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Atropisomer-selective 1,1'-binaphthyl synthesis via chirality transfer from sulfur

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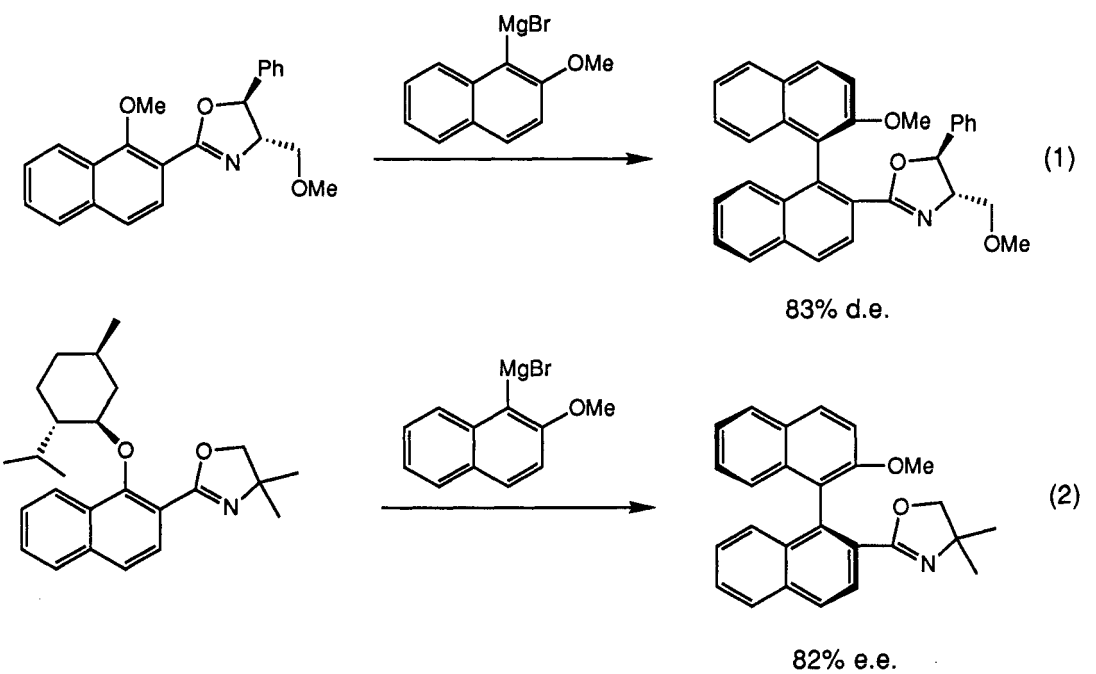
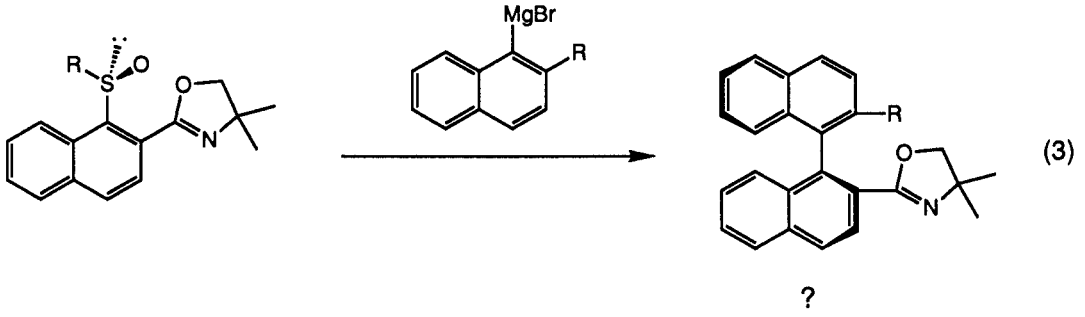
Abstract: 1-(Alkyl- or aryl-sulfinyl)naphthalenes activated by electron-withdrawing substituents at the 2-position undergo substitution reactions on treatment with Grignard reagents. Evidence suggesting that this transformation proceeds through a ligand coupling reaction of σ-sulfuranes is discussed. The ligand coupling reaction of homochiral sulfoxides with 1-naphthylmagnesium bromide furnishes atropisomeric 1,1'-binaphthyls in 60-95% e.e.

