groups. Lithium amido sulfide Li-**6** gave a similar enantioselectivity of 65% while Li-**3** offers a slightly higher enantioselectivity of 69%. However, the conversions are quite low for all additions (except for entries 2 and 5). When lithium phenylacetylide was used as a nucleophile, all lithium amides displayed similar enantioselectivities, 82–91%, while the chiral lithium amido sulfides Li-**3** and Li-**6** were again the most efficient of the lithium amides at inducing asymmetry in the reaction.

In order to test the efficiency of the reactions when performed on a larger scale, a few experiments were conducted with the amount of solvent, chiral amine and organolithium reagent increased by a factor of 10 and the amount of aldehyde increased by a factor of 20. The product obtained was purified and isolated using flash chromatography and the chiral amine used, recovered through an acid–base extraction (Scheme 4). The results of the reactions are given in Table 4.

The scaled up additions of *n*-butyllithium and lithioacetonitrile to benzaldehyde offered the alcohol products in high isolated yields and enantiomeric purities equal to or even



Scheme 3. Asymmetric 1,2-addition of lithium acetylides to benzaldehyde mediated by chiral lithium amides.



Scheme 4. Asymmetric 1,2-addition of organolithium reagents to aldehydes mediated by Li-**2**.

Table 4. Isolated yields, enantiomeric excesses and amounts of chiral amine recovered of the 1,2-addition of organolithium reagents (1.0 mmol) to aldehydes (1.0 mmol) mediated by (*R*)-**2** (2.0 mmol) in Et_2O/THF (20.0 mL) at −116 °C

Entry	R	R′	Isolated yield (%)	ee (%)	Amine recovered (%)
1	Ph	$(CH_2)_3CH_3$	80	85 (*S*)	97
2	*c*-C_6H_{11}	Ph	24	81 (*R*)	98
3	Ph	CH_2CN	87	55 (*S*)	98
4	Ph	C≡CPh	44	80 (*S*)	95

slightly greater than those obtained in the small scale reactions showing that those two reactions easily can be scaled up. The addition of lithium phenylacetylide offered only a modest isolated yield of 44% of the alkynyl alcohol product. It is possible that the 1:1 stoichiometry of the aldehyde versus organolithium reagent in the reaction is not optimal as we do not know what kind of mixed complexes are formed between the lithium amide and lithium phenylacetylide in solution. It has previously been reported that 2 equiv of lithium acetylide was required for full conversion of a 1,2-addition of lithium cyclopropylacetylide to a ketone.[21] More disappointing was the low isolated yield of the product obtained by the addition of phenyllithium to cyclohexanecarboxaldehyde. Since phenyllithium is a strong base, but a weak nucleophile, it is likely that it only offers low yields in the 1,2-addition to enolizable aldehydes. The chiral amine was recovered almost quantitatively after each experiment.

Interestingly, the 1,2-addition of all organolithium reagents in this study occur on the same side of the aldehyde substrate indicating that similar reaction paths, including transition state structures, are formed in the reactions. Extensive low-temperature NMR-studies have shown that the chiral lithium amido ethers and sulfides derived from amino acids exclusively form mixed dimers with *n*-butyllithium in THF.[14,16,33,34] The lithiums of the mixed dimers have been shown to be coordinated by one THF molecule, each with one lithium also internally chelated by the coordinating group of the lithium amide.[35] The bulky substituents on the nitrogen and carbon backbone of the amide are positioned in a *trans* arrangement, based on DFT calculations, as shown in Figure 1.

When the aldehyde substrates coordinate to the tricoordinated lithium, it can approach from either the *endo* or *exo* side of the mixed complex although the bulky substituent on the nitrogen makes the *exo* side considerably less accessible than the *endo* side. The aldehyde has to orient itself so that the hydrogen is located within the cavity of the mixed complex while the more sterically demanding substituent is pointing away from the complex before reaching the transition state resulting in the product with the experimentally observed configuration. The mixed complexes between the chiral lithium amides and methyl-, *n*-butyl- and phenyllithium are most likely similar but it is not certain the lithium acetylides form the same kind of mixed dimers in THF solution. The solution structures of the mixed complexes between chiral lithium amides and lithioacetonitrile are different, as lithioacetonitrile is predominantly N-lithiated in THF,[18,29] and possible transition state structures for the 1,2-addition to aldehydes are more difficult to predict.

