

Atropisomer-selective 1,1-Binaphthyl Synthesis via Chirality Transfer from Sulfur

Robert W. Baker,* Geoffrey R. Pocock and Melvyn V. Sargent*

Department of Chemistry, University of Western Australia, Nedlands, Western Australia, 6009

4,5-Dihydro-2-(1-alkyl- or 1-aryl-sulfinyl)naphthalen-2-yl)-4,4-dimethyloxazoles **3–6** undergo substitution reactions on treatment with Grignard reagents; the optically active sulfoxide **14** on treatment with 1-naphthylmagnesium bromide furnished the 1,1-binaphthyl **15** in 60% enantiomeric excess (e.e.).

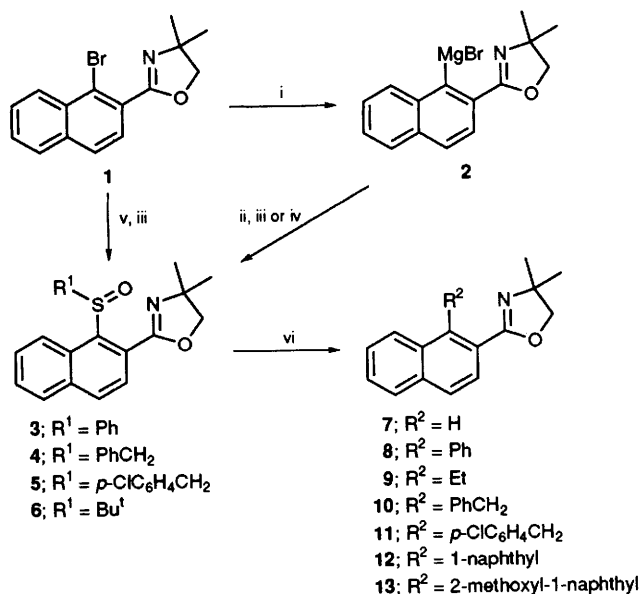
Atropisomeric 1,1-binaphthyl compounds have been widely used in the construction of chiral catalysts and auxiliaries for asymmetric synthesis.¹ The preparation of enantiomerically pure atropisomeric 1,1-binaphthyls has usually depended upon classical resolution procedures, although a few atrop-

isomer-selective syntheses have been developed.² Strategies based on the nucleophilic aromatic substitution (S_NAr) of a methoxyl group *ortho* to a chiral oxazoline moiety by 1-naphthyl Grignard reagents,³ or alternatively through the S_NAr displacement of a chiral alkoxy group *ortho* to an

achiral oxazoline⁴ or hindered carboxylic ester,⁵ have provided 1,1-binaphthyls in optical yields of up to 98%. Furukawa and coworkers⁶ 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-substituent, with a 1-naphthyl Grignard reagent. 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. In this communication we report the enantioselective synthesis of an atropisomeric 1,1-binaphthyl through an apparent S_NAr displacement of a chiral sulfinyl substituent. Evidence suggesting that this transformation proceeds through a ligand coupling reaction of σ -sulfurane intermediates is also presented.

Racemic phenylsulfinyl oxazoline **3**[†] was prepared through reaction of the Grignard reagent **2** (derived from the known bromo oxazoline **1**⁴) with diphenyl disulfide, followed by oxidation of the product with *m*-chloroperoxybenzoic acid (*m*-CPBA), in 64% overall yield (Scheme 1). Reaction of the sulfoxide **3** with 3–4 equiv. of phenylmagnesium bromide in tetrahydrofuran (THF) solution at -20°C for 7 h furnished the phenyl-substituted product **8** in 35% yield, together with the desulfurised product **7** in 44% yield. Also isolated from the reaction mixture was diphenyl sulfoxide (39% yield), generated through a ligand exchange reaction⁷ giving rise to **7**, and a 2:1 mixture of diphenyl disulfide and diphenyl thiosulfonate (*ca.* 40% combined yield), arising from the disproportionation of the phenylsulfenic acid generated on acidic work-up. When the reaction was carried out at room temp. for 15 min the yield of **8** was 72%, accompanied by 19% of **7**.

Results from the laboratories of Oae *et al.*⁸ suggested that the displacement of the phenylsulfinyl group of **3** may not occur through a direct S_NAr route, but through initial attack by the Grignard reagent at the sulfur centre, generating a hypervalent σ -sulfurane intermediate. Evidence for the operation of this mechanism is the occurrence of coupling between the ligands of the sulfoxide on treatment with Grignard

