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Sulfoxides as 'traceless' resolving agents for the synthesis of atropisomers by dynamic or classical resolution

Jonathan Clayden,[a,*] Przemyslaw M. Kubinski,[a] Federica Sammiceli,[a] Madeleine Helliwell[a] and Louis Diorazio[b]

[a]*Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK*
[b]*AstraZeneca PRD, Charter Way, Silk Road Business Park, Macclesfield, Cheshire SK10 2NA, UK*

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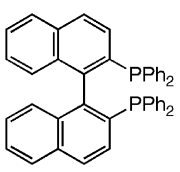
Abstract—Reacting (−)-menthyl sulfinate with an atropisomeric but racemic aryllithium gives two atropdiastereoisomeric sulfoxides. Separation (by chromatography or crystallisation) and sulfoxide–lithium exchange of each diastereoisomer regenerates the aryllithium in enantiomerically pure form which can be quenched with a range of electrophiles with retention of stereochemical integrity. Overall the reaction sequence is a resolution but without the need for an acidic or basic substituent—a 'traceless' method. In certain instances, for example when the nucleophile is an ortholithiated *peri*-substituted 1-naphthamide, the diastereoisomeric sulfoxides may be interconverted thermally. This allows a dynamic resolution, under thermodynamic control, and hence in principle can give yields of the final products of greater than 50%. The utility of the method is demonstrated by the synthesis of a known atropisomeric phosphine ligand.

1. Introduction

Many of the most effective ligands for asymmetric catalysis by metals are atropisomeric.[1–3] Although there are an increasing number of asymmetric methods for the construction of atropisomeric biaryls by asymmetric coupling methods,[4,5] almost all practical syntheses of ligands rely on resolution.[6,7] The acidic or basic groups required for resolution are rarely present in the final target ligand, and this can place constraints on the choice of synthetic route and therefore the ability to vary a single route to provide a range of ligands. In the case of BINAP **1**, a resolution of the bis-phosphine oxide **2** is carried out—one enantiomer of this compound fortunately forms a much more crystalline 1:1 complex with di-*O*-benzoyl tartrate than the other.[6] The general asymmetric synthesis of chiral binaphthyls from a single precursor is made harder by the unfortunate fact that although the diamine **3** can be resolved, racemisation of the intermediates in its diazotisation–substitution reactions is rapid.[8]



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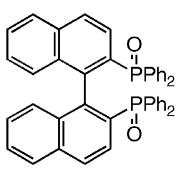

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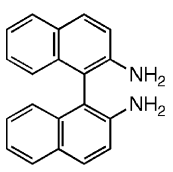

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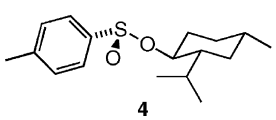

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We recently reported the use of sulfoxides as 'chiral equivalents' of anions in the asymmetric synthesis of some atropisomeric amides.[9] The sulfoxides have several features which make them amenable to use in this way: firstly, they may be constructed in enantiomerically pure form by any of a number of methods, the most important for our purposes being the Andersen substitution of (−)-menthyl sulfinate **4**.[10,11] Secondly, they have electronic properties which exaggerate the contrast between the physical properties of the two stereoisomeric atropisomers, mainly because of dipole orientation.[9] Thirdly, they may undergo sulfoxide–lithium exchange—nucleophilic substitution at sulfur—to regenerate a nucleophilic organometallic (organolithium) for use in further substitution reactions.[12–19]

In this paper we show that these properties are also applicable to the synthesis of some binaphthyl atropisomers, along with a known atropisomeric amidophosphine ligand. In one sequence, we aim to exploit the influence of the dipole of the intermediate binaphthylsulfoxide on the relative polarity of the atropisomeric diastereoisomers, allowing their chromatographic separation. In the other, the dipole governs the relative stability of a pair of diastereoisomeric atropisomers, and allows the quantitative

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* Corresponding author. Tel.: +44-161-275-4612; fax: +44-161-275-4939; e-mail address: j.p.clayden@man.ac.uk

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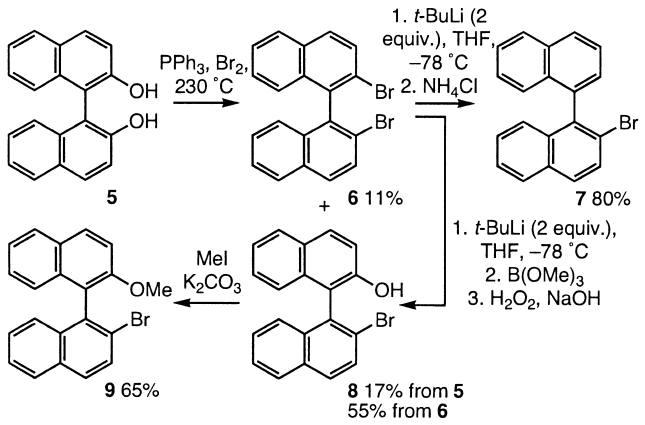
conversion of one diastereoisomer to the other. The resolution may therefore be dynamic in nature, and can yield significantly more than 50% of an enantiomerically pure product.

2. Results and discussion

2.1. Synthesis of atropisomeric binaphthyls by resolution via sulfoxides

Our plan was to use sulfoxide–lithium exchange[20] from an enantiomerically pure binaphthylsulfoxide **12** to generate a chiral, atropisomeric binaphthyllithium **10** which we hoped to quench with retention of stereochemistry, yielding enantiomerically enriched binaphthyls **11**. While the configurational stability about the chiral axis of biaryllithiums has not been studied in detail, it appears to depend on the nature of the substituent at the 2-position of the other ring. For example, 2-lithio-2′-phosphanyl-substituted binaphthyls are configurationally unstable while their borane adducts are configurationally stable.[21–23] 2,2′-Dilithio-1,1′-binaphthyl is known to be configurationally stable to −44 °C.[24]



Scheme 1. Synthesis of starting bromobinaphthalenes.

We found the reported synthesis of 2,2′-dibromobinaphthyl **6** from 2,2′dihydroxybinaphthyl (binaphthol) **5** to be a useful source of starting bromobinaphthalenes **7** and **9**:[6] in our hands **8** was always formed as a by-product during the vigorous conversion of **5** to **6**. The phenol **8** was methylated, giving **9** (Scheme 1).

Further supplies of the phenol **8** were obtained from the dibromobinaphthyl **6**. Clean monolithiation with 2 equiv. *t*-BuLi gave an organolithium, which was quenched with trimethyl borate and then oxidised to yield **8**. The same organolithium was hydrolysed to yield the bromide **7**.

The bromobinaphthyls **6**, **7** and **9** were used as starting materials for the synthesis of some sulfoxides **12**. *t*-BuLi gave the racemic organolithiums **10**, and reaction with (1*R*,2*S*,5*R*,S_S)-(−)-menthyl *p*-toluenesulfinate **4**[25] generated diastereoisomeric pairs of sulfoxides *M*- and *P*-**12a**–**c**. Reaction of **10** with achiral electrophiles MeI, NH_4Cl and *p*-Tol_2S_2 gave racemic standards **11a**, **11b** and **11c** for comparison with the enantiomerically pure samples produced later (see below).

The diastereoisomers **12b** were obtained, as expected, in a 1:1 ratio, and were readily separated by fractional crystallisation, which gave a 35% yield of *P*-**12b** and, by crystallisation from the mother liquors, a 31% yield of *M*-**12b**, both of which were identified by X-ray crystallography (Figs. 1 and 2).[26] Nucleophilic substitution with (−)-menthyl *p*-toluenesulfinate occasionally proceeds with incomplete stereospecificity:[15] later results, however, confirmed that both *M*-**12b** and *P*-**12b** obtained in this way were enantiomerically pure.

The diastereoisomers of sulfoxides **12a** and **12c** unfortunately turned out to be inseparable apart from by HPLC, which permitted the isolation of small amounts of each diastereoisomer of the two compounds, though in these cases we were unable to unequivocally assign stereochemistry to the products. The diastereoisomers of **12a** obtained in this way were compared with the racemic sulfoxides obtained when the racemic sulfide **11c** was oxidised with *m*-CPBA, and were >99% enantiomerically pure by HPLC.

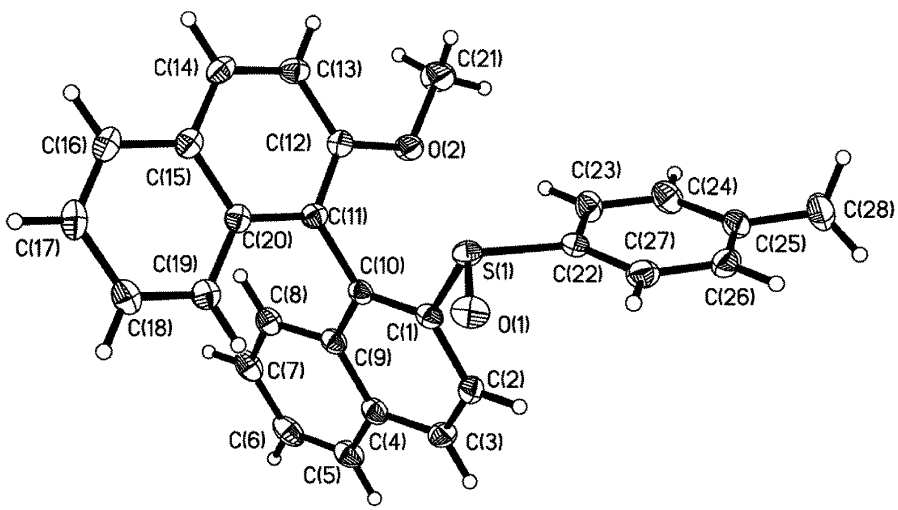


Figure 1. X-ray crystal structure of *P*-**12b**.