3. Conclusion

Chiral lithium amido sulfide, Li-**6**, has been shown to be superior to the other ligands tested in all reactions, yielding enantioselectivities ranging from good to excellent. Li-**6** appears to be a very versatile chiral inducer, able to induce high levels of selectivity with various organolithium nucleophiles in the 1,2-addition reaction (Scheme 5). The chiral lithium amido ethers offer decent selectivities in the additions of alkyllithiums, phenyllithium and lithium phenylacetylide but are not as effective as the lithium amido sulfide analogues. The lithium amido ether which forms a six-membered chelate, Li-**4**, is generally equally or less able than its shorter homologue, Li-**2**, at inducing asymmetry in the 1,2-addition reactions. The chiral lithium amide without a chelating group, Li-**1**, exhibits very low enantioselectivities except when lithium acetylides were used as nucleophiles.

Investigations of the mixed complexes between chiral lithium amides and the organolithium reagents phenyllithium and lithium acetylides by spectroscopic and computational methods are currently underway in order to increase the understanding of these mixed complexes and how they react.

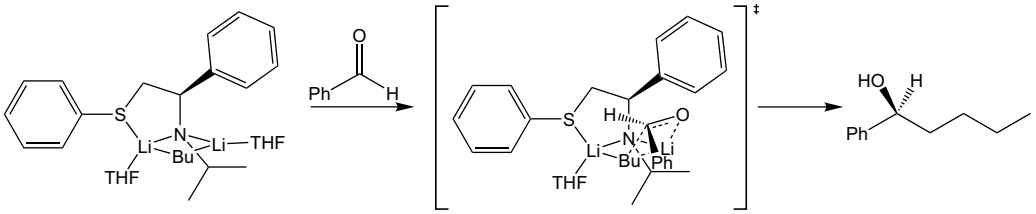
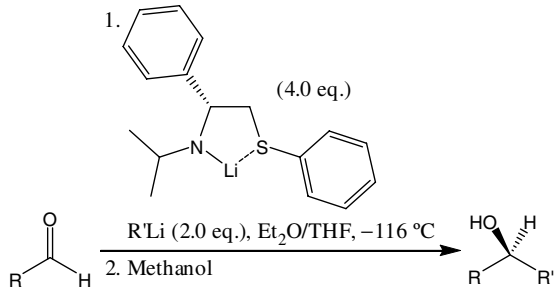


Figure 1. The solution structure of a mixed dimer between Li-**6** and *n*-butyllithium and a possible transition state structure rationalizing the experimentally observed product configuration.



R = Ph, R' = *n*-Bu	98% ee
R = *o*-CH_3Ph, R' = *n*-Bu	96% ee
R = *c*-C_6H_{11}, R' = *n*-Bu	93% ee
R = Ph, R' = Me	96% ee
R = *o*-CH_3Ph, R' = Me	87% ee
R = Ph, R' = CH_2CN	75% ee
R = Ph, R' = C≡CPh	91% ee
R = Ph, R' = C≡C$(CH_2)_2CH_3$	65% ee
R = *c*-C_6H_{11}, R' = Ph	96% ee

Scheme 5. Enantiomeric excesses obtained in a variety of asymmetric 1,2-additions using Li-**6** as chiral ligand.

4. Experimental

4.1. General

NMR spectra were recorded on a Varian 500 MHz or 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. High-resolution mass spectroscopy was carried out on a Micromass LCT spectrometer. GC analyses were performed using a Varian Star 3400 CX gas chromatograph equipped with the chiral stationary phase column CP-Chirasil-DEX CB (25 m, 0.32 mm) from Chrompack. Analyses were done using He (1.5 mL min^{-1}) as carrier gas (injector 225 °C, detector 250 °C). The organolithium reagents were purchased from Acros Organics and used as received. Dried solvents were distilled from sodium/benzophenone.