In 1982 Meyers (1) and Cram (2) and their coworkers in seminal papers described an extension of the Meyers biaryl synthesis, in which an aryl Grignard reagent displaces a methoxy group at a position *ortho* to an oxazoline moiety on an aromatic ring, to the stereoselective synthesis of atropisomeric biaryls. In the work of Meyers the chiral auxiliary was the oxazoline moiety (Eq. 1) and in Cram's work the leaving alkoxide was chiral (Eq. 2).

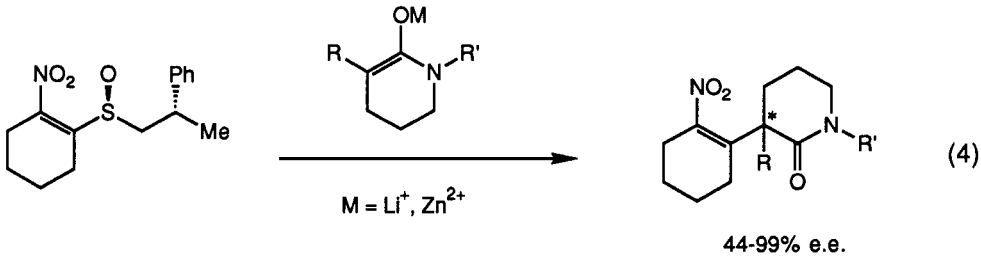


It occurred to us that a logical extension of these ideas would be to use a chiral nucleofuge in which the chiral centre is directly attached at the point of substitution. For this purpose we therefore selected a sulfinyl group (Eq. 3).



(3)

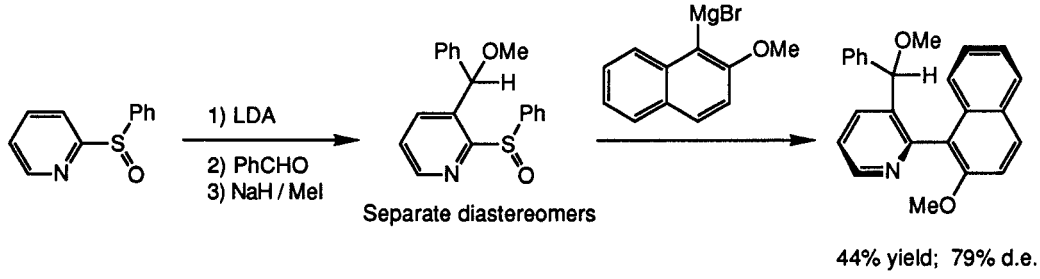
Fuji *et al.* (3) have demonstrated a conceptually similar addition-elimination strategy for chiral induction in the reaction of lactam-enolates with β-nitro-αβ-unsaturated cyclic sulfoxides (Eq. 4).



(4)

Furakawa and coworkers (4) have described the diastereoselective formation of an atropisomeric 2-pyridyl-1'-naphthyl system through a cross-coupling reaction of a 2-pyridyl sulfoxide, containing a chiral 3-substitutent, with a 1-naphthyl Grignard reagent (Scheme 1). However, it is not apparent whether the stereoselectivity in this reaction is dependent on the carbon-centred chirality of the 3-substituent on the pyridyl nucleus or the chirality of the sulfoxide moiety. Given the high chiral induction demonstrated by Meyers (Eq. 1) with a relatively remote chiral element and by Cram (Eq. 2) with a chiral element equidistant from the reaction site, compared with Furakawa's case, the role of the carbon-centred chirality is likely to be significant.