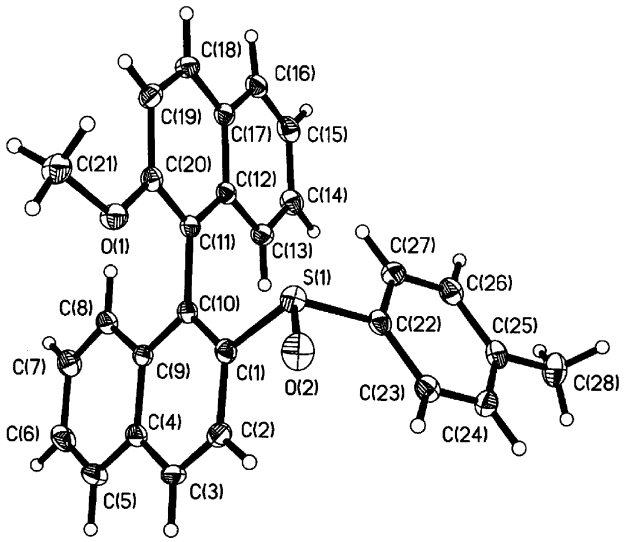
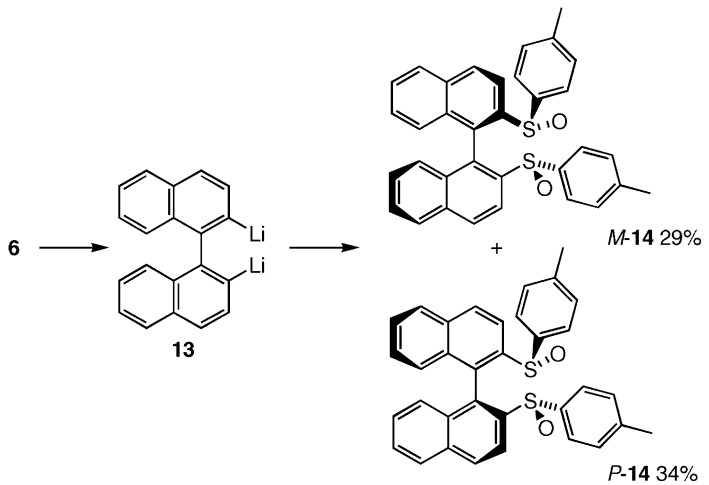


Figure 2. X-ray crystal structure of *M*-**12b**.

The oxidation of **11c** gave the diastereoisomers of **12a** in a 54:46 ratio.

Treatment of **6** with 4 equiv. of *t*-BuLi and 2 equiv. of sulfinate **4** yielded a much more readily separable pair of diastereoisomeric bis-sulfoxides **14**, whose identity was confirmed by X-ray crystal structure of the more crystalline of the pair (Fig. 3).

The separated diastereoisomers of the sulfoxides **12b** were subjected to sulfoxide–lithium exchange[9,18,20] by treatment with 2.1 equiv. *t*-BuLi to yield the enantiomerically pure binaphthyllithiums *M*- and *P*-**10b**. These organolithiums were evidently configurationally stable about the Ar–Ar axis over the period of the reaction, because methylation of each enantiomer yielded the enantiomerically pure binaphthyls *M*- and *P*-**11a** in good yield and with >99% ee in each case. Protonation yielded the enantiomerically enriched binaphthyls **11b** with some loss of enantiomeric excess (Scheme 2), which we attribute to partial racemisation of the product during isolation.



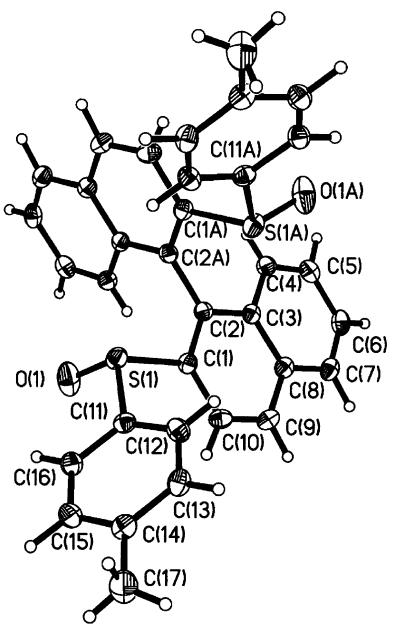
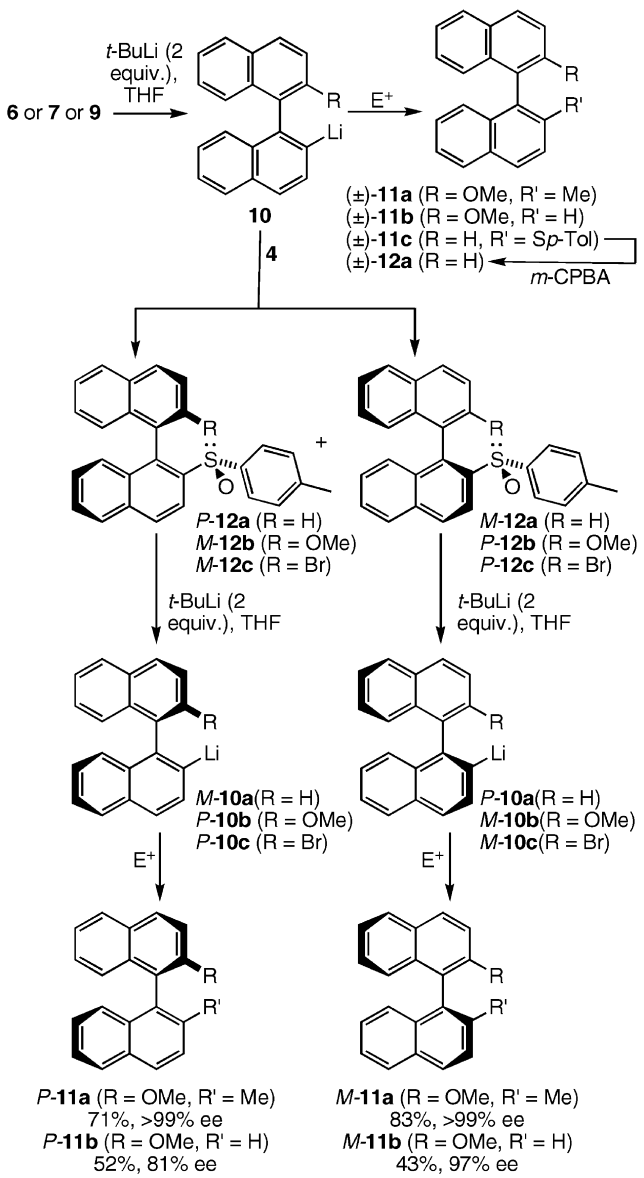


Figure 3. X-ray crystal structure of *P*-**14**.



Scheme 2. Resolution via binaphthylsulfoxides.

The asymmetric synthesis of **11a** and **11b**, although it is accomplished by resolution, is significant because of the lack of functionality in the final products of the sequence—the sulfoxide is 'traceless" as a resolving agent. In the model cases chosen here, extension of the method to further compounds was hampered by the unexpected inability to separate the sulfoxide diastereoisomers in some cases. However, the strategy clearly has potential for application to more valuable biaryl targets. We had furthermore hoped that heating mixtures of the diastereoisomers of **12a** or **12b** would allow enrichment of the mixture in the more stable of each diastereoisomeric pair, and thus allow us to convert the binaphthyl resolutions into dynamic resolutions under thermodynamic control.[9,27,28] However, in no case (heating either diastereoisomer separately or a mixture at temperatures up to 135 °C in xylene) did we see a change in the diastereoisomeric ratio. In Section 2.2, we describe the synthesis of a known ligand by a related sulfoxide-based method, which avoids the loss of 50% yield inherent in a classical resolution by incorporating just such an equilibration step into the resolution.

2.2. Synthesis of an atropisomeric amidophosphine by dynamic resolution

In 2002, Dai reported that the amidophosphine **18** (R=PPh_2) catalysed the asymmetric allylic alkylation of dimethylmalonate.[29] Secondary amidophosphines had previously been used as chiral ligands by Trost,[30] and we had shown that the chiral axis in tertiary amidophosphine ligands is the stereochemistry-controlling feature in some similar allylic alkylations.[31,32] Dai made phosphine **18**, whose configurational stability is ensured by the electronegative *peri* substituent,[33] by resolving the precursor phenol as a pair of diastereoisomeric camphanate esters.