4.2. General procedure for the addition of alkyl- and phenyllithium to aldehydes

The organolithium reagent (0.30 mmol, 6.0 equiv) was added dropwise to a solution of the chiral amine (0.20 mmol, 4.0 equiv) in dry Et_2O/THF 1:1 (2.0 mL) at −78 °C under an N_2-atmosphere. After 15 min, the solution was cooled to −116 °C using a Et_2O/liquid nitrogen cooling bath and after a further 15 min at this temperature, a solution of the aldehyde (1.0 M in hexane, 50 μL, 0.05 mmol, 1.0 equiv) was added slowly, dropwise. The mixture was allowed to react for 15 min before methanol (1.0 mL) was added to quench the reaction. The mixture was allowed to warm up to room temperature and HCl (10%, 1.0 mL) and Et_2O (2.0 mL) were added. A portion of the organic phase was dried over Na_2SO_4 and analyzed using chiral stationary phase gas chromatography.

4.3. General procedure for the addition of lithioacetonitrile and lithium acetylides to benzaldehyde

n-Butyllithium (2.5 M in hexanes, 125 μL, 0.30 mmol, 6.0 equiv) was added dropwise to a solution of the chiral amine (0.20 mmol, 4.0 equiv) in dry Et_2O/THF 1:1 (2.0 mL) at −78 °C under an N_2-atmosphere. After 15 min, a solution of acetonitrile or the acetylene (2.0 M in toluene or hexane, 55 μL, 0.11 mmol, 2.2 equiv) was added dropwise. After a further 15 min, the solution was cooled to −116 °C using a Et_2O/liquid nitrogen cooling bath. After 15 min at this temperature a solution of benzaldehyde (1.0 M in hexane, 50 μL, 0.05 mmol, 1.0 equiv) was added slowly, dropwise. The mixture was allowed to react for 15 min before methanol (1.0 mL) was added to quench the reaction. The mixture was allowed to warm up to room temperature and HCl (10%, 1.0 mL) and Et_2O (2.0 mL) were added. A portion of the organic phase was dried over Na_2SO_4 and analyzed using chiral stationary phase gas chromatography.

4.4. General procedure for the scaled up addition of organolithium reagents to aldehydes

Chiral amine (*R*)-**2** (0.387 g, 2.0 mmol, 2.0 equiv) dissolved in dry Et_2O/THF 1:1 (20.0 mL) was lithiated and the organolithium reagent (1.0 mmol, 1.0 equiv) was prepared at −78 °C under an N_2-atmosphere as described above. After 30 min at −78 °C, the solution was cooled to −116 °C over a Et_2O/liquid nitrogen cooling bath. After 15 min at this temperature, the aldehyde (1.0 mmol, 1.0 equiv) was added dropwise and the mixture allowed to react for 30 min before being quenched with methanol (10 mL). The mixture was allowed to reach room temperature and was washed with HCl (10%, 3 × 10 mL). The combined aqueous phases were extracted with Et_2O (3 × 10 mL) and the combined organic phases dried over Na_2SO_4 and the solvent removed under reduced pressure. The resulting yellowish oil was purified using flash chromatography (silica, ethyl acetate–hexane) yielding the product as a clear colourless oil, which was analyzed using chiral stationary phase gas chromatography. The combined aqueous phases were made strongly basic using NaOH (5 M, 40 mL) and extracted using CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent removed under reduced pressure yielding the recovered (*R*)-**2** as a pale yellow oil in close to quantitative yield.