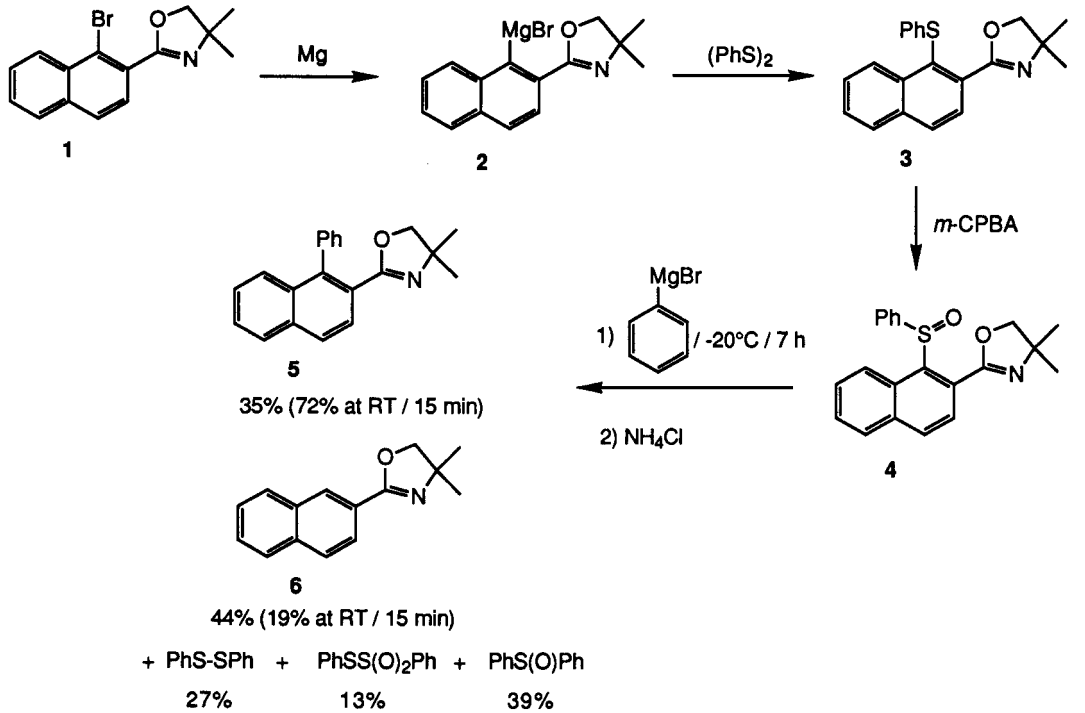
Scheme 1



The racemic phenylsulfinyl oxazoline **4** (Scheme 2) was prepared by reaction of the Grignard reagent **2** (prepared from the known bromo oxazoline **1** (2)) with diphenyldisulfide, followed by oxidation of the product with *m*-chloroperoxybenzoic acid (*m*-CPBA) in 64% overall yield. This sulfoxide **4** was caused to react with 3-4 equiv. of phenylmagnesium bromide in tetrahydrofuran (THF) solution at -20°C for 7 h

and furnished the phenyl-substituted product **5** in 35% yield, together with the desulfurised product **6** in 44% yield. Also isolated from the reaction mixture was diphenyl sulfoxide (39%), generated through a ligand exchange reaction (5) giving rise to **6**, and a 2:1 mixture of diphenyl disulfide and diphenyl thiosulfonate (*ca.* 40% combined yield), arising from disproportionation of the phenylsulfenic acid generated on acidic work-up. When the reaction was carried out at room temperature for 15 min the yield of **5** was 72%, accompanied by 19% of **6**.

Scheme 2

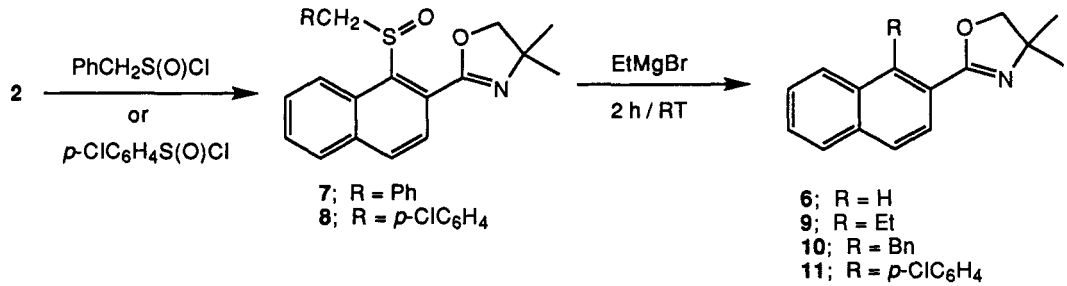


Results from the laboratories of Oae and Furakawa (6) suggested that the displacement of the phenylsulfinyl group of **4** may not occur through a direct S_NAr route, but through initial attack by the Grignard reagent at the sulfur centre. Nucleophilic attack by the Grignard reagent is considered to occur along an axial trajectory, generating a hypervalent σ-sulfurane intermediate. Subsequent ligand coupling occurs, in a concerted manner, between the axial Grignard derived ligand and the equatorial ligand activated towards nucleophilic substitution. Rearrangement of the initially formed σ-sulfurane may also occur through pseudorotation, resulting in coupling between the ligands of the original sulfoxide. This outcome is particularly facile if the sulfoxide is substituted with an apicophilic ligand such as benzyl.