For our asymmetric synthesis of **18**, which was under way before Dai's publication, we employed the sulfoxide-based strategy outlined above. We hoped that the known ability of the sulfoxide dipole to bias the conformation of an adjacent aromatic amide such that the C=O and S–O dipoles oppose

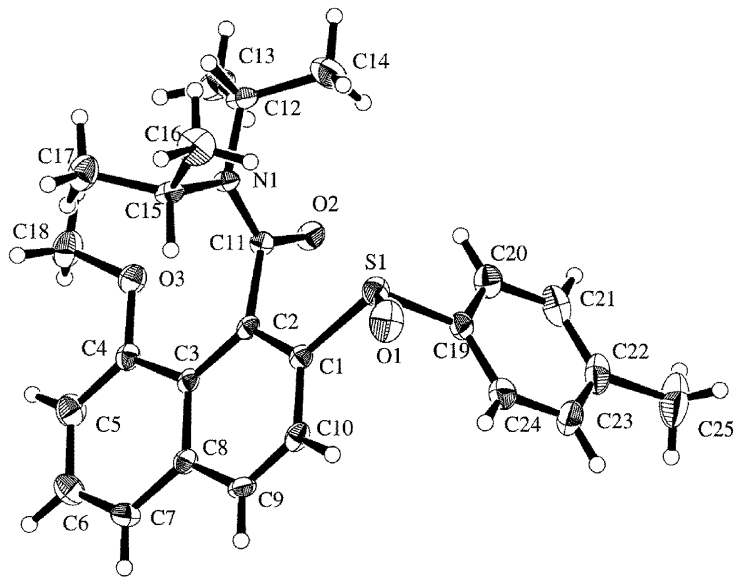


Figure 4. X-ray crystal structure of *P*-**17**.

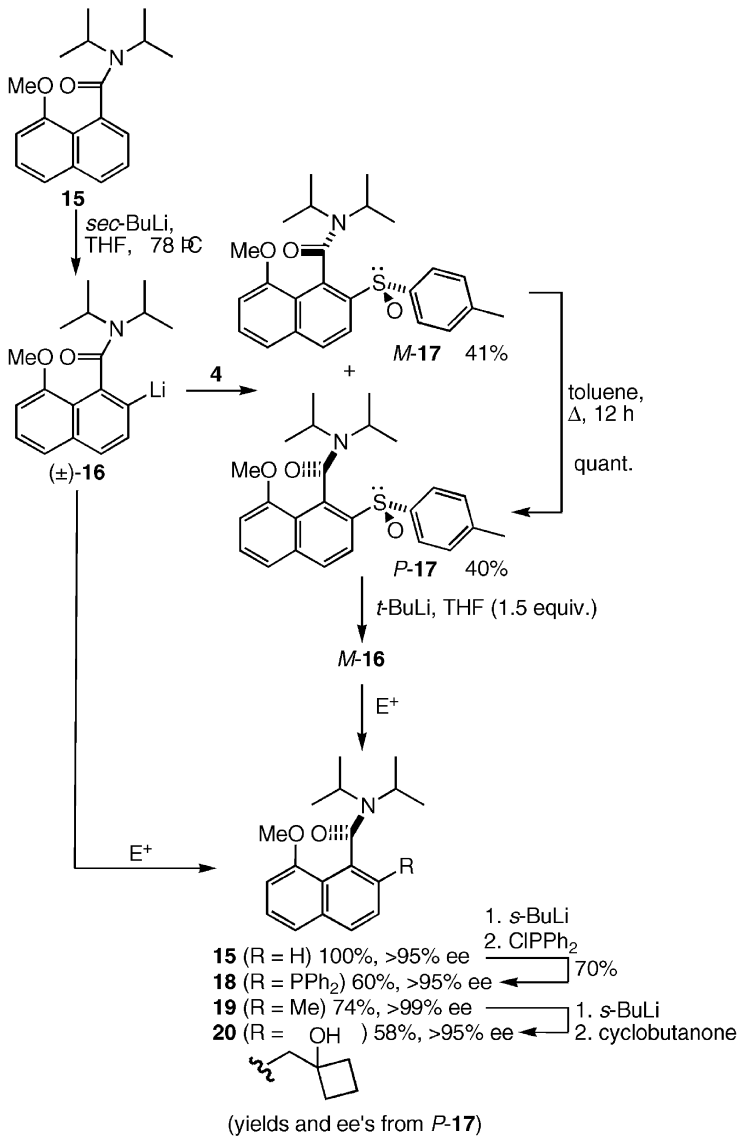
one another,[9] along with the relatively poor ability of second row elements (Si, P, S) to provide a steric barrier to amide bond rotation,[32,34] would allow us to make this ligand without recourse to a classical resolution, with the associated maximum 50% yield.

The 8-methoxynaphthamide **15** was made on a multigram scale by a published route[35] from 1,8-naphthalic anhydride. Ortholithiation with *sec*-BuLi in THF and reaction with (−)-menthyl sulfinate **4** gave the sulfoxides **17** in as a mixture of diastereoisomers. The diastereoisomers could be separated by flash chromatography, allowing the isolation of the diastereoisomers in 41 and 40% yield, respectively, and an X-ray crystal structure (Fig. 4) of one of them *P*-**17**) confirmed their relative and absolute stereochemistry.

In the light of previous studies of the preferred conformation of 2-sulfinyl amides,[9] we expected *M*-**17** to be the less stable of the two diastereoisomers. 8-Substituted naphthamides typically have very high barriers to Ar–CO rotation, especially when a non-hydrogen 2-substituent is present.[33] However, in the case of **17**, we found that heating to 100 °C for 12 h quantitatively converted *M*-**17** to *P*-**17**, while the same treatment of *P*-**17** left it unchanged. Clearly, under conditions where *M*- and *P*-**17** may interconvert, the equilibrium favours *P*-**17** to a very great extent. Application of the thermal equilibration step in the synthesis of the sulfoxides gave us a way of making, in a single transformation, the enantiomerically and diastereoisomerically pure sulfoxide *P*-**17** from the racemic amide **15** with an overall yield of >80%.

On treatment with *t*-BuLi (1.5 equiv.) in THF, the sulfoxide *P*-**17** underwent sulfoxide–lithium exchange to yield the enantiomerically pure organolithium *M*-**16**, which was quenched with the selection of electrophiles as shown in Scheme 3. Racemic standards of **18** and **19** were made by direct lithiation-electrophilic quench from **15**.

With chlorodiphenylphosphine, the ligand **18** (R=PPh_2) was formed in 60% yield (provided a non-aqueous work-up was employed[32]) and with >95% ee. Most of the remaining



Scheme 3. Asymmetric synthesis of atropisomeric amides by dynamic resolution employing amidosulfoxides.

material (30% isolated yield) was enantiomerically enriched (>95% ee) **15**, which was also easily synthesised in quantitative yield simply by protonation of *M*-**16**, a reaction which amounts to a direct dynamic thermodynamic resolution[28] of **15**. Use (or recycling) of this protonated material gives the phosphine in an improved 70% yield, but over two steps, and allows the overall yield of phosphine after a couple of recycling steps to approach 85–90%.

Methylation of *M*-**16** gave the amide **19** in 74% yield and >99% ee, which was laterally lithiated and quenched with cyclobutanone to return **20** in 58% yield and >95% ee.[36]

3. Conclusion

A sulfinyl substituent can bias the relative stability of a pair of diastereoisomeric *peri*-substituted atropisomeric amides such that one becomes much more stable than the other, allowing an efficient and high yield dynamic resolution to be achieved under thermodynamic control. The products of the resolution include an unusual amidophosphine ligand previously shown to be useful in allylic alkylation.