4.5. Synthesis of (*R*)-1-isopropylamino-1-phenyl-2-thiomethylethane (*R*)-3

(*R*)-1-(*tert*-Butoxycarbonylamino)-2-methanesulfonyloxy-1-phenylethane (20.12 g, 63.8 mmol, 1.0 equiv) dissolved in THF (150 mL) was added slowly to a suspension of sodium thiomethoxide (8.94 g, 127.6 mmol, 2.0 equiv) in dry THF (150 mL) over 30 min while stirring. The mixture was then allowed to react for 13 h. Water (100 mL) was added and

the solution concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (3×100 mL), the combined organic phases were washed with brine (100 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure yielding a slightly yellow powder (15.44 g, 97%). The crude product was purified with column chromatography (silica, CH_2Cl_2) yielding white crystals. Mp = 98.8 °C; $[\alpha]_D^{20} = -36.4$ (*c* 1.01, CH_2Cl_2); IR (KBr) ν_{max} 3384, 2975, 2905, 1679, 1523, 1363, 1268, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H, $C(CH_3)_3$), 2.01 (s, 3H, SCH_3), 2.90 (d, $J = 6.3$ Hz, 2H, $PhCHCH_2$), 4.86 (br, 1H, $PhCHCH_2$), 5.15 (br, 1H, NH), 7.25–7.37 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2 (CH_3), 28.6 ($C(CH_3)_3$), 41.2 ($PhCHCH_2$), 53.9 ($PHCHCH_2$), 80.0 ($C(CH_3)_3$), 126.5 (*p* − Ph), 127.8 (*o*-Ph), 128.9 (*m*-PH), 141.6 (*i*-Ph), 155.4 (CO); HRMS (ESI+): found 268.1378. $C_{14}H_{22}NO_2S$ requires 268.1371.

(*R*)-1-(*tert*-Butoxycarbonylamino)-1-phenyl-2-thiomethyl ethane (7.36 g, 29.5 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (50 mL). Trifluoroacetic acid (13.5 mL, 177.1 mmol, 6.0 equiv) was added and the solution stirred overnight. Water (100 mL) was added, the water phase then separated and the organic phase was extracted with aqueous hydrochloric acid (10%, 3×50 mL). The combined water phases were basified with aqueous sodium hydroxide (5 M, 800 mL). The milky mixture was extracted with CH_2Cl_2 (4×100 mL). The combined organic phases were washed with brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, which afforded a pale yellow oil (2.87 g, 58%). The crude product was purified with column chromatography (silica, CH_2Cl_2–MeOH–Et_3N 97:2:1) yielding a yellow oil. $[\alpha]_D^{20} = -36.9$ (*c* 1.01, CH_2Cl_2); IR (neat) ν_{max} 3366, 3022, 2907, 2838, 2355, 1758, 1597, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.78 (br, 2H, NH_2), 2.10 (s, 3H, CH_3), 2.68 (dd, 1H, $J = 9.2$, 13.5 Hz, $PhCHCH_2$), 2.83 (dd, 1H, $J = 4.2$, 13.5 Hz, $PhCHCH_2$), 4.12 (dd, 1H, $J = 4.2$, 9.2 Hz, $PhCHCH_2$), 7.27–7.40 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1 (CH_3), 44.6 ($PhCHCH_2$), 54.7 ($PhCHCH_2$), 126.6 (*p*-Ph), 127.6 (*o*-Ph), 128.7 (*m*-Ph), 144.8 (*i*-Ph); HRMS (ESI+): found 168.0846. $C_9H_{14}NS$ requires 168.0847.