Accordingly, the racemic benzylsulfinyl oxazoline **7** (Scheme 3) was prepared by reaction of the Grignard reagent **2** with benzylsulfinyl chloride (43% yield), and was allowed to react with an excess of ethylmagnesium bromide in THF solution at room temperature for 2 h. This supplied the ethyl-substituted product **9** in 75% yield, together with the benzyl-substituted product **10** (13%) and the ligand exchange product **6** (11%). Oae and coworkers (7) reported that chlorine substitution on the benzylic group of benzyl aryl sulfoxides enhances the rate of pseudorotation of σ-sulfurane intermediates formed on reaction with Grignard reagents. The reaction of the *p*-chlorobenzylsulfinyl oxazoline **8** (prepared analogously to **7** in 53% yield) with ethylmagnesium bromide resulted in an increase in the yield of the benzyl-substitution product **11** to 26% (accompanied by 63% of **9** and 5% of **6**). These results are

consistent with the substitution reaction proceeding through a ligand coupling reaction of σ-sulfurane intermediates, rather than through a direct S_NAr reaction.

Scheme 3

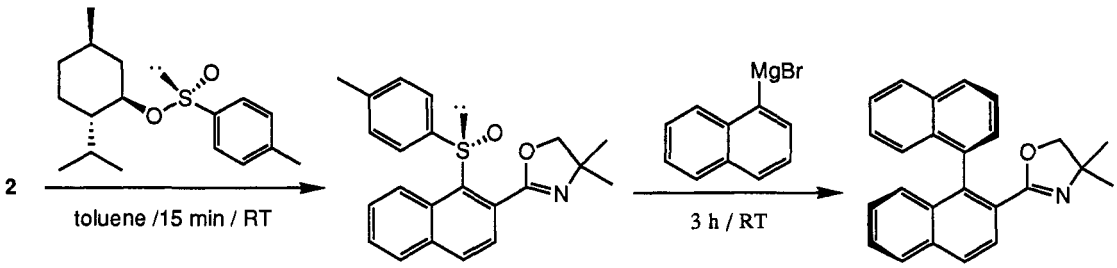


7; R = Ph
8; R = *p*-ClC$_6$H$_4$

6; R = H
9; R = Et
10; R = Bn
11; R = *p*-ClC$_6$H$_4$

The non-racemic *p*-tolylsulfinyl oxazoline **12** (Scheme 4) was next prepared by causing the Grignard reagent **2** to react with (1*R*)-menthyl (*S*)-toluene-*p*-sulfinate (0.5 equiv.) in toluene at room temperature for 15 min. The sulfoxide **12** was thus obtained in 82-89% yield and 85-95% e.e. as estimated by ^{1}H NMR spectroscopy in the presence of Eu(*hfc*)$_3$. Longer reaction times furnished a product of lower enantiomeric purity, presumably through ligand exchange reaction involving excess Grignard reagent (see below). The sulfoxide **12** is an oil, whilst the racemic material is crystalline. The enantiomeric purity of **12** could, therefore, be improved to ≥ 95%, $[\alpha]_D$ -155 (*c* 1.3, toluene), through precipitation of the racemate from hexane. The absolute configuration at the sulfur centre of **12** has been assigned as *S*, assuming that inversion of configuration accompanies nucleophilic attack by the Grignard reagent on (1*R*)-menthyl (*S*)-toluene-*p*-sulfinate (8).