In the binaphthyl series, the barriers to rotation are too high for similar dynamic resolutions to be achieved, but in limited cases the sulfoxide can be used as a means of resolving the binaphthyls classically, and then replaced with any of a range of substituents, including H or Me. The products of such 'traceless' resolutions are rather more difficult to obtain by standard resolution methods. Whether sulfoxides will have a use in the asymmetric synthesis of less hindered biaryls under dynamic resolution conditions remains to be seen.[37]

4. Experimental

4.1. General methods have been published previously[32]

4.1.1. 2,2′-Dibromo-[1,1′]binaphthalenyl 6.[8] By the method of Miyashita and co-workers,[8] a 500 mL three-neck round bottom flask was equipped with mechanical stirrer, thermometer and dropping funnel. The flask was charged with triphenylphosphine (48 g, 0.183 mol) and acetonitrile (150 mL), previously distilled over calcium hydride under nitrogen; the solid was dissolved by warming the flask with hot water while stirring. The solution was then cooled by means of an ice bath, and bromine (10 mL, 0.194 mol) was added dropwise over a period of 30 in. The cold bath was removed and commercially available (±)-2,2′-hydroxy-1,1′-binaphthyl **5** (24 g, 0.084 mol) was added; the resulting slurry was heated with an oil bath at 60 °C while stirring for 30 min. Most of the solvent was removed by distillation under reduced pressure slowly increasing the temperature from 60 to 150 °C. The temperature was raised carefully to 230 °C with a sand bath, and an exothermic reaction occurred, with evolution of HBr. The reaction mixture was stirred at this temperature for 1 h. The temperature was increased and kept at 300 °C with a heating mantle for 30 min. The reaction mixture was allowed to cool to ca. 200 °C while stirring. Celite (200 mL) was added to the resulting thick black paste, and the flask was heated with an oil bath to facilitate stirring. The reaction mixture, cooled below 70 °C, was dissolved in 100 mL of hot toluene, and filtered through a sintered-glass funnel. The solid material was extracted with a boiling mixture of toluene and petrol, and the combined extracts were evaporated. The resulting brown oil was repeatedly purified by flash chromatography with a mixture petrol/EtOAc (4:1) as eluent to give the title compound **6** (3.81 g, 9.24 mmol, 11%) as white plates. δ_H (300 MHz, $CDCl_3$): 7.98 (2H, d, *J*=8.2 Hz), 7.92 (2H, d, *J*=8.8 Hz), 7.86 (2H, d, *J*=8.8 Hz), 7.54 (2H, dd, *J*=6.9, 8.1 Hz), 7.35 (2H, dd, *J*=6.9, 8.5 Hz), 7.13 (2H, d, *J*=8.5 Hz); δ_C (75 MHz, $CDCl_3$): 137.1, 133.3, 132.2, 129.9, 129.7, 128.2, 127.3, 126.3, 125.8, 122.7.

Also obtained was 2′-bromo-[1,1′]binaphthalenyl-2-ol **8** (4.98 g, 14.28 mmol, 17%).

4.1.2. 2-Bromo-[1,1′]binaphthalenyl 7.[38] *t*-BuLi (0.57 mL, 1.7 M solution in pentane, 2.00 equiv., 0.976 mmol) was added dropwise at −78 °C to a solution of 2,2′-dibromo-[1,1′]binaphthalenyl **6** (0.200 g, 0.488 mmol) in dry THF (5 mL) and stirred for 15 min under nitrogen. The reaction was then quenched with a saturated solution of NH_4Cl (10 mL) and allowed to warm to room temperature. The two layers were separated; the organic phase was washed with sat. NH_4Cl, dried over $MgSO_4$ and evaporated, to give a crude product which was purified by flash chromatography with eluent petrol/EtOAc (20:1); the title compound was obtained as yellow solid (0.1296 g, 0.390 mmol, 80%), R_f 0.53 (10% EtOAc in petrol). δ_H (300 MHz, $CDCl_3$): 8.07–8.01 (2H, m), 7.96 (1H, dd, *J*=8.4, 0.6 Hz), 7.90–7.80 (2H, m), 7.69 (1H, dd, *J*=8.1, 7.2 Hz) 7.57–7.50 (3H, m), 7.47 (1H, dd, *J*=7.2, 1.2 Hz), 7.40–7.23 (3H, m).

4.1.3. 2′-Bromo-[1,1′]binaphthalenyl-2-ol 8. *t*-BuLi (0.84 mL, 1.7 M solution in pentane, 1.95 equiv., 1.427 mmol) was added dropwise at −78 °C to a solution of 2,2′-dibromo-[1,1′]binaphthalenyl **6** (0.300 g, 0.732 mmol) in dry THF (10 mL) and stirred for 15 min under nitrogen. Dry trimethyl borate (0.10 mL, 1.20 equiv., 0.878 mmol) was added dropwise at −78 °C, and the cold bath was replaced by an ice bath. After 1 h the reaction was quenched with 2.5 M NaOH solution in 30% hydrogen peroxide (10 mL) and then allowed to warm to room temperature. The reaction mixture was acidified with 2 M HCl solution to pH <6 and the two layers were separated; the aqueous phase was extracted with EtOAc (2×20 mL) and the combined organic fractions were washed with brine (50 mL). The organic phase was dried over $MgSO_4$ and evaporated, to give a crude product, which was purified by flash chromatography eluting with petrol/EtOAc (20:1). The title compound was obtained as a yellow solid (0.1401 g, 0.403 mmol, 55%), R_f 0.38 (petrol/EtOAc 5:1), mp 166–169 °C;. ν_{max} ($CHCl_3$)/cm^{-1} 3583–3274 (OH), 1619, 1581, 1503, 811, 747; δ_H (300 MHz, $CDCl_3$): 8.02–7.86 (5H, m), 7.58 (1H, td, *J*=8.1, 1.6 Hz), 7.43–7.30 (5H, m), 7.05 (1H, d, *J*=8.4 Hz), 4.89 (1H, br, OH); δ_C (75 MHz, $CDCl_3$): 150.7, 134.2, 132.9, 132.7, 131.9, 130.5, 130.4, 130.3, 129.0, 128.3, 128.2, 127.8, 126.9, 126.8, 126.1, 124.8, 124.3, 123.6, 118.2, 117.7; *m/z* (EI) 350 ($M+^{81}Br$, 100%), 348 ($M+^{79}Br$, 79%), 269 (73%). Found M^+ 348.0148, $C_{20}H_{13}BrO$ requires M^+ 348.0150.

4.1.4. 2′-Bromo-2-methoxy-[1,1′]binaphthalenyl 9. Methyl iodide (0.51 mL, 10.00 equiv., 10.540 mmol) and potassium carbonate (0.7280 g, 5.00 equiv., 5.270 mmol) were added to a stirred solution of 2′-bromo-[1,1′]-binaphthalenyl-2-ol **8** (0.3681 g, 1.054 mmol) in acetone (7.50 mL) under nitrogen. The reaction mixture was heated under reflux for 24 h. After cooling, the mixture was filtered and the filtrate was evaporated to yield the title compound as a yellow solid (0.2480 g, 0.685 mmol, 65%), R_f 0.52 (30% EtOAc in petrol), mp 146–150 °C, *m/z* (EI) 364 ($M+^{81}Br$, 88%), 268 (100%), 239 (84%). Found M^+ 362.0308, $C_{21}H_{15}BrO$ requires M^+ 362.0307. ν_{max} ($CHCl_3$)/cm^{-1} 2930, 2838, 1620, 1588, 808, 745. δ_H (300 MHz, $CDCl_3$): 8.08 (1H, d, *J*=9.1 Hz), 7.96–7.88 (3H, m), 7.54–7.49 (2H, m), 7.42–7.22 (5H, m), 7.06 (1H, d, *J*=8.4 Hz), 3.85 (3H, s). δ_C (75 MHz, $CDCl_3$): 154.4, 134.8, 134.1, 133.0, 132.4, 130.0 (2CH), 129.1, 129.0, 128.0 (2CH), 126.8 (2CH), 126.3, 125.9, 124.6, 123.7, 123.3, 122.1, 113.8, 56.7.

4.1.5. (R_S,*P*) and (R_S,*M*)-2-Methoxy-2′-(toluene-4-sulfinyl)-[1,1′]binaphthalenyl 12b. *t*-BuLi (1.76 mL, 1.7 M solution in pentane, 2.10 equiv., 2.991 mmol) was added dropwise at −78 °C to a solution of 2′-bromo-2-methoxy-[1,1′]binaphthalenyl **9** (0.5157 g, 1.424 mmol) in dry THF (15 mL) and stirred for 15 min under nitrogen. The reaction was quenched with (−)-menthyl-(*S*)-*p*-toluene sulfinate (0.9647 g, 2.30 equiv., 3.276 mmol) dissolved in THF (10 mL). The mixture was left to warm to room temperature, and a saturated solution of NH_4Cl (10 mL) was added. The layers were separated, and the organic phase was washed with sat. NH_4Cl, dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography with eluent petrol/EtOAc (4:1) to give a mixture of two diastereoisomers of the title compound; this mixture afforded separately the two diastereoisomers by repeated fractional crystallisation from EtOAc (Diastereoisomer A 0.4418 g, 35%; Diastereoisomer B 0.3913 g, 31%). Compounds **12b** show ν_{max} ($CHCl_3$)/cm^{-1} 2926, 2842, 1621, 1593, 1508, 1046 (S=O), 809, 747, 731; *m/z* (EI) 422 (M, 5%), 318 (49%), 268 (100%). Found M^+ 422.1335, $C_{28}H_{22}O_2S$ requires M^+ 422.13404.

