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Directed Metalation/Ligand Coupling Approach to the Enantioselective Synthesis of 1,1'-Binaphthyls

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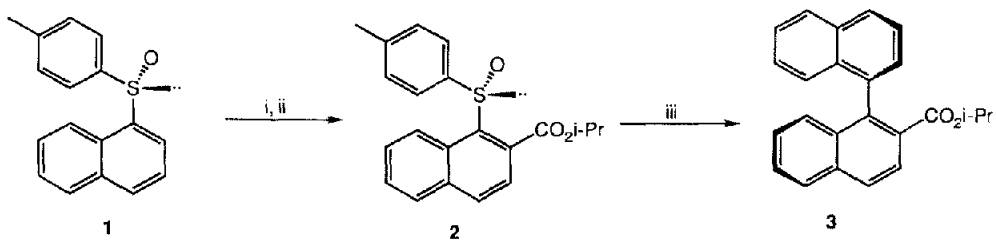
Abstract: Introduction of a 2-isopropoxycarbonyl or 2-*N*,*N*-dimethylcarbamoyl group into homochiral 1-*p*-tolyl- or 1-t-butyl-sulfinylnaphthalenes, *via* directed metalation reaction, followed by ligand coupling reaction with 1-naphthylmagnesium bromide, furnished atropisomeric 1,1'-binaphthyls in 82-95% enantiomeric excess (e.e.).

Recently,[1] we described the enantioselective synthesis of an atropisomeric 1,1'-binaphthyl through the displacement of a homochiral *p*-tolylsulfinyl substituent, *ortho* to an oxazoline moiety, by 1-naphthylmagnesium bromide. Evidence suggesting that this reaction proceeds through a ligand coupling reaction[2] of σ-sulfurane intermediates was also presented. In this communication further examples of this reaction are disclosed, the precursors being prepared through directed metalation of 1-*p*-tolyl- or 1-t-butyl-sulfinylnaphthalenes.[3] A rationalisation of the sense of asymmetric coupling in these reactions is also proposed.

When the known[4] (*S*)-1-*p*-tolylsulfinylnaphthalene **1** (Scheme 1) was treated with lithium diisopropylamide (LDA, 1.1 equiv.) in tetrahydrofuran (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 **2** was obtained in 36% yield and >99.5% e.e.,[5,6] $[\alpha]_D$ -94 (*c* 1.05, toluene). Regioisomeric products were not evident by TLC analysis. Care was taken in this reaction to avoid employing excess n-BuLi in the generation of LDA, since it has been shown[7] that n-BuLi may initiate ligand exchange and racemisation reactions of diaryl sulfoxides. The sulfoxide **2** on reaction with 1-naphthylmagnesium bromide (3 equiv.) in THF solution at 25°C for 30 min, gave the (*S*)-1,1'-binaphthyl **3**[8] in 78% yield and 82% e.e.,[9] $[\alpha]_D$ -11 (*c* 1.98, toluene).