Scheme 4



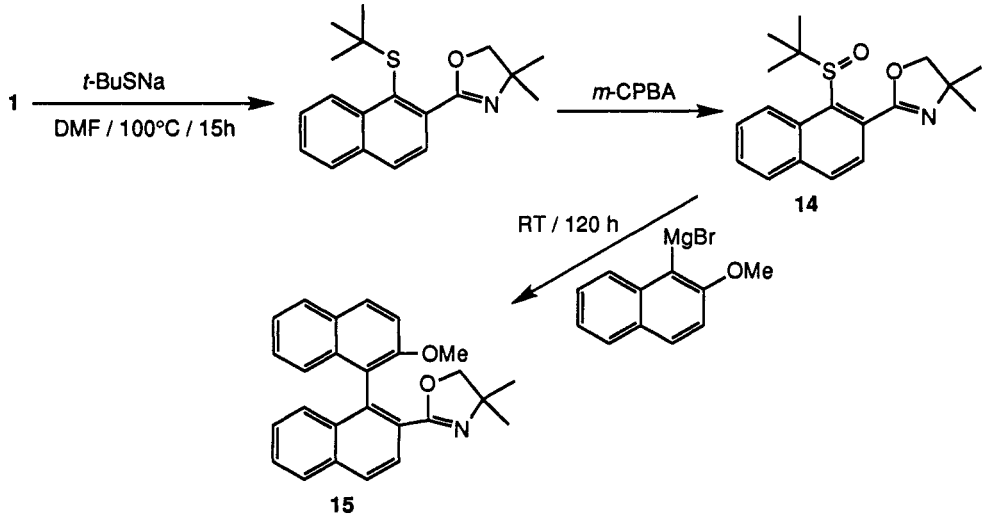
12 **13**

Reaction of **12** with 1-naphthylmagnesium bromide for 3.5 h at room temperature furnished the optically active (*S*)-1,1'-binaphthyl **13** in 71% yield and 60% e.e., $[\alpha]_{578}$ +70 (*c* 2.3, THF) (2). The recovered starting sulfoxide **12** (13%) from this reaction was found to have partially racemised (*ca.* 60% e.e.). This observation can be accounted for by initial ligand exchange reaction generating the Grignard reagent **2**, which is then able to racemise **12** by further ligand exchange reactions. When this reaction was quenched after 1.5 h the starting sulfoxide **12** (27%) with *ca.* 85% e.e. was isolated; after 30 min **12** (64%) was isolated in *ca.* 95% e.e. In neither case was the e.e. of the product **13** significantly higher than in the original experiment, confirming that the rate of racemisation is substantially lower than the rate of ligand coupling for the major part of the reaction.

Sulfoxide **12** failed to undergo a coupling reaction with 2-methoxy-1-naphthylmagnesium bromide, only the ligand exchange product **6** being isolated after several hours at room temperature. Oae *et al.* (6) have reported that *tert*-butyl 2-pyridyl sulfoxide fails to undergo ligand exchange reaction with Grignard

reagents, since this reaction can be likened to an S_N2 reaction at a neopentyl centre. The racemic *tert*-butylsulfinyl oxazoline **14** (Scheme 5) was prepared by treating the bromooxazoline **1** with sodium *tert*-butylthiolate in dimethyl formamide solution (100°C, 15 h), followed by oxidation with *m*-CPBA (87% overall yield). Reaction of **14** with an excess of 2-methoxy-1-naphthylmagnesium bromide in THF solution for 120 h at room temperature furnished the 1,1'-binaphthyl **15** in 44% yield. We are currently exploring methods for the preparation of **14** in non-racemic form.

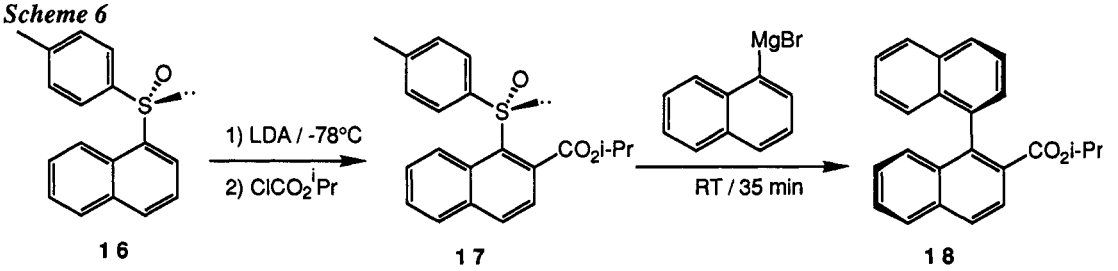
Scheme 5



An obvious extension of this work was the exploration of activating substituents other than the oxazoline moiety. We therefore chose to explore the isopropoxycarbonyl substituent since earlier workers (9) had shown that isopropyl 1-alkoxy-2-naphthoates underwent S_NAr reaction rather than carbonyl addition on treatment with 1-naphthyl Grignard reagents.