Diastereoisomer A, colourless needles, shown by X-ray crystallography to be *P*-**12b**, mp 218–221 °C, R_f 0.30 (40% EtOAc in petrol); δ_H (300 MHz, $CDCl_3$): 8.07 (1H, d, *J*=8.8 Hz), 8.00 (1H, d, *J*=8.8 Hz), 7.93 (1H, d, *J*=9.1 Hz), 7.82 (1H, d, *J*=8.4 Hz), 7.78 (1H, d, *J*=8.2 Hz), 7.43–7.37 (1H, m), 7.27–7.17 (5H, m), 7.15 (1H, d, *J*=9.1 Hz), 7.12 (2H, d, *J*=8.0 Hz), 7.01 (2H, d, *J*=8.0 Hz), 3.28 (3H, s), 2.20 (3H, s); δ_C (75 MHz, $CDCl_3$): 154.8, 142.3, 142.0, 140.9, 134.6, 134.3, 133.5, 132.5, 131.0, 129.7, 129.3, 128.7, 128.3, 128.0, 127.6, 127.0, 126.4, 125.9, 124.5, 124.0, 120.6, 117.1, 112.0, 55.2, 21.3.

Diastereoisomer B, colourless needles, shown by X-ray crystallography to be *M*-**12b**, mp 208–212 °C, R_f 0.23 (40% EtOAc in petrol); δ_H (300 MHz, $CDCl_3$): 8.23 (1H, d, *J*=8.7 Hz), 8.07 (1H, d, *J*=8.8 Hz), 7.98 (1H, d, *J*=9.1 Hz), 7.86 (1H, d, *J*=8.1 Hz), 7.73 (1H, d, *J*=8.2 Hz), 7.43 (1H, d, *J*=9.1 Hz), 7.43 (1H, t, *J*=8.1 Hz), 7.21–7.10 (3H, m), 6.76–6.71 (1H, m), 6.64 (2H, d, *J*=8.2 Hz), 6.60 (2H, d, *J*=8.4 Hz), 6.16 (1H, d, *J*=8.5 Hz), 3.84 (3H, s), 2.04 (3H, s); δ_C (75 MHz, $CDCl_3$): 154.5, 141.2, 140.8, 134.5, 133.6, 132.8, 132.5, 130.9, 129.4, 129.0, 128.6, 128.3, 127.8, 127.3, 126.9, 126.4, 126.2, 125.4, 124.6, 123.2, 119.8, 117.0, 113.2, 56.5, 21.1.

4.1.6. 2-*p*-Toluenesulfanyl-[1,1′]binaphthalenyl 11c. *t*-BuLi (0.40 mL, 1.7 M solution in pentane, 2.10 equiv., 0.681 mmol) was added dropwise at −78 °C to a solution of 2-bromo-[1,1′]binaphthalenyl **7** (0.1076 g, 0.324 mmol) in dry THF (4 mL) and stirred for 15 min under nitrogen. The temperature was warmed to −20 °C to destroy the excess of *t*-BuLi, and then decreased again to −78 °C. The reaction was quenched with *p*-tolyl disulfide (0.1837 g, 2.30 equiv., 0.745 mmol). The mixture was then left to warm to room temperature, and a saturated solution of NH_4Cl (5 mL) was added. The two layers were separated; the organic phase was washed with NaOH (2 M), dried over $MgSO_4$ and evaporated. The product sulfide was employed without further purification.

4.1.7. (R_S,*P*) and (R_S,*M*)-2-(Toluene-4-sulfinyl)-[1,1′]binaphthalenyl 12a. (a) By lithiation of 2-bromo-[1,1′]binaphthalenyl **7** and reaction with (−)-menthyl-(*S*)-*p*-toluene sulfinate. *t*-BuLi (1.12 mL, 1.7 M solution in pentane, 2.10 equiv., 1.897 mmol) was added dropwise at −78 °C to a solution of 2-bromo-[1,1′]binaphthalenyl **7** (0.3000 g, 0.904 mmol) in dry THF (10 mL) and the mixture was stirred for 15 min under nitrogen. The reaction was quenched with (−)-menthyl-(*S*)-*p*-toluene sulfinate[11] (0.6119 g, 2.30 equiv., 2.079 mmol) dissolved in THF (10 mL). The mixture was allowed to warm to room temperature, and a saturated solution of NH_4Cl (20 mL) was added. The layers were separated, the organic phase was washed with sat. NH_4Cl, dried over $MgSO_4$ and evaporated. Purification by flash chromatography with eluent petrol/EtOAc (4:1) gave a mixture of two diastereoisomers of the title compound (0.0338 g, 0.086 mmol, 10%). Analytical HPLC was carried out with Sphereclone column, flow 0.5 mL/min, at room temperature in hexane/IPA (95:5), t_r 16.32 min (60.4%) and 17.01 min (39.6%). Small samples (ca. 2 mg) of each diastereoisomer were obtained by preparative HPLC.

(b) By oxidation of 2-*p*-tolylsulfanyl-[1,1′]binaphthalenyl (**7**) with *m*-CPBA. A 75% solution of *m*-chloroperoxybenzoic acid (0.1099 g, 1.00 equiv., 0.478 mmol) was added to a solution of 2-*p*-tolylsulfanyl-[1,1′]binaphthalenyl **11c** (0.1796 g, 0.478 mmol) in DCM (5 mL). The reaction mixture was stirred at room temperature for 2 h, washed with a solution of $NaHCO_3$, dried over $MgSO_4$ and evaporated. Purification by flash chromatography with eluent petrol/EtOAc (19:1) gave the title compound as a mixture of two diastereoisomers (0.0125 g, 0.032 mmol, 7%). Analytical HPLC was carried out with Sphereclone column, flow 0.5 mL/min, at room temperature in hexane/IPA (95:5), t_r 16.25 min (53.9%) and 16.99 min (46.1%). Compounds **12a** show R_f 0.24 (30% EtOAc in petrol), *m/z* (EI) 392 (M, 49%), 269 (100%), 49 (84%). Found M^+ 392.1235, $C_{27}H_{20}OS$ requires M^+ 392.1235. ν_{max} ($CHCl_3$)/cm^{-1} 2921, 2852, 1044 (S=O), 805, 781.

Diastereoisomer A. δ_H (300 MHz, $CDCl_3$): 8.29 (1H, d, *J*=8.7 Hz), 8.19 (1H, d, *J*=8.8 Hz), 8.06 (1H, dd, *J*=7.5, 1.7 Hz), 7.99 (1H, d, *J*=8.2 Hz), 7.92 (1H, d, *J*=8.2 Hz),

7.75–7.68 (2H, m), 7.59–7.53 (1H, m), 7.43–7.37 (1H, m), 7.34–7.28 (1H, m), 7.21 (1H, d, *J*=8.7 Hz), 6.95 (1H, ddd, *J*=8.2, 6.9, 1.2 Hz), 6.80 (2H, d, *J*=8.4 Hz), 6.75 (2H, d, *J*=8.1 Hz), 6.53 (1H, d, *J*=8.5 Hz), 2.16 (3H, s).

Diastereoisomer B. δ_H (300 MHz, $CDCl_3$): 8.29 (1H, d, *J*=8.7 Hz), 8.19 (1H, d, *J*=8.8 Hz), 8.07–7.98 (3H, m), 7.58–7.55 (3H, m), 7.50–7.27 (5H, m), 7.18 (2H, d, *J*=8.1 Hz), 7.03 (2H, dd, *J*=7.5, 1.1 Hz), 2.37 (3H, s).

4.1.8. (R_S,*P*) and (R_S,*M*)-2′-Bromo-2-(toluene-4-sulfinyl)-[1,1′]binaphthalenyl 12c. *t*-BuLi (0.63 mL, 1.7 M solution in pentane, 2.10 equiv., 1.076 mmol) was added dropwise at −78 °C to a solution of 2,2′-dibromo-[1,1′]-binaphthalenyl **6** (0.2100 g, 0.512 mmol) in dry THF (5 mL) and stirred for 15 min under nitrogen. (−)-Menthyl-(*S*)-*p*-toluene sulfinate[11] (0.3469 g, 2.30 equiv., 1.178 mmol) dissolved in THF (5 mL) was added. The mixture was left to warm to room temperature, and a saturated solution of NH_4Cl (10 mL) was added. The layers were separated, the organic phase was washed with sat. NH_4Cl, dried over $MgSO_4$ and evaporated. Purification by flash chromatography with eluent petrol/EtOAc (4:1) gave a mixture of two diastereoisomers of the title compound (0.0975 g, 0.207 mmol, 40%). Separation of the diastereoisomers of **12c** by flash chromatography failed, but analytical HPLC carried out with Sphereclone column, flow 0.5 mL/min, at room temperature in hexane/IPA (9:1) showed t_r 11.79 min (58%) and 13.04 min (42%). *m*/*z* (EI) 473 (MH^++^{81}Br, 33%), 268 (100%), 49 (87%). Found M^+ 470.0348, $C_{27}H_{19}BrOS$ requires M^+ 470.0340. νmax film/$CHCl_3$ (cm^{-1}) 2922 (CH_3), 1581, 1500 (two Ar C–C bands), 1044 (S=O), 809 (Ar C–H), 732 (C–Br); δ_H (300 MHz, $CDCl_3$): 8.42 (1H diast. A, d, *J*=8.7 Hz), 8.31–8.25 (1H diast. B, m), 8.22–6.71 (14H diast. A+15H diast. B, m), 6.28 (1H diast. A, d, *J*=8.4 Hz), 2.38 (3H diast. B, s), 2.16 (3H diast. A, s).