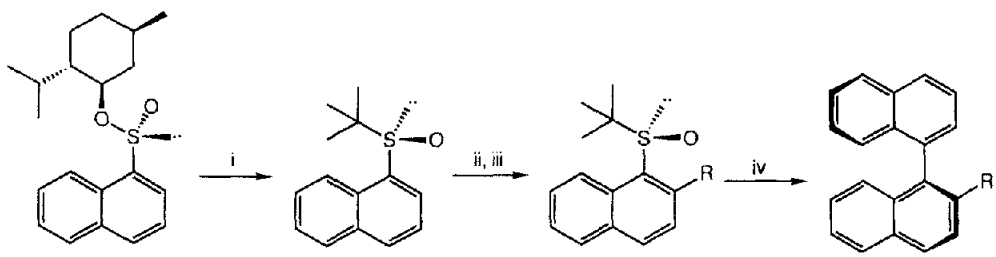
The known[4] (1*R*)-menthyl (*S*)-1-naphthalenesulfinate **4** (Scheme 2) was allowed to react with t-butylmagnesium chloride (2 equiv.) in toluene solution at 0°C for 45 min, and furnished (*R*)-1-t-butylsulfinylnaphthalene **5** in 78% yield and 90% e.e.[6] The absolute configuration of **5** has been assigned assuming inversion of configuration accompanies nucleophilic attack by the Grignard reagent on the sulfinate ester.[10] Sulfoxide **5** is a low melting solid (m.p. 61-63°C, dec.) and, although its optical purity could be improved through crystallisation {>99% e.e.,[6] $[\alpha]_D$ +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 recrystallised to optical purity. Metalation of **5** was slow with LDA, however, treatment of **5** with n-BuLi [11] (1.1 equiv.) in THF solution at -78°C for 30 min, followed by inverse addition to isopropyl chloroformate (1.1 equiv.) in THF at -78°C, furnished the 2-isopropoxycarbonyl sulfoxide **6** in 39% yield. Again, regioisomeric products were not evident by TLC analysis. After a single crystallisation **6** was of 99.5% e.e.,[6] $[\alpha]_D$ +129 (*c* 1.30, toluene). It was not anticipated in this instance that the use of n-BuLi as metalating agent would initiate ligand exchange and racemisation reactions of **5**, based on the precedent of reactions of 2-t-butylsulfinylpyridine with Grignard reagents.[12] The sulfoxide **6** 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 **8** in 90% yield and 95% e.e.,[9] $[\alpha]_D$ +12.8 (*c* 1.72, toluene).



1 **2** **3**

Scheme 1. *Reagents and Conditions:* i, LDA, THF, -78°C; ii, i-PrOCOCl, THF, -78°C; iii, 1-naphthylmagnesium bromide, THF, 25°C.



4 **5** **6** R = CO_2i-Pr, **7** R = $CONMe_2$ **8** R = CO_2i-Pr, **9** R = $CONMe_2$

Scheme 2. *Reagents and Conditions:* i, t-BuMgCl, toluene, 0°C; ii, n-BuLi, THF, -78°C; iii, i-PrOCOCl, THF, -78°C or Me_2NCOCl, THF, TMEDA, -78°C; iv, 1-naphthylmagnesium bromide, THF, 25°C.

The 2-lithio derivative of **5** 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 **7** in 34% yield. After a single crystallisation **7** had ≥95% e.e.,[13] $[\alpha]_D$ +109 (*c* 0.375, toluene). The sulfoxide **7** on treatment with 1-naphthylmagnesium bromide (3.5 equiv.) in THF solution at 25°C for 25 h, gave the (*R*)-1,1'-binaphthyl **9**[14] in 65% yield and 94.8% e.e.,[6] $[\alpha]_D$ +86 (*c* 0.925, toluene). The sulfoxides **2**, **6** and **7** failed to undergo a ligand coupling reaction with the more hindered Grignard reagent,

2-methoxy-1-naphthylmagnesium bromide. We have achieved a coupling reaction with this Grignard reagent using a 1-t-butylsulfinylnaphthalene activated by a 2-oxazoline moiety,[1] but have yet to prepare this in homochiral form.

A plausible rationalisation of the sense of asymmetric coupling is illustrated in Figures 1 and 2. Based on the work of Oae and Furukawa[2] it is proposed that initial attack of 1-naphthylmagnesium bromide on sulfoxide **2** occurs axially from the side opposite the oxygen ligand, leading to a σ-sulfurane with the oxymagnesium bromide ligand in an apical position (Figure 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 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 subsequent ligand coupling reaction.