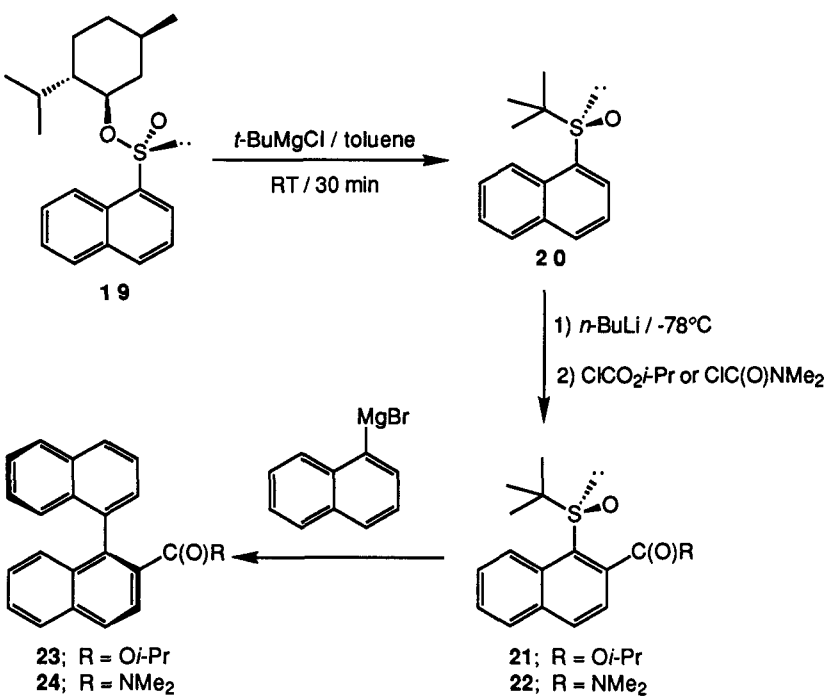
When the known (*S*)-1-*p*-tolylsulfinylnaphthalene **16** (10) (Scheme 6) was treated with lithium diisopropylamide (LDA, 1.1 equiv.) in THF solution at -78°C for 20 min, followed by inverse addition of the anion to a solution of isopropyl chloroformate (1.1 equiv.) in THF at -78°C, 2-isopropoxycarbonyl sulfoxide **17** was obtained in 36% yield and > 99.5% e.e., $[\alpha]_D$ -94 (*c* 1.05, toluene), as determined by HPLC using a (*R*)-(-)-*N*-(3,5-dinitrobenzoyl)phenylglycine Pirkle column. Regioisomeric products were not evident by TLC analysis. Care was taken in this reaction to avoid employing excess butyllithium in the generation of LDA, since it has been shown (5,10) that it may initiate ligand exchange and racemisation reactions of diaryl sulfoxides. The sulfoxide **17** on reaction with 1-naphthylmagnesium bromide (3 equiv.) in THF solution at 25°C for 30 min gave the (*S*)-1,1'-binaphthyl **18** (11) in 78% yield and 82% e.e., $[\alpha]_D$ -11 (*c* 1.98, toluene), as estimated by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$. The sulfoxide **17** failed to couple with 2-methoxy-1-naphthylmagnesium bromide.