4.1.9. (R_S,R_S,*P*) and (R_S,R_S,*M*)-2,2′-Bis-(toluene-4-sulfinyl)-[1,1′]binaphthalenyl 14. *t*-BuLi (2.30 mL, 1.7 M solution in pentane, 4.00 equiv., 3.903 mmol) was added dropwise at −78 °C to a solution of 2,2′-dibromo-[1,1′]binaphthalenyl **9** (0.4000 g, 0.976 mmol) in dry THF (10 mL) and stirred for 15 min under nitrogen. The reaction mixture was then allowed to reach a temperature of about −20 °C, and added via cannula to a flask containing (−)-menthyl-(*S*)-*p*-toluene sulfinate[11] (0.7183 g, 2.50 equiv., 2.440 mmol) dissolved in THF (10 mL). The mixture was allowed to warm to room temperature, and a saturated solution of NH_4Cl (20 mL) was added. The layers were separated, the organic phase was washed with saturated NH_4Cl, dried over $MgSO_4$ and evaporated. Purification by flash chromatography with eluent petrol/EtOAc (4:1 to 1:1) gave the two diastereoisomers of the title compound: diastereoisomer A (0.1771 g, 0.334 mmol, 34%), and diastereoisomer B (0.1485 g, 0.280 mmol, 29%). *m*/*z* (EI) 531 (M, 3%), 268 (100%), 49 (64%). Found M^+ 531.1449, $C_{34}H_{26}O_2S_2$ requires M^+ 530.13741. ν_{max} ($CHCl_3$)/cm^{-1} 296, 2923 (two CH_3 bands), 1464 (CH_3), 1044 (S=O), 809 (Ar C–H).

Diastereoisomer A, identified by X-ray crystal structure as *P*-**14**: mp 248–252 °C, R_f 0.28 (petrol/EtOAc 2:3); δ_H (300 MHz, $CDCl_3$): 8.13 (2H, d, *J*=8.7 Hz), 7.99 (2H, d, *J*=8.1 Hz), 7.67–7.59 (4H, m), 7.49–7.44 (2H, m), 7.33 (2H, d, *J*=8.1 Hz), 7.24 (4H, d, *J*=8.4 Hz), 7.16 (4H, d, *J*=8.1 Hz), 2.36 (6H, s). δ_C (75 MHz, $CDCl_3$): 142.2, 141.3, 140.4, 136.7, 135.0, 133.0, 131.7, 130.4, 130.0, 129.7, 129.1, 128.5, 128.4, 127.8, 126.3, 126.0, 21.6.

Diastereoisomer B: mp 81–85 °C, R_f 0.15 (petrol/EtOAc 2:3); δ_H (300 MHz, $CDCl_3$): 8.48 (2H, d, *J*=8.8 Hz), 8.20 (2H, d, *J*=8.8 Hz), 7.80 (2H, d, *J*=8.2 Hz), 7.28 (2H, t, 7.2), 6.70–6.64 (2H, m), 6.54 (4H, d, *J*=8.2 Hz), 6.46 (4H, d, *J*=8.2 Hz), 6.06 (2H, d, *J*=8.5 Hz), 1.96 (6H, s). δ_C (75 MHz, $CDCl_3$): 142.8, 141.8, 140.7, 134.3, 132.5, 131.0, 130.3, 129.4, 128.4, 127.2, 127.1, 126.3, 125.9, 119.9, 21.4.

Also obtained were two diastereoisomers of bis-sulfoxide **14** as side products: diastereoisomer A (0.0351 g, 0.066 mmol, 13%) and diastereoisomer B (0.0239 g, 0.045 mmol, 9%).

4.1.10. (±)-2-Methoxy-2′-methyl-[1,1′]binaphthalenyl 11a.[39] *t*-BuLi (1.7 M solution in pentane, 0.34 mL, 0.580 mmol, 2.10 equiv.) was added dropwise at −78 °C to a solution of 2-bromo **7** (0.100 g, 0.276 mmol) in dry THF (5 mL) and stirred for 15 min under nitrogen. Iodomethane (0.09 mL, 1.381 mmol, 5.00 equiv.) was added at −78 °C and the mixture allowed to warm to room temperature. A saturated solution of NH_4Cl (5 mL) was added, and the two layers were separated; the organic phase was washed with sat. NH_4Cl, dried over $MgSO_4$ and evaporated under reduced pressure and without heating, to give the title compound (0.0409 g, 50%) as a yellow solid, *m*/*z* (EI) 298 (M, 100%), 268 (26%). Analytical HPLC was carried out with Chiralpak OT (+) column, flow 0.5 mL/min, at 5 °C in methanol, t_r 29.53 and 33.68 min. Spectroscopic data were consistent with the literature.[39] δ_H (300 MHz, $CDCl_3$): 8.04 (1H, d, *J*=9.1 Hz), 7.93 (2H, d, *J*=7.8 Hz), 7.91 (1H, d, *J*=9.0 Hz), 7.56 (1H, d, *J*=8.3 Hz), 7.51 (1H, d, *J*=9.1 Hz), 7.45–7.35 (2H, m), 7.30–7.23 (2H, m), 7.17 (1H, d, *J*=8.4 Hz), 7.05 (1H, d, *J*=8.5 Hz), 3.81 (3H, s), 2.15 (3H, s); δ_C (75 MHz, $CDCl_3$): 154.7, 135.3, 133.9, 133.5, 132.6, 132.4, 129.8, 129.6–122.3 (12 Ar C), 114.1, 56.9, 20.6.

4.1.11. (*M*)-2-Methoxy-2′-methyl-[1,1′]binaphthalenyl *M*-11a. In a similar way, *P*-**12b** (0.0864 g) gave *M*-**11a**, 0.0509 g, 83%, with >99% ee [Chiralpak OT (+)].

4.1.12. (*P*)-2-Methoxy-2′-methyl-[1,1′]binaphthalenyl *P*-11a. In a similar way, *M*-**12b** (0.0780 g) gave *P*-**11a**, 0.0390 g, 71%, with >99% ee [Chiralpak OT (+)].

4.1.13. (±)-2-Methoxy-[1,1′]binaphthalenyl (±)-11b.[40] In a similar way, but quenching with NH_4Cl instead of MeI, bromonaphthalene **7** (0.0894 g, 0.247 mmol) gave, after work up and evaporation under reduced pressure and without heating, the title compound as a yellow solid, 0.0542 g, 77%, R_f 0.30 (5% EtOAc in petrol). Analytical HPLC was carried out with Chiralpak OT (+) column, flow 0.7 mL/min, at 5 °C in methanol, t_r 25.63 and 29.61 min. Spectroscopic data were consistent with the literature.[40] δ_H (300 MHz, $CDCl_3$): 8.01 (2H, t, *J*=9.1 Hz), 7.99 (1H, d, *J*=9.2 Hz), 7.92 (1H, d, *J*=8.1 Hz), 7.66 (1H, dd, *J*=8.2,

7.0 Hz), 7.51–7.47 (3H, m), 7.38–7.21 (5H, m), 2.22 (3H, s).

4.1.14. (*M*)-2-Methoxy-[1,1′]binaphthalenyl *M*-11b (enantiomer A). In a similar way, *P*-**12b** (0.0383 g, 0.091 mmol) gave *M*-**11b**, 0.0111 g, 43%, 97% ee [Chiralpak OT (+)].

4.1.15. (*P*)-2-Methoxy-[1,1′]binaphthalenyl *P*-11b (enantiomer B). In a similar way, *M*-**12b** (0.0231 g, 0.055 mmol) gave *P*-**11b**, 0.0081 g, 52%, 81% ee [Chiralpak OT (+)].

4.1.16. (R_S,*P*) and (R_S,*M*)-8-Methoxy-2-(toluene-4-sulfinyl)-naphthalene-1-carboxylic acid diisopropylamide 17. *sec*-Butyllithium (1.3 equiv.) was added to naphthamide **15**[35] (0.7 g) dissolved in dry THF (10 mL) at −78 °C under nitrogen atmosphere. A light green colour appeared after 10 min, and after 2 h (−)-menthyl (*S*)-*p*-toluenesulfinate[11] (1.5 equiv.) was added. After 24 h at −78 °C the reaction mixture was allowed to warm slowly to room temperature and quenched with saturated NH_4Cl. The organic layer was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (EtOAc/petroleum ether (40–60 °C) 1:3 then 1:1 to obtain diastereoisomer A, then using EtOAc/DCM 1:1 in order to collect polar diastereoisomer B) gave two diastereoisomers in 1:1 ratio [0.43 g (41%) and 0.42 g (40%)].

