Asymmetric 9-(1′-Naphthyl)fluorenes: Enantioselective Synthesis, Determination of Absolute Configuration and Retention of Axial Chirality in the Fluorenyl Carbanions

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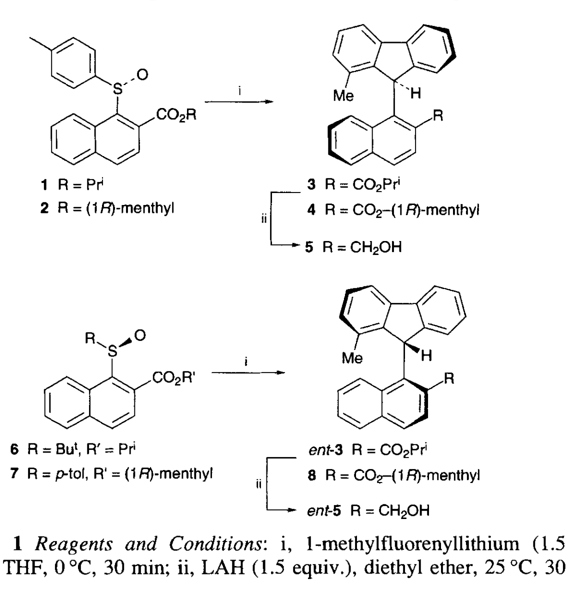
The rotamers of 1-methyl-9-[2′-(methoxymethyl)-1′-naphthyl]fluorene **10** and **11** were synthesised enantioselectively *via* ligand coupling reactions of 1-(alkyl or arylsulfinyl)naphthalene-2-carboxylate esters with 1-methylfluorenyllithium and the absolute configurations established by a single crystal X-ray study of the (1*R*)-menthyl ester **4**; deprotonation of **10** and **11** affords fluorenyl carbanions, *ent*-**12** and **12**, respectively, which retain axial chirality.

Organometallic complexes containing chiral cyclopentadienyl ligands are finding an increasing number of applications in asymmetric catalysis.[1] However, obtaining stereochemically pure metal complexes is often problematic when the cyclopentadienyl ring is asymmetrically substituted, requiring the resolution of a racemic metal complex or the separation of diastereoisomeric metal complexes. In addition, these complexes may be stereolabile, possibly compromising the enantioselectivity of reactions catalysed by them.[2] As a potential solution to these problems, we were interested in the design and synthesis of chelating cyclopentadienyl ligands in which the second metal coordination site is constrained to one diastereoface through hindered rotation about the bond between the cyclopentadienyl ring and a rigid tether. In this communication we report the enantioselective synthesis of 1-methyl-9-(2′-substituted-1′-naphthyl)fluorenes and, in the case of the 2′-(methoxymethyl) rotamers, demonstrate the retention of axial chirality in the derived fluorenyl carbanions.

The properties and reactions of rotational isomers of 9-arylfluorenes have been the subject of a number of investigations, particularly by Ōki and coworkers.[3] However, the preparation of asymmetrically substituted 9-arylfluorenes in non-racemic form has not been previously reported. Recently,[4] we described an enantioselective synthesis of 1,1′-binaphthyls through a ligand coupling reaction of 1-(alkyl or arylsulfinyl)naphthalenes, bearing electron-withdrawing 2-substituents, with 1-naphthyl Grignard reagents. In adapting this reaction to the enantioselective synthesis of asymmetric 9-(1′-naphthyl)fluorenes, we first chose to introduce a 1-methyl substituent into the fluorenyl ligand, this position being the most likely to influence the stereochemical course of the coupling reaction. Reaction of the known[4] *p*-tolyl sulfoxide **1** (Scheme 1) with 1-methylfluorenyllithium (1.5 equiv.) in THF solution at 0 °C for 30 min furnished the +*ac*(*R*)-fluorene **3**† (determination of absolute configuration discussed below) in quantitative yield, $[\alpha]_D$ −73 (*c* 2.5, toluene). The ester **3** was quantitatively reduced to the alcohol **5**, $[\alpha]_D$ −82 (*c* 1.2, toluene), on treatment with LAH in diethyl ether solution. The enantiomeric excess of **5** was determined to be 57% by HPLC analysis of the benzoate derivative.‡ Reaction of the known[4] *tert*-butyl sulfoxide **6** (Scheme 1) with 1-methylfluorenyllithium (1.5 equiv.) in THF solution at 0 °C for 30 min furnished the −*ac*(*S*)-fluorene *ent*-**3** in quantitative yield, $[\alpha]_D$ +96 (*c* 2.5, toluene). Reduction of *ent*-**3** furnished *ent*-**5**, $[\alpha]_D$ +108 (*c* 1.35, toluene), with 78% ee.‡