Scheme 6



The known (1*R*)-menthyl (*S*)-1-naphthalenesulfinate **19** (8) (Scheme 7) was allowed to react with *tert*-butylmagnesium chloride (2 equiv.) in toluene solution at 0°C for 45 min, and furnished (*R*)-1-(*tert*-butylsulfinyl)naphthalene **20** in 78% yield and 90% e.e. (Pirkle column). The absolute configuration of **20** was assigned on the assumption that inversion of configuration accompanies nucleophilic attack by the Grignard reagent on the sulfinate ester (8). The sulfoxide **20** is a low melting solid (m.p. 61-63°C, dec.) and, although its optical purity could be improved by crystallisation [>99% e.e., $[\alpha]_D$ +333 (*c* 1.10, toluene)], the recovery was poor. The material of 90% e.e. was, therefore, usually employed in subsequent transformations, since the products could be efficiently crystallised to optical purity. Metalation of **20** was slow with LDA, however, treatment with butyllithium (1.1 equiv.) in THF solution at -78°C for 30 min (12), followed by inverse addition to isopropyl chloroformate (1.1 equiv.) in THF at -78°C, furnished the 2-isopropoxycarbonyl sulfoxide **21** in 39% yield. Again, regioisomeric products were not evident by TLC analysis. After a single crystallisation **21** was of 99.5% e.e., $[\alpha]_D$ +129 (*c* 1.30, toluene) (Pirkle column). It was not anticipated that in this instance that the use of butyllithium as metalating agent would initiate ligand exchange and racemisation reactions of **20**, based on the precedent of reactions of 2-(*tert*-butylsulfinyl)pyridine with Grignard reagents (13). The sulfoxide **21** was treated with 1-naphthylmagnesium bromide (2.5 equiv.) in THF solution at 25°C for 35 min, and gave the (*R*)-1,1'-binaphthyl **23** in 90% yield and 95% e.e., $[\alpha]_D$ +12.8 (*c* 1.72, toluene), as estimated by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$.

Scheme 7



The 2-lithio derivative of **20** was caused to react with *N,N*-dimethylcarbamoyl chloride (2 equiv.) in THF solution containing TMEDA (5 equiv.) at -78°C for 18 h, and furnished the 2-*N,N*-dimethylcarbamoyl sulfoxide **22** in 34% yield. After a single crystallisation **22** had ≥ 95% e.e., $[\alpha]_D$ +109 (*c* 0.375, toluene). The sulfoxide **22** on treatment with 1-naphthylmagnesium bromide (3.5 equiv.) in THF solution at 25°C for 25 h, gave the (*R*)-1,1'-binaphthyl **24** in 65% yield and 94.8% e.e., $[\alpha]_D$ +86 (*c* 0.925, toluene) (Pirkle column). Unlike the *tert*-butylsulfinyl oxazoline **14**, the sulfoxides **21** and **22** failed to undergo ligand coupling reaction with 2-methoxy-1-naphthylmagnesium bromide.

A plausible rationalisation of the sense of asymmetric coupling is illustrated in Figs. 1 and 2. Based on the work of Oae and Furukawa (6) it is proposed that initial attack of 1-naphthylmagnesium bromide on the sulfoxide **17** occurs axially from the side opposite the oxygen ligand, leading to a σ-sulfurane with the oxymagnesium bromide ligand in an apical position (Fig. 1). The equatorial 2-isopropoxycarbonyl-1-naphthyl ligand may then be oriented with the isopropoxycarbonyl group *syn* or *anti* to the *p*-tolyl group on sulfur, with the *anti* orientation being preferred for steric reasons, chelation of the magnesium to the carbonyl oxygen atom being possible for either orientation. The orientation of the axial 1-naphthyl ligand is such that non-bonded repulsions are minimised and this governs the configuration of the new asymmetric element created by the subsequent ligand coupling reaction.