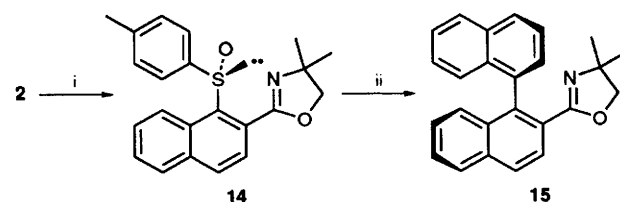


Scheme 1 Reagents and conditions: i, Mg, THF, 25 °C, 18 h; ii, (PhS)₂, THF, 25 °C, 24 h; iii, *m*-CPBA, CH₂Cl₂, 0 °C, 10–60 min; iv, inverse addition to PhCH₂S(O)Cl or *p*-ClC₆H₄CH₂S(O)Cl, cyclohexane, 25 °C, 10 min; v, Bu^tSNa, DMF, 100 °C, 15 h; vi, Grignard reagent (3–4 equiv.), THF, -20 or 25 °C, 15 min–120 h

reagents, an outcome that is particularly facile if the sulfoxide is substituted with an apicophilic ligand such as benzyl. Accordingly, the racemic benzylsulfinyl oxazoline **4** was prepared through 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 temp. for 2 h. This furnished the ethyl-substituted product **9** in 75% yield, together with the benzyl-substituted product **10** (13%) and the ligand exchange product **7** (11%). Oae *et al.*⁹ reported that chlorine substitution on the benzylic group of benzylic aryl sulfoxides enhances the level of coupling between the sulfoxide ligands on reaction with Grignard reagents. The reaction of the *p*-chlorobenzylsulfinyl oxazoline **5** (prepared analogously to **4** 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 **7**). 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.

Reaction of the racemic phenylsulfinyl oxazoline **3** with an excess of 1-naphthylmagnesium bromide in THF solution at room temp. for 3.5 h furnished the racemic 1,1-binaphthyl **12** in 67% yield, together with the ligand exchange product **7** in 9% yield. The non-racemic *p*-toluenesulfinyl oxazoline **14** was next prepared by treating the Grignard reagent **2** with (1*R*)-menthyl (*S*)-toluene-*p*-sulfinate (0.5 equiv.) in toluene at room temp. for 15 min (Scheme 2). The sulfoxide **14** was thus obtained in 82–89% yield and 85–95% e.e.[‡] Longer reaction times furnished a product of lower enantiomeric purity, presumably through ligand exchange reaction involving excess Grignard reagent (see below). The sulfoxide **14** is an oil, while the racemic material is crystalline. The enantiomeric purity of **14** could, therefore, be improved to $\geq 95\%$, [α]_D -155 (*c* 1.3, toluene), through precipitation of the racemate from hexane solution. The absolute configuration at the sulfur centre of **14** has been assigned as *S*, assuming inversion of configuration accompanies nucleophilic attack by the Grignard reagent **2** on (1*R*)-menthyl (*S*)-toluene-*p*-sulfinate.¹⁰ Reaction of **14** with 1-naphthylmagnesium bromide for 3.5 h at room temp. furnished the optically active (*S*)-1,1-binaphthyl **15** in 71% yield and 60% e.e.,[‡] [α]₅₇₈ $+70$ (*c* 2.3, THF) [extrapolated literature rotation for optically pure (*S*)-enantiomer [α]₅₇₈ $+118$ (*c* 2.6, THF)].⁴ The recovered starting sulfoxide **14** (13%) from this reaction was found to have partially racemised (*ca.* 60% e.e.). This observation can be accounted for through initial ligand exchange reaction generating the Grignard reagent **2**, which is then able to racemise **14** through further ligand exchange reactions. Quenching the reaction after 1.5 h provided the starting sulfoxide **14** (27%) in *ca.* 85% e.e.; after 30 min **14** (64%) was isolated in *ca.* 95% e.e. In neither case was the e.e. of the product **15** 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 **14** failed to undergo a coupling reaction with



Scheme 2 Reagents and conditions: i, (1*R*)-menthyl (*S*)-toluene-*p*-sulfinate (0.5 equiv.), toluene, 25 °C, 15 min; ii, 1-naphthylmagnesium bromide, THF, 25 °C, 3.5 h

[†] New compounds gave satisfactory elemental analyses or high resolution mass spectral molecular ions and spectra (IR, ¹H and ¹³C NMR) in accord with the assigned structures.

[‡] Optical purity was estimated by ¹H NMR spectroscopy (500 or 300 MHz) in the presence of Eu(hfc)₃.

2-methoxy-1-naphthylmagnesium bromide, only the ligand exchange product **7** being isolated after several hours at room temp. Oae *et al.*⁸ 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 **6** was prepared by treating the bromo oxazoline **1** with sodium *tert*-butylthiolate in dimethylformamide solution (100 °C, 15 h), followed by oxidation with *m*-CPBA (87% overall yield). Reaction of **6** with an excess of 2-methoxy-1-naphthylmagnesium bromide in THF solution for 120 h at room temp. furnished the 1,1-binaphthyl **13** in 44% yield. We are currently exploring methods for the preparation of **6** in non-racemic form and the further application of this reaction to systems activated by alternative electron-withdrawing substituents.

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