Scheme 1 *Reagents and Conditions*: i, 1-methylfluorenyllithium (1.5 equiv.), THF, 0 °C, 30 min; ii, LAH (1.5 equiv.), diethyl ether, 25 °C, 30 min

The 2-lithio derivative of (*S*)-1-(*p*-tolylsulfinyl)naphthalene, obtained through metalation with lithium diisopropylamide (1.1 equiv., THF solution, −78 °C, 20 min),[4] was treated with (1*R*)-menthyl chloroformate (1.1 equiv.) in THF solution at −78 °C for 5 h, furnishing the (1*R*)-menthyl ester **2**, $[\alpha]_D$ −120 (*c* 1.8, toluene), in 28% yield. Reaction of **2** (Scheme 1) with 1-methylfluorenyllithium (1.5 equiv.) in THF solution at 0 °C for 30 min furnished the + *ac*(*R*)-fluorene **4** in 93% yield and with 75% de.§ Several recrystallisations from aqueous acetone furnished crystals of **4** (96% de§) suitable for X-ray crystallographic analysis (Fig. 1),¶ thus allowing the inference of absolute configuration at C-9 of the fluorene moiety (C-11 of Fig. 1, crystallographic numbering). Reduction of **4** (75% d.e.§) furnished **5** (quantitative yield) with 75% ee,‡ $[\alpha]_D$ −103 (*c* 1.1, toluene), establishing the absolute configuration of **5** and related compounds. The (1*R*)-menthyl ester **7**, $[\alpha]_D$ +52 (*c* 2.3, toluene), was obtained in 37% yield by reaction of the 2-lithio derivative of (*R*)-1-(*p*-tolylsulfinyl)naphthalene with (1*R*)-menthyl chloroformate (1.1 equiv., THF solution, −78 °C, 3.5 h). Reaction of **7** (Scheme 1) with 1-methylfluorenyllithium (1.5 equiv.) in THF solution at 0 °C for 30 min furnished the −*ac*(*S*)-fluorene **8** in 91% yield and with 70% de.§ Comparison of the stereoselectivities for the coupling reactions of **1**, **2** and **7** indicates that the bulkier menthyl group significantly enhances the stereoselectivity compared to the isopropyl case. However, the chirality of the menthyl moiety has only a minor influence on the stereoselectivity of the coupling reactions.

Ōki and coworkers[5] investigated the rates of deprotonation of 9-[2-(methoxymethyl)-6-methylphenyl]fluorene rotamers with a large excess of butyllithium (BuLi) in benzene–hexane solution and determined that the *sp* rotamer shows pseudo-first order kinetics, while the *ap* rotamer shows pseudo-second order kinetics. The ^{1}H NMR spectra of both reactions indicated the

