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

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4,5-Dihydro-2-(1-alkyl- or 1-aryl-sulfinylnaphthalen-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 atropisomer-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 alkoxyl group *ortho* to an

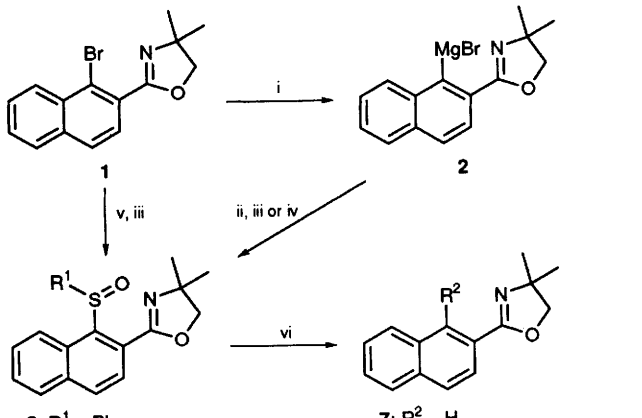
achiral oxazoline[4] or hindered carboxylic ester,[5] have provided 1,1-binaphthyls in optical yields of up to 98%. Furukawa and coworkers[6] have described the diastereoselective formation of an atropisomeric 2-pyridyl-1-naphthyl system through a cross-coupling reaction of a 2-pyridyl sulfoxide, containing 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 reaction[7] 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**.

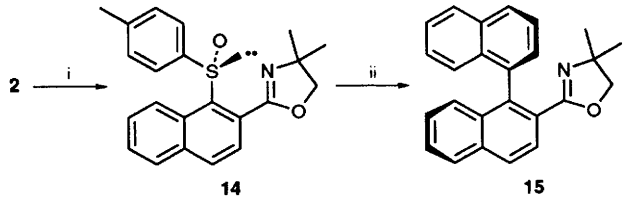
Results from the laboratories of Oae *et al.*[8] suggested that the displacement of the phenylsulfinyl group of **3** may not occur through a direct S_NAr route, but through initial attack by the Grignard reagent at the sulfur centre, generating a hypervalent σ-sulfurane intermediate. Evidence for the operation of this mechanism is the occurrence of coupling between the ligands of the sulfoxide on treatment with Grignard 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 ≥95%, $[\alpha]_D$ − 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.,‡ $[\alpha]_{578}$ +70 (*c* 2.3, THF) [extrapolated literature rotation for optically pure (*S*)-enantiomer $[\alpha]_{578}$ +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 1 *Reagents and conditions*: i, Mg, THF, 25 °C, 18 h; ii, $(PhS)_2$, THF, 25 °C, 24 h; iii, *m*-CPBA, CH_2Cl_2, 0 °C, 10–60 min; iv, inverse addition to $PhCH_2S(O)Cl$ or *p*-$ClC_6H_4CH_2S(O)Cl$, 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



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 ^{13}C 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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