(*R*)-1-Amino-1-phenyl-2-thiomethylethane (4.60 g, 27.5 mmol, 1.0 equiv) was dissolved in THF (40 mL) and DMPU (40 mL). Sodium carbonate (5.83 g, 55.0 mmol, 2.0 equiv) and isopropyl iodide (9.10 g, 5.2 mL, 55.0 mmol, 2.0 equiv) were added and the solution was refluxed. After 16 h of reflux, water (100 mL) was added and the mixture was allowed to reach room temperature. The mixture was concentrated under reduced pressure and extracted with Et_2O (3×100 mL). The combined organic extracts were washed with water (3×100 mL) and the solvent removed under reduced pressure. The crude product was purified with column chromatography (silica, CH_2Cl_2–Et_3N 99:1) followed by Kügelrohr distillation, yielding (*R*)-**3** as a colourless oil (4.22 g, 73%). Bp = 138 °C, 0.09 mbar; $[\alpha]_D^{20} = -61.0$ (*c* 1.05, CH_2Cl_2); IR (neat) $\nu_{max} = 3290$, 3023, 2926, 2854, 1946, 1707, 1451, 1365, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 (d, 3H, $J = 6.3$ Hz, $CH(CH_3)_2$), 1.07 (d, 3H, $J = 6.3$ Hz, $CH(CH_3)_2$), 1.71 (br, 1H, NH), 2.07 (s, 3H, SCH_3), 2.65 (sept., 1H, $J = 6.3$ Hz, $CH(CH_3)_2$), 2.68 (dd, 1H, $J = 8.8$, 13.2 Hz, $PhCH_2CH$), 2.78 (dd, 1H, $J = 4.6$, 13.2 Hz, $PhCH_2CH$), 3.90 (dd, 1H, $J = 4.6$, 8.8 Hz, $PhCH_2CH$), 7.18–7.38 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.9 (CH_3), 22.3 ($NHCH(CH_3)_2$), 24.6 ($NHCH(CH_3)_2$), 43.3 ($PHCHCH_2$), 46.1 ($NHCH(CH_3)_2$), 58.7 ($PhCHCH_2$), 127.4 (*p*-Ph), 128.4 (*o*-Ph), 128.7 (*m*-Ph), 143.8 (*i*-Ph); HRMS (ESI+): found 210.1302. $C_{12}H_{20}NS$ requires 210.1316.

4.6. Synthesis of (*R*)-1-isopropylamino-1-phenyl-2-phenoxyethane (*R*)-5

A suspension of potassium trifluorophenylborate (2.32 g, 12.6 mmol, 2.0 equiv), copper(II)acetate monohydrate (1.40 g, 7.0 mmol, 1.1 equiv), DMAP (0.16 g, 1.3 mmol, 0.2 equiv) and 4 Å molecular sieves (6.0 g) in CH_2Cl_2 (75 mL) under an oxygen atmosphere was stirred for 5 min before (*R*)-2-(*tert*-butoxycarbonylamino)-2-phenylpropanol (1.50 g, 6.3 mmol, 1.0 equiv) was added. The resulting mixture was stirred at room temperature overnight before being decanted into a separatory funnel. The reaction flask and molecular sieves were rinsed with CH_2Cl_2 (15 mL) and water (100 mL) was added to the funnel and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were washed with brine (75 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified through flash chromatography (silica, ethyl acetate–hexane 1:6) yielding (*R*)-1-(*tert*-butoxycarbonylamino)-1-phenyl-2-phenoxyethane as a clear colourless oil (0.44 g, 22% yield) that slowly crystallized upon standing. Mp = 83.2 °C; $[\alpha]_D^{20} = -15.0$ (*c* 1.00, CH_2Cl_2); IR (neat) ν_{max} 3384, 2976, 2925, 1686, 1598, 1521, 1366, 1245 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.44 (s, 9H, $C(CH_3)_3$), 4.16 (s (br), 1H, CH_2O), 4.25 (dd, $J = 4.4$, 9.6 Hz, 1H, CH_2O), 5.07 (s (br), 1H, PhCH), 5.33 (s (br), 1H, NH), 6.89–6.96 (m, 3H, Ph), 7.25–7.49 (m, 7H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.6 (CH_3), 54.1 (PhCH), 70.7 ($(CH_3)_3C$), 80.0 (CH_2O), 114.2 (*o*-OPh), 121.4 (*p*-OPh), 127.0 (Ar), 127.8 (Ar), 128.7 (Ar), 129.7 (Ar), 140.0 (*i*-Ph), 155.5 (CO), 158.5 (*i*-OPh); HRMS (ESI+): found 214.1227. $C_{14}H_{16}NO$ requires 214.1232.