Diastereoisomer A, shown by X-ray crystallography to be *P*-**17**: mp 117–119 °C; R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:1] 0.08; $[\alpha]_D^{23}$ −212.3 (*c*=1.25, $CDCl_3$); ν_{max} (film)/cm^{-1} 2970(CH), 1628 (C=O); δ_H (300 MHz, $CDCl_3$) 7.85 (1H, d, *J*=9 Hz, Ar*H*), 7.50 (5H, m, Ar*H*), 7.27 (2H, d, *J*=9 Hz, Ar*H*), 7.00 (1H, d, *J*=10 Hz, Ar*H*), 4.00 (3H, s, OCH_3), 3.59 [2H, 2 septets, *J*=7 Hz, NCH(CH_3)$_2$], 2.44 (3H, s, ArCH_3), 1.75 [6H, dd, *J*=7, 10 Hz, NCH(CH_3)$_2$], 1.08 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 0.94 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$]; δ_C ($CDCl_3$) 166.7 (C=O), 156.4, 141.6, 140.9, 138.7, 136.7, 136.5, 129.8, 129.6, 128.9 (×2), 126.3 (×2), 124.1, 121.0, 120.8, 107.3, 55.4, 50.7, 46.5, 21.3, 21.0, 20.4, 20.3, 19.6; *m*/*z* (CI) 424 (90%, $(M+H)^+$), (EI) 424 (15%, $M+H^+$); Found (EI): M^+, 423.1870, $C_{25}H_{29}NO_3S$ requires M, 423.1868.

Diastereoisomer B *M*-**17**): mp 200–201 °C; R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:1] 0.53; $[\alpha]_D^{23}$ −305.2 (*c*=0.85, $CDCl_3$); ν_{max} (film)/cm^{-1} 2972 (CH), 1629 (C=O); δ_H (300 MHz, $CDCl_3$) 7.80 (4H, m, Ar*H*), 7.45 (2H, m, Ar*H*), 7.25 (2H, d, *J*=8 Hz, Ar*H*), 6.98 (1H, d, *J*=8 Hz, Ar*H*), 4.02 (3H, s, OCH_3), 3.65 [2H, 2× septet, *J*=7 Hz, NCH(CH_3)$_2$], 2.37 (3H, s, ArCH_3), 1.80 [6H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.31 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.12 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$]; δ_C ($CDCl_3$) 168.0 (C=O), 156.1, 141.9, 140.7, 140.3, 136.1, 133.3, 130.0, 129.6, 128.5, 124.4, 121.3, 121.0, 120.2, 106.8, 55.2, 51.3, 46.3, 21.2, 20.8, 20.4, 20.2, 19.6; *m*/*z* (EI) 423 (5%, M^+); Found (EI): M^+, 423.1860, $C_{25}H_{29}NO_3S$ requires M, 423.1868.

Equilibration of the diastereoisomeric sulfoxides. Sulfoxide *M*-**17** (100 mg) was heated in toluene at 100 °C for 12 h. The solvent was evaporated under reduced pressure. Flash chromatography (EtOAc/petroleum ether (bp 40–60 °C) 1:3) gave the sulfoxide *P*-**17** as a white solid (95 mg, 95%).

4.1.17. (*M*)-8-Methoxynaphthalene-1-carboxylic acid diisopropylamide *M*-15. *t*-Butyllithium (1.5 equiv.) was added to sulfoxide *P*-**17** (40 mg, 0.1 mmol) in THF (5 mL) at −78 °C under nitrogen. After 24 h at this temperature, saturated ammonium chloride solution was added, and the mixture was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography [EtOAc/petroleum ether (bp 40–60 °C) 1:3] yielded *M*-**15** as a white solid (29 mg, 100%).[35] The enantiomeric excess was determined by HPLC on a chiral column (Whelk-O1) and was found to be greater than 99%.

4.1.18. (±)-2-Diphenylphosphanyl-8-methoxy-naphthalene-1-carboxylic acid diisopropylamide (±)-18 (R=PPh_2). Amide **15** (1 g, 3.51 mmol) was dissolved in 15 mL of degassed THF under nitrogen atmosphere at −78 °C. *sec*-Butyllithium (1.2 equiv.) was added dropwise to the reaction mixture. The brown-orange solution was stirred at −78 °C for 2 h. Chlorodiphenylphosphine (2 equiv., 7.02 mmol) was added dropwise to the solution, and after a further 24 h at −78 °C the mixture was allowed to warm to RT, poured through celite and concentrated under reduced pressure. Flash chromatography (EtOAc/petroleum ether (bp 40–60 °C) 1:7) gave the phosphine (±)-**18** (R=PPh_2) as a white solid (1.15 g, 70%); R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:1] 0.67; δ_H (300 MHz; $CDCl_3$) 7.70 (1H, d, *J*=8 Hz, Ar*H*), 7.40 (13H, m, Ar*H*), 6.92 (1H, d, *J*=7 Hz, Ar*H*), 3.96 (3H, s, OCH_3), 3.64 [2H, 2 septets, *J*=7 Hz, NCH(CH_3)$_2$], 1.82 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.76 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.15 [3H, d, *J*=6 Hz, NCH(CH_3)$_2$], 1.05 [3H, d, *J*=6 Hz, NCH(CH_3)$_2$]; *m*/*z* (CI) 470 (80%, $(M+H)^+$), (EI) 470 (5%, $(M+H)^+$); Found (EI): $(M+H)^+$, 470.2248, $C_{30}H_{32}NPO_4$ requires $(M+H)^+$ 470.2249.

4.1.19. (−)-2-Diphenylphosphanyl-8-methoxynaphthalene-1-carboxylic acid diisopropylamide (−)-18 (R=PPh_2).[29] (a) From *M*-**15**. By the method reported for (±)-**18**, *M*-**15** (100 mg, 3.51 mmol) gave phosphine (−)-**18** (115 mg, 70%) as a white solid, mp 207–209 °C (lit.[29] 209–211 °C) $[\alpha]_D^{23}$ −75.8 (*c*=0.25, $CHCl_3$); R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:1] 0.67; δ_H (300 MHz; $CDCl_3$) 7.70 (1H, d, *J*=8 Hz, Ar*H*), 7.40 (13H, m, Ar*H*), 6.92 (1H, d, *J*=7 Hz, Ar*H*), 3.96 (3H, s, OCH_3), 3.64 [2H, 2 septets, *J*=7 Hz, NCH(CH_3)$_2$], 1.82 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.76 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.15 [3H, d, *J*=6 Hz, NCH(CH_3)$_2$], 1.05 [3H, d, *J*=6 Hz, NCH(CH_3)$_2$]; *m*/*z* (CI) 470 (80%, $(M+H)^+$), (EI) 470 (5%, $(M+H)^+$); Found (EI): $(M+H)^+$, 470.2248, $C_{30}H_{32}NPO_4$ requires $(M+H)^+$ 470.2249. Enantiomeric excess was determined by HPLC (Whelk-O1) and was found to be greater than 95%.

(b) By direct sulfoxide lithium exchange: *t*-Butyllithium (1.5 equiv.) was added to sulfoxide *P*-**17** (40 mg, 0.1 mmol) in degassed THF (5 mL) at −78 °C under nitrogen. After 10 min freshly distilled chlorodiphenylphosphine was added. The mixture was stirred for a further 24 h at −78 °C, allowed to warm to RT, poured through celite and evaporated under reduced pressure. Flash chromatography

(EtOAc/petroleum ether (bp 40–60 °C) 1:7) gave the phosphine (−)-**18** as a white solid (27 mg, 60%); $[\alpha]_D^{23}$ −77.6 (c=0.5, $CHCl_3$). The enantiomeric excess was determined by HPLC on a chiral column (Whelk-O1) and was found to be greater than 95%.

4.1.20. (±)-8-Methoxy-2-methyl-naphthalene-1-carboxylic acid diisopropylamide (±)-19. Amide **15** (1.00 g, 3.51 mmol) was dissolved in 15 mL of THF under nitrogen atmosphere at −78 °C. *sec*-Butyllithium (1.3 equiv.) was added dropwise to the reaction mixture. The brown-orange solution was stirred at −78 °C for 2 h and iodomethane (2 equiv., 7.02 mmol) was added dropwise. After a further 1.5 h, saturated NH_4Cl was added. The mixture was extracted with CH_2Cl_2 (30 mL). The extracts were washed with water, dried with $MgSO_4$ and evaporated under reduced pressure. Flash chromatography (EtOAc/petroleum ether (bp 40–60 °C) 1:3) gave the amide (±)-**18** (R=Me) as a white solid (1.00 g, 95%); mp 223–224 °C; R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:1] 0.36; ν_{max} (film)/cm^{-1} 2963 (CH), 1622 (C=O); δ_H (300 MHz; $CDCl_3$) 7.60 (1H, d, J=8 Hz, Ar*H*), 7.25 (3H, m, Ar*H*), 6.76 (1H, d, J=7 Hz, Ar*H*), 3.83 (3H, s, OCH_3), 3.45 [2H, 2 septets, J=7 Hz, NC*H*(CH$_3$)$_2$], 2.41 (3H, s, ArCH_3), 1.60 [6H, m, NCH(CH_3)$_2$], 0.94 [6H, m, NCH(CH_3)$_2$]; δ_C (75 MHz; $CDCl_3$) 171.0 (C=O), 155.2, 133.5, 131.7 (×2), 129.4, 127.4, 125.3, 122.0, 120.8, 105.8, 55.2, 50.7, 45.7, 20.6, 20.5, 20.4, 19.7, 19.3; *m/z* (CI) 300 (100%, (M+H)$^+$), (EI) 299 (35%, M$^+$); Found (EI): M$^+$, 299.1893, $C_{19}H_{25}NO_2$ requires M, 299.1885.