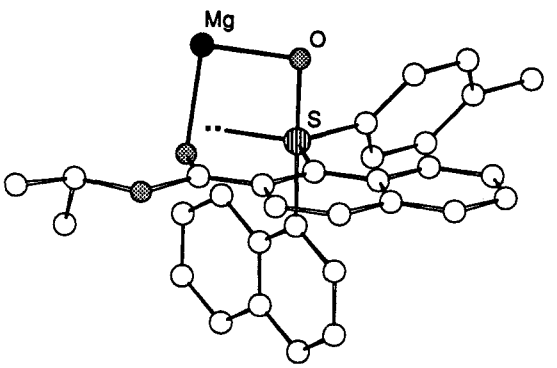


Figure 1

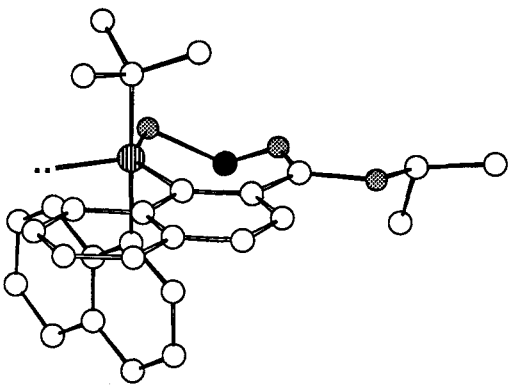
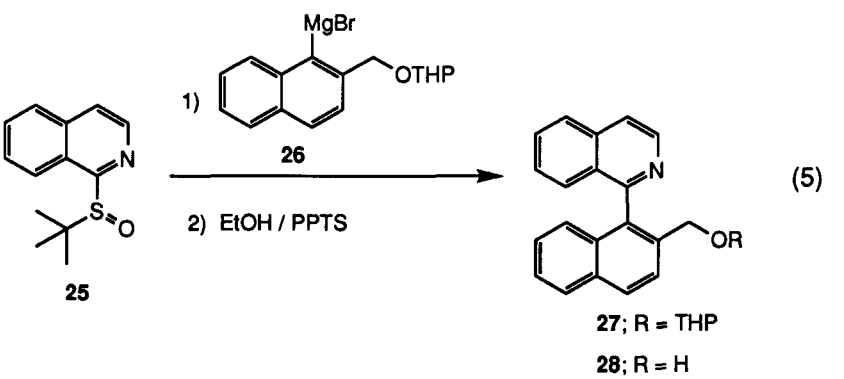


Figure 2

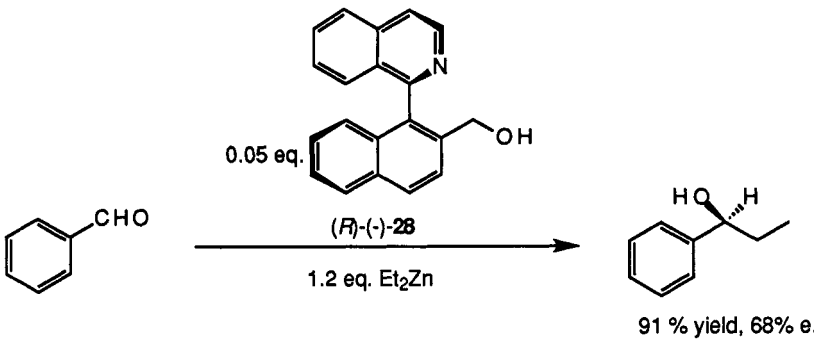
For the *tert*-butyl sulfoxide **21** it is proposed that the initial attack of 1-naphthylmagnesium bromide occurs axially from the side opposite the *tert*-butyl ligand, thus avoiding non-bonding repulsions with the bulky *tert*-butyl group. The resulting σ-sulfurane has the oxymagnesium bromide ligand in an equatorial position (Fig. 2), so that chelation of the magnesium to the carbonyl oxygen atom of the isopropoxycarbonyl group fixes the orientation of the equatorial 2-isopropoxycarbonyl-1-naphthyl ligand. The orientation of the axial 1-naphthyl ligand is again such that non-bonded repulsions are minimised.

Alcock *et al.* (14) have recently described the synthesis and resolution of an atropisomerically chiral 1-(1-naphthyl)isoquinoline P-N chelating ligand. We are currently examining possible asymmetric syntheses of similar compounds. We have synthesised racemic 1-(1-isoquinolinyl)-2-naphthalenemethanol **28** (Eq. 5) by ligand coupling reaction of the sulfoxide **25** with the Grignard reagent **26** and subsequent deprotection of the product **27**.



(5)

Resolution of the alcohol **28** was achieved *via* derivatisation with (+)-Noe lactol®. The resultant (*R*)-(-)-enantiomer of **28** failed to racemise in boiling benzene during 24 h, and was shown to enantioselectively catalyse the addition of diethylzinc to benzaldehyde to afford (*S*)-1-phenyl-1-propanol in 91% yield and 68% e.e. (Eq. 6). Routes to the non-racemic sulfoxide **25** are currently being investigated.



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