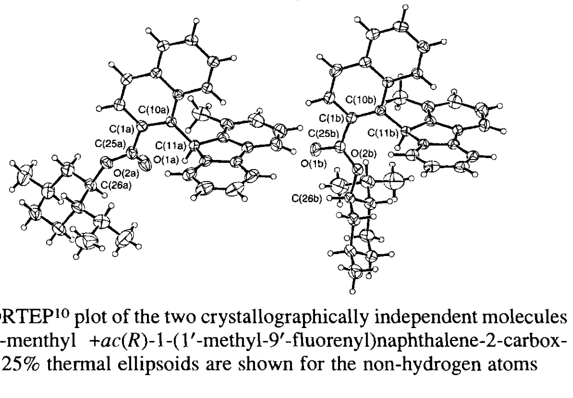
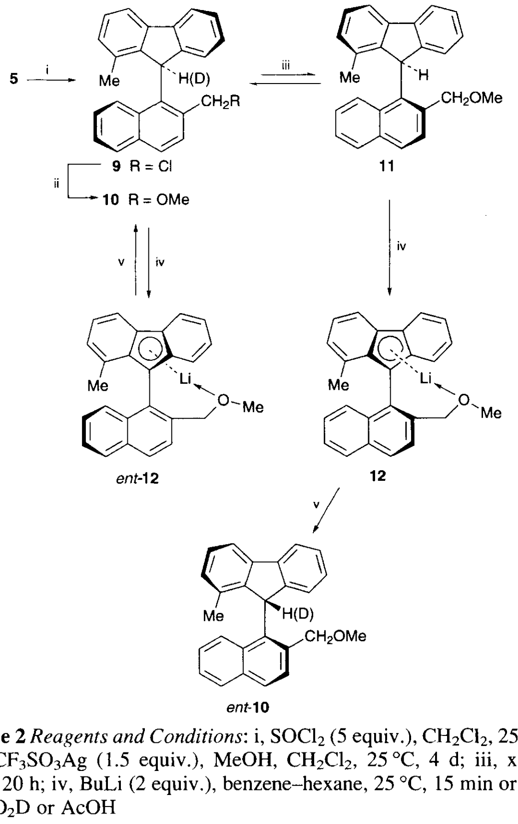


Fig. 1 ORTEP[10] plot of the two crystallographically independent molecules of (1*R*)-menthyl +*ac*(*R*)-1-(1′-methyl-9′-fluorenyl)naphthalene-2-carboxylate **4**, 25% thermal ellipsoids are shown for the non-hydrogen atoms

formation of a common fluorenyllithium species, which on reprotonation gave exclusively the *sp* rotamer. Since it can be expected[6] in hydrocarbon solution for protonation to occur on the same face of the fluorenyl carbanion with which the lithium cation is associated (as a contact ion pair[7]), it was proposed that in the case of the *ap* rotamer, facile rotation about the fluorenyl–phenyl bond occurs in the initially formed ion pair so as to allow internal chelation of the lithium by the methoxyl group. It was suggested that ground state destabilisation through unfavourable steric interactions between the carbanion and the lithium counter-ion was responsible for lowering the barrier to rotation.

In order to determine whether this was indeed the correct mechanism, the alcohol **5** (75% ee[‡]) was, on treatment with thionyl chloride, converted to the +*ac*(*R*)-chloride **9** (Scheme 2), $[\alpha]_D$ −101 (*c* 1.15, toluene), in 97% yield. Methanolysis of the chloride in the presence of CF_3SO_3Ag then furnished the +*ac*(*R*)-methyl ether **10**, $[\alpha]_D$ −114 (*c* 1.4, toluene), in 89% yield and with 75% ee[‖] Heating **10** in a solution of xylenes under reflux for 20 h furnished a 2.2 : 1 mixture of **10** and the −*sc*(*R*)-fluorene **11**, with no loss of enantiomeric purity evident during thermal isomerisation.[‖] Separation of the mixture by preparative HPLC afforded **11**, $[\alpha]_D$ −152 (*c* 1.5, toluene). Addition of a solution of BuLi in hexane (2.7 mol dm^{-3}, 2 equiv.) to a solution of **11** in benzene (*ca.* 0.25 mol dm^{-3}) resulted in the slow generation of the (*R*)-fluorenyl carbanion **12**. Quenching the reaction with CD_3CO_2D after 3 h at 25 °C gave a 1 : 1.1 mixture of **11** and *ent*-**10** (72% recovery). The ^1H NMR spectrum of the mixture revealed > 98% incorporation of deuterium at C-9 of *ent*-**10** and no evidence of deuterium incorporation at C-9 of **11**, demonstrating that the reprotonation of the fluorenyl carbanion **12** is stereospecific. Analysis of the AcOH quenched reaction revealed no loss of enantiomeric purity in the products.[‖] This experiment clearly demonstrates the retention of axial chirality in the fluorenyl carbanion **12**; formation of the internally chelated ion pair on lithiation of **11** does not involve rotation about the fluorenyl–naphthyl bond, which would be expected to return **10** on reprotonation. In contrast to the behaviour of **11**, lithiation of **10** under the same conditions was complete within 15 min (CD_3CO_2D quench, > 98% deuterium incorporation at C-9 by ^1H NMR analysis), reprotonation of the (*S*)-fluorenyl carbanion *ent*-**12** returning **10** (96% recovery) with no loss of enantiomeric purity.[‖]