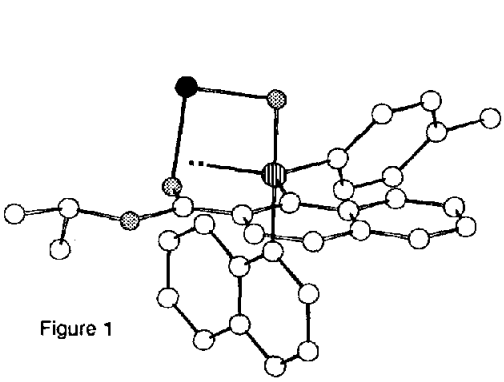


Figure 1

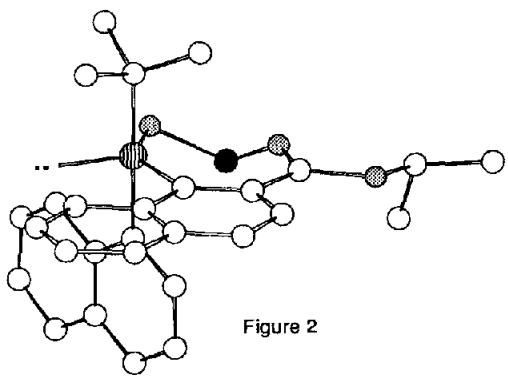


Figure 2

C O Mg S

For the t-butyl sulfoxide **6** it is proposed that initial attack of 1-naphthylmagnesium bromide occurs axially from the side opposite the t-butyl ligand, avoiding non-bonding repulsions with the bulky t-butyl group. The resulting σ-sulfurane has the oxymagnesium bromide ligand in an equatorial position (Figure 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.

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References and Notes

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3. Directed metalation of a 2-pyridyl sulfoxide, introducing a chiral blocking substituent in the 3-position, followed by ligand coupling reaction with a 1-naphthyl Grignard reagent, leading to the *diastereoselective* formation of an atropisomeric 2-pyridyl-1'-naphthyl system has been described: T. Shibutani, H. Fujihara and N. Furukawa, *Tetrahedron Lett.*, 1991, **32**, 2943.
4. K.K. Andersen, W. Gaffield, N.E. Papanikolaou, J.W. Foley and R.I. Perkins, *J. Am. Chem. Soc.*, 1964, **86**, 5637.
5. New compounds gave satisfactory elemental analyses or high resolution mass spectral ions and spectra (IR, ^{1}H and ^{13}C NMR) in accord with the assigned structures.
6. Optical purity was determined by HPLC using a (*R*)-(-)-*N*-(3,5-dinitrobenzoyl)phenylglycine Pirkle column (ES industries).
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8. The absolute configuration of **3** has been previously determined: T. Hattori, H. Hotta, T. Suzuki and S. Miyano, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 613; $[\alpha]_D$ -6.8 (*c* 1.03, $CHCl_3$) for (*S*)-**3** of 80% e.e. We observed for a sample with $[\alpha]_D$ -12.7 (*c* 1.45, toluene), a corresponding rotation $[\alpha]_D$ -8.5 (*c* 1.15, $CHCl_3$).
9. Optical purity was estimated by ^{1}H NMR spectroscopy (300 MHz) in the presence of Eu(hfc)$_3$.
10. The absolute configuration of **5** has been confirmed as *R* through X-ray crystallographic analysis of the 2-bromo derivative, as will be reported elsewhere.
11. C. Quesnelle, T. Iihama, T. Aubert, H. Perrier and V. Snieckus, *Tetrahedron Lett.*, 1992, **33**, 2625.
12. S. Oae, T. Kawai and N. Furukawa, *Phosphorus and Sulfur*, 1987, **34**, 123.
13. It was not possible to determine the e.e. of sulfoxide **7** directly. The enantiomers were not separable by HPLC on a Pirkle column and, in the presence of Eu(hfc)$_3$, the ^{1}H NMR spectrum was excessively broadened. The e.e. can be inferred as ≥95% from the subsequent transformation to **9**.
14. The absolute configuration was determined through transformation of the isopropyl ester **8** to the amide **9**.