(*R*)-1-(*tert*-Butoxycarbonylamino)-1-phenyl-2-phenoxyethane (0.44 g, 1.4 mmol, 1.0 equiv) and trifluoroacetic acid (0.96 g, 0.63 mL, 8.4 mmol, 6.0 equiv) were dissolved in CH_2Cl_2 (10 mL) and the resulting solution stirred at room temperature overnight. NaOH (5 M, 20 mL) was added and the aqueous phase extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated in vacuo. The resulting oil was purified through flash chromatography (silica, ethyl acetate–hexane–Et_3N 20:80:1) yielding (*R*)-1-phenyl-2-phenoxyethaneamine as a clear colourless oil (0.30 g, 100% yield). $[\alpha]_D^{20} = -39.6$ (*c* 1.04, CH_2Cl_2); IR (neat) ν_{max} 3379, 3032, 2925, 1595, 1495, 1241 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.40 (s (br), 2H, NH_2), 3.95 (dd, $J = 9.0$, 9.3 Hz, 1H, CH_2O), 4.11 (dd, $J = 3.6$, 9.3 Hz, 1H, CH_2O), 4.44 (dd, $J = 3.6$, 9.0 Hz, 1H, PhCH), 6.89–6.99 (m, 3H, Ph), 7.24–7.35 (m, 3H, Ph), 7.39 (m, 2H, Ph), 7.47 (m, 2H, Ph); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 55.4 (PhCH), 73.9 (CH_2O), 114.8 (*o*-OPh), 121.2 (*p*-OPh), 127.2 (*o*-Ph), 128.0 (*p*-Ph), 128.8 (*m*-Ph), 129.7 (*m*-OPh), 141.7 (*i*-Ph), 158.8 (*i*-OPh); HRMS (ESI+): found 214.1227. $C_{14}H_{16}NO$ requires 214.1232.

(*R*)-1-Phenyl-2-phenoxyethaneamine (0.30 g, 1.4 mmol, 1.0 equiv) and acetone (0.33 g, 0.41 mL, 5.6 mmol, 4 equiv) were dissolved in benzene (25 mL) and the solution refluxed with a Dean–Stark trap overnight. The mixture was cooled to room temperature and the solvent and excess acetone removed in vacuo. The residue was dissolved in dry ethanol (15 mL), and $NaBH_4$ (0.11 g, 2.8 mmol, 2.0 equiv) was added. The resulting mixture was stirred at room temperature for 4 h before water (15 mL) was added. The ethanol was removed under reduced pressure and the aqueous phase extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (silica, ethyl acetate–hexane–Et_3N 10:90:1) yielding (*R*)-**5** as a clear viscous colourless oil (0.33 g, 92% yield). $[\alpha]_D^{20} = -51.5$ (*c* 1.06, in CH_2Cl_2); IR (neat) ν_{max} 3330, 3063, 2962, 2866, 1949, 1596, 1494, 1458, 1239 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.06 (d, $J = 6.3$ Hz, 3H, CH_3), 1.10 (d, $J = 6.3$ Hz, 3H, CH_3), 2.75 (sept, $J = 6.3$ Hz, 1H, $(CH_3)_2CH$), 4.01 (t, $J = 8.7$ Hz, 1H, CH_2O), 4.07 (dd, $J = 4.0$, 9.4 Hz, 1H, CH_2O), 4.25 (dd, $J = 4.0$, 8.3 Hz, 1H, PhCH), 6.90–6.99 (m, 3H, Ph), 7.24–7.33 (m, 3H, Ph), 7.38 (m, 2H, Ph), 7.47 (m, 2H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.3 (CH_3), 24.5 (CH_3), 46.3 ($(CH_3)_2CH$), 59.9 (PhCH), 73.1 (CH_2O), 115.0 (*o*-OPh), 121.2 (*p*-OPh), 127.8 (*p*-Ph), 127.9 (*o*-Ph), 128.7 (*m*-Ph), 129.6 (*m*-OPh)141.3 (*i*-Ph), 158.9 (*i*-OPh); HRMS (ESI+): found 256.1699. $C_{17}H_{22}NO$ requires 256.1701.