Scheme 2 *Reagents and Conditions*: i, $SOCl_2$ (5 equiv.), CH_2Cl_2, 25 °C, 23 h; ii, CF_3SO_3Ag (1.5 equiv.), MeOH, CH_2Cl_2, 25 °C, 4 d; iii, xylenes, reflux, 20 h; iv, BuLi (2 equiv.), benzene–hexane, 25 °C, 15 min or 3 h; v, CD_3CO_2D or AcOH

We are currently investigating the further elaboration of the 9-(1′-naphthyl)fluorene system and the preparation of transition metal complexes with the fluorenyl ligands. Approaches to other axially chiral cyclopentadienyl systems [*e.g.* 1-(1′-naphthyl)indenyl ligands] are also being explored. The present work was partly supported by a University of Sydney Research Grant (to R. W. B.) and an Australian Research Council grant (to T. W. H.).

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Footnotes

[†] 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.

[‡] A 4.6 × 250 mm column [Chiralpak OT(+), Daicel] was used with methanol as eluent at a flow rate of 0.5 ml min^{-1}, column temp. 3 °C, detection 254 nm, t_R = 33.5 min for **5**-benzoate and 42.2 min for *ent*-**5**-benzoate.

[§] Diastereoisomeric purity was determined by the ^1H NMR (400 MHz) signals due to the fluorene 1-methyl group [$\delta(C_6D_6)$ 1.98 and 1.93, respectively, for **4** and **8**].

[¶] *Crystal data* for **4**: $C_{35}H_{36}O_2$, M = 488.67, colourless prism 0.25 × 0.20 × 0.55 mm, orthorhombic, space group $P2_12_12_1$, a = 14.318(1), b = 36.548(3), c = 10.816(2) Å, V = 5660(1) Å^3, D_c (Z = 8, two crystallographically independent molecules) = 1.147 g cm^{-3}, μ(Cu-Kα) = 5.346 cm^{-1}, λ(Cu-Kα) = 1.5406 Å, $F(000)$ = 2096 electrons. Ranges of *hkl* 0–16, 0–41, 0–12; 4–120° 2θ, N = N(unique) = 4757, N_0 = 3743 [$I > 2.0\sigma(I)$], N_{var} = 668, R = 0.043, R_w = 0.043, residual electron density −0.16 to 0.19 e Å^{-3}. Unique data set collected using graphite monochromated Cu-Kα radiation from a 12 kW direct drive rotating anode generator equipped Rigaku AFC7R diffractometer. The structure was solved by direct methods with SIR92[8] and refined using TEXSAN.[9] Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

[‖] Enantiomeric purity was determined by the ^1H NMR (400 MHz) signals due to the fluorene 1-methyl group in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (5 equiv., *ca.* 0.6 mol dm^{-3}) [$\delta(C_6D_6)$ 1.66 and 1.68, respectively, for **10** and *ent*-**10**; 1.59 and 1.56, respectively, for **11** and *ent*-**11**].

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