4.1.21. (−)-8-Methoxy-2-methylnaphthalene-1-carboxylic acid diisopropylamide (−)-19. *t*-Butyllithium (1.5 equiv.) was added to sulfoxide *P*-**17** (40 mg, 0.1 mmol) in THF (5 mL) at −78 °C under nitrogen. After 10 min, methyl iodide was added, and after a further 2 h at −78 °C the mixture was allowed to warm to room temperature. The product was extracted with DCM, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography [EtOAc/petroleum ether (bp 40–60 °C) 1:3] yielded a white solid (20 mg, 74%) $[\alpha]_D^{23}$ −106.6 (c=0.2, $CHCl_3$). The enantiomeric excess was determined by HPLC on a chiral stationary phase (Whelk-O1) and was found to be >99%.

4.1.22. (±)-2-(1-Hydroxycylobutylmethyl)-8-methoxynaphthamide-1-carboxylic acid diisopropylamide (±)-20. *sec*-Butyllithium (1.1 equiv.) was added to amide (±)-**19** (100 mg, 0.27 mmol) in THF (5 mL) at −78 °C under nitrogen atmosphere. The resulting purple solution was stirred at −78 °C for 20 min and cyclobutanone was added dropwise. After 3 h the reaction mixture was allowed to warm to RT and saturated NH_4Cl was added. The mixture was extracted with CH_2Cl_2 (10 mL). The extracts were washed with water, dried with $MgSO_4$ and evaporated under reduced pressure. Flash chromatography (EtOAc/petroleum ether (bp 40–60 °C) 1:3) gave the alcohol **20** as a white solid (72 mg, 58%). Mp 147–149 °C; R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:5] 0.20; ν_{max} (film)/cm^{-1} 3311 (OH), 2972 (CH), 1603 (C=O); δ_H (300 MHz; $CDCl_3$) 7.80 (1H, d, J=8 Hz, Ar*H*), 7.40 (3H, m, Ar*H*), 6.90 (1H, d, J=7 Hz, Ar*H*), 5.10(1H, s, OH), 3.96 (3H, s, OCH_3), 3.60 [1H, septet, J=6 Hz, NC*H*(CH$_3$)$_2$], 3.35 [1H, septet, J=6 Hz, NC*H*(CH$_3$)$_2$], 3.12(1H, s, ArCH_2R), 3.10 (1H, s, ArCH_2R), 2.40 [1H, m, CH$_2$COH(CH_2)$_2$CH$_2$], 2.30 [1H, m, CH$_2$COH(CH_2)$_2$CH$_2$], 2.00 [2H, m, CH$_2$COH(CH_2)$_2$CH$_2$], 1.72 [8H, m, NCH(CH_3)$_2$ and CH$_2$COH(CH_2)$_2$CH$_2$], 1.00 [6H, m, NCH(CH_3)$_2$]; δ_C ($CDCl_3$) 173.3 (C=O), 155.2, 134.1, 133.2, 132.2, 129.4, 128.3, 126.7, 126.3, 121.7, 121.2, 106.2, 74.8, 55.6, 51.3, 45.5, 42.0, 39.1, 34.7, 20.9, 20.8, 20.6, 19.5; *m/z* (CI) 370 (100%, (M+H)$^+$), (EI) 470 (10%, (M+H)$^+$); Found (EI): (M)$^+$, 369.2290, $C_{23}H_{31}NO_3$ requires (M)$^+$ 369.2304.

4.1.23. (−)-2-(1-Hydroxy-cylobutylmethyl)-8-methoxynaphthamide-1-carboxylic acid diisopropylamide (−)-20. In a similar way, enantiomerically pure amide (−)-**19** (100 mg, 0.27 mmol) in THF (5 mL) gave, after flash chromatography (EtOAc/petroleum ether (bp 40–60 °C) 1:3) alcohol (−)-**20** as a white solid (72 mg, 58%). $[\alpha]_D^{23}$ −96 (c=0.2, $CHCl_3$). ee >95% [HPLC, Whelk-O1].

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References and notes

1. Noyori, R. *Asymmetric catalysis in organic synthesis*; Wiley: New York, 1994.
2. Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503.
3. Pu, L. *Chem. Rev.* **1998**, *98*, 2405.
4. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.
5. Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723, and references therein.
6. Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1989**, *67*, 20.
7. Toda, F.; Tanaka, K.; Stein, Z.; Golderberg, I. *J. Org. Chem.* **1994**, *59*, 5748.
8. Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.
9. Clayden, J.; Mitjans, D.; Youssef, L. H. *J. Am. Chem. Soc.* **2002**, *124*, 5266.
10. Andersen, K. K. *Tetrahedron Lett.* **1962**, 93.
11. Solladié, G.; Hutt, J.; Girardin, A. *Synlett* **1987**, 173.
12. Lockard, J. P.; Schroeck, C. W.; Johnson, C. R. *Synthesis* **1973**, 485.
13. Durst, T.; LeBelle, M. J.; van den Elzen, R.; Tin, K.-C. *Can. J. Chem.* **1974**, *52*, 761.
14. Farnum, D. G.; Veysoglu, T.; Carde, A. M.; Duhl-Emswiler, B.; Pancoast, T. A.; Reitz, T. J.; Carde, R. T. *Tetrahedron Lett.* **1977**, 4009.
15. Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1998**, *63*, 3511.
16. Argouarch, G.; Samuel, O.; Riant, O.; Daran, J.-C.; Kagan, H. B. *Eur. J. Org. Chem.* **2000**, 2893.
17. Hoffmann, R. W.; Nell, P. G.; Leo, R.; Harms, K. *Chem. Eur. J.* **2000**, 3359.

18. Annunziata, M.; Caponi, M.; Cardellicchio, C.; Naso, F.; Tortorella, P. *J. Org. Chem.* **2000**, *65*, 2843.
19. Pedersen, H. L.; Johanssen, M. *Chem. Commun.* **1999**, *40*, 2517.
20. Clayden, J. *Organolithiums: selectivity for synthesis*; Pergamon: Oxford, 2002.
21. Shimada, T.; Kurushima, H.; Cho, Y.-H.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 8854.
22. Cereghetti, M.; Schmid, R.; Schönholzer, P.; Rageot, A. *Tetrahedron Lett.* **1996**, *37*, 5343.
23. Cereghetti, M.; Arnold, W.; Broger, E. A.; Rageot, A. *Tetrahedron Lett.* **1996**, *37*, 5347.
24. Brown, K. J.; Berry, M. S.; Waterman, K. C.; Lingenfelter, D.; Murdoch, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 4717.
25. Mioskowski, C.; Solladié, G. *Tetrahedron* **1980**, *36*, 227.
26. Data deposited with the Cambridge Crystallographic Database. Deposition numbers: *P*-**12b** 224505, *M*-**12b** 224506, *P*-**14** 224507, *P*-**17** 224508.
27. Clayden, J.; Lai, L. W. *Angew. Chem. Int. Ed.* **1999**, *38*, 2556.
28. Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715.
29. Dai, W.-M.; Yeung, K. K. Y.; Liu, J.-T.; Zhang, Y.; Williams, I. D. *Org. Lett.* **2002**, 1615.
30. Trost, B. M.; van Vranke, D. L. *Chem. Rev.* **1996**, *96*, 395.
31. Clayden, J.; Lai, L. W.; Helliwell, M. *Tetrahedron Asymmetry* **2001**, *12*, 695.
32. Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033.
33. Clayden, J.; McCarthy, C.; Helliwell, M. *Chem. Commun.* **1999**, 2059.
34. Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.
35. Clayden, J.; Frampton, C. S.; McCarthy, C.; Westlund, N. *Tetrahedron* **1999**, *55*, 14161.
36. Lateral lithiation of 8-unsubstituted 2-alkyl naphthamides leads to rapid rotation about the Ar–CO bond and loss of ee (Stimson, C. C., Clayden, J., unpublished work), but clearly the 8-methoxy substituent of lithiated **19** is able to prevent this. We made **20** believing, from previous work (Pink, J. H., Clayden, J. unpublished work), that it may be a powerful ligand for use in dialkyl zinc additions to aldehydes, but unfortunately this turned out not to be the case.
37. Anderson, J. C.; Cran, J. W.; King, N. P. *Tetrahedron Lett.* **2003**, *44*, 7771.
38. Schilling, B.; Kaufmann, D. E. *Eur. J. Org. Chem.* **1998**, *4*, 701.
39. Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162.
40. Lipshutz, B. H. S. K.; Garcia, E.; Kayser, F. *J. Am. Chem. Soc.* **1993**, *115*, 9276.