Acknowledgements

Financial support from The Swedish Research Council and the Knut and Alice Wallenberg Foundation is gratefully acknowledged. We thank Docent Ö. Davidsson and Dr. A. Dahlén at AstraZeneca Research and Development, Mölndal (Sweden), for the high-resolution mass spectrometry analyses.

References

1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.
2. *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Springer: Heidelberg, 2003; Vol. 5.
3. Goldfuss, B. *Synthesis* **2005**, *14*, 2271–2280.
4. Nozaki, H.; Aratani, T.; Toraya, T. *Tetrahedron Lett.* **1968**, *38*, 4097–4098.
5. Seebach, D.; Dörr, H.; Bastani, B.; Ehrig, V. *Angew. Chem.* **1969**, *81*, 1002–1003.
6. Seebach, D.; Crass, G.; Wilka, E.-M.; Hilvert, D.; Brunner, E. *Helv. Chim. Acta* **1979**, *62*, 2695–2698.
7. Mukaiyama, T.; Suzuki, K.; Kobayashi, S. *Chem. Lett.* **1978**, 219–222.
8. Ye, M.; Logaraj, S.; Jackman, L. M.; Hillegass, K.; Hirsh, K. A.; Bollinger, A. M.; Grosz, A. L.; Mani, V. *Tetrahedron* **1994**, *50*, 6109–6116.
9. Schön, M.; Naef, R. *Tetrahedron: Asymmetry* **1999**, *10*, 169–176.
10. Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1984**, *25*, 5187–5190.
11. Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1519–1523.
12. Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266–8275.
13. Corruble, A.; Davoust, D.; Desjardins, S.; Fressigné, C.; Giessner-Prettré, C.; Harrison-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267–15279.
14. Arvidsson, P. I.; Hilmersson, G.; Davidsson, Ö. *Chem. Eur. J.* **1999**, *5*, 2348–2355.
15. Arvidsson, P. I.; Davidsson, Ö.; Hilmersson, G. *Tetrahedron: Asymmetry* **1999**, *10*, 527–534.
16. Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* **2002**, *58*, 4717–4725.
17. Soai, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3371–3376.
18. Sott, R.; Granander, J.; Hilmersson, G. *Chem. Eur. J.* **2002**, *8*, 2081–2087.
19. Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *Chem. Lett.* **1979**, 447–448.
20. Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 8937–8940.
21. Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028–2038.
22. Jiang, B.; Feng, Y. *Tetrahedron Lett.* **2002**, *43*, 2975–2977.
23. Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron: Asymmetry* **2003**, *14*, 439–447.
24. Juaristi, E.; Murer, P.; Seebach, D. *Synthesis* **1993**, 1243–1246.
25. Sott, R.; Granander, J.; Williamson, C.; Hilmersson, G. *Chem. Eur. J.* **2005**, *11*, 4785–4792.
26. Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381–1384.
27. Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455–1460.
28. Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2003**, *69*, 2532–2543.
29. Sott, R.; Granander, J.; Hilmersson, G. *J. Am. Chem. Soc.* **2004**, *126*, 6798–6805.
30. Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339–1342.
31. Briggs, T. F.; Winemiller, M. D.; Xiang, B.; Collum, D. B. *J. Org. Chem.* **2001**, *66*, 6291–6298.
32. Li, Z.; Upadhyay, V.; Decamp, A. E.; Dimichele, L.; Reider, P. J. *Synthesis* **1999**, 1453–1458.
33. Sott, R.; Granander, J.; Dinér, P.; Hilmersson, G. *Tetrahedron: Asymmetry* **2004**, *15*, 267–274.
34. Hilmersson, G.; Davidsson, Ö. *J. Organomet. Chem.* **1995**, *489*, 175–179.
35. Granander, J.; Sott, R.; Hilmersson, G. *Chem. Eur. J.* **2006**, *12*, 4191–4197.