Pergamon

Tetrahedron 57 (2001) 2545–2554

TETRAHEDRON

Resolution and coupling of 1-(2′-hydroxy-1′-naphthyl)isoquinolines

Sonia C. Tucker,[a] John M. Brown,[a,*] John Oakes[b] and David Thornthwaite[b]

[a]*Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK*
[b]*Unilever Research Laboratory, Bebington, Wirral L63 3JW, UK*

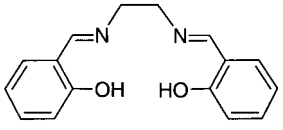
In appreciation of the inventive contributions of Henri Kagan to asymmetric catalysis

Received 25 July 2000; revised 12 October 2000; accepted 16 October 2000

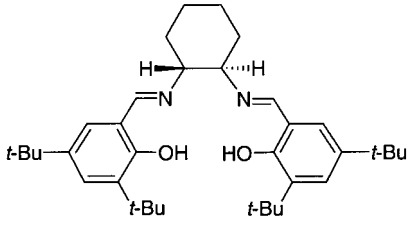
Abstract—The synthesis of bridged dimeric isoquinolylnaphthols has been developed. A simple method for the resolution of 1,1′-isoquinolyl-2′-naphthol permits measurement of the optical stability of the monomer, and in several cases slow racemisation at ambient temperature was observed. The enantiomeric stability is not greatly affected by steric buttressing. An unusual enhancement of the rate of atropisomerism is provided by the 3-bromomethylisoquinolines, and undermines the possibility of coupling pure enantiomeric components to provide a single stereoisomer of a tetradentate ligand. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

There exists extensive literature on transition metal complexes of the tetradentate Schiff base ligand *N*,*N*′-disalicylidene-1,2-diaminoethane **1** and various derivatives.[1] These Salen ligands have recently been the focus of renewed attention as a result of their successful application in various catalytic processes. Particularly prominent has been the emergence of 'Jacobsen epoxidation' using chiral manganese Salen catalyst **2**, which constitutes a practical, reliable method for achieving highly enantioselective epoxidations of several classes of olefin.[2] Modifications to the basic ligand structure have enabled advances to be made in various other catalytic asymmetric processes such as sulfoxidation or sulfimidation,[3] cycloadditions,[4] cyanohydrin formation,[5] cyclopropanation,[6] aziridination,[7] C–H oxidative activation,[8] and in the desymmetrisation or kinetic resolution of epoxides.[9] We became interested in the synthesis of stereochemically defined polydentate ligands comprising naphthol-isoquinoline donor sets exemplified by the simple unit 1-(2′-hydroxy-1′-naphthyl)isoquinoline **3**. These ligands offer a coordinating environment related to the one present in the Salen ligands, but with chirality that stems from restricted rotation about the biaryl axis, rather than from central asymmetry in a diamine bridge.



1



2

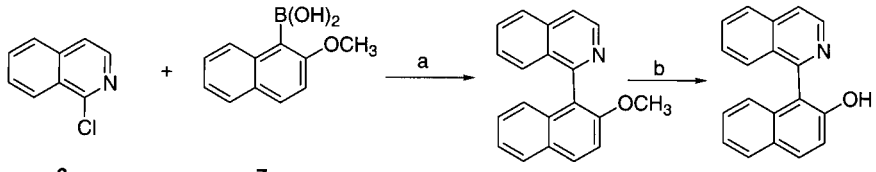
The strategy adopted involved various rational modifications to the simple unit **3**, which led ultimately to structures **4** and **5**. Two main issues were addressed:

1. The introduction of a suitable substituent at C_3 of the isoquinoline, thereby opening up a route to a potentially tetradentate ligand by bridged dimer formation.
2. Bridging two racemic biaryls would lead to complexity in the product as both an (R^*R^*) racemic pair and an (R^*S^*) *meso*-diastereomer could be produced. The logical step, therefore, was to resolve the biaryl moiety before bridging. Biaryl **3** was anticipated to be optically labile at room temperature and the possible requirement for the introduction of substituents that would block the racemisation pathway was foreseen. The effect of such substitution was found to be unpredictable, and forms the basis for much of this work.

Keywords: racemisation; enantiomers; palladocycles; isoquinolines; atropisomerism.

* Corresponding author. Tel.: +44-1865-275642; fax: +44-1865-275674; e-mail: bjm@ermine.ox.ac.uk

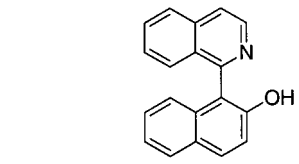
PII: S0040-4020(01)00064-3



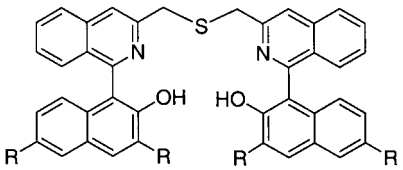
6 7 3

Key (a) $Pd(PPh_3)_4$, aq. K_2CO_3, DME, EtOH, 80 °C, 67%. (b) BBr_3, CH_2Cl_2, 30 min, 91%.

Scheme 1. Synthetic route to compound **1**.



3



4 R = H
5 R = *t*-Bu

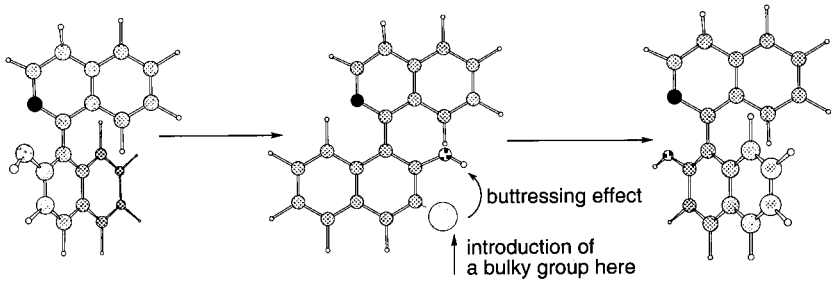
2. Results and discussion

2.1. Synthesis of precursors

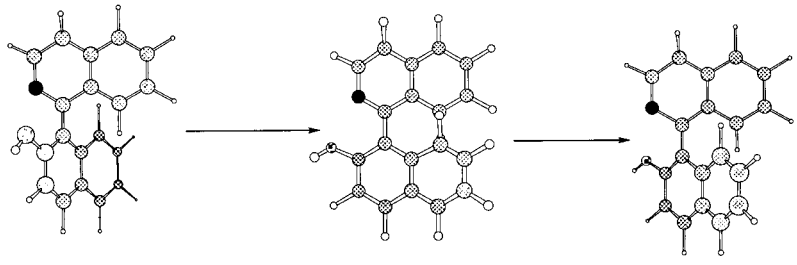
Biaryl **3** was readily available on a large scale according to a previously published route in which the key step involved a Suzuki coupling reaction between isoquinoline **6** and boronic acid **7** (Scheme 1).[10]

By treatment of **3** with one equivalent of (+)-tartaric acid, recrystallisation from acetone and subsequent treatment with ammonia to liberate scalemic **3** it was evident from polarimetry that the parent biaryl was prone to racemisation at ambient temperature. It was thought that the introduction of a *tert*-butyl group at $C_{3'}$ would buttress the hydroxyl group, thereby increasing its interaction with H_8 and raising the energy barrier to biaryl rotation sufficiently so as to halt racemisation (Scheme 2).

Synthesis of **13**, the 3,6-di-*tert*-butylated analogue of **3** has been published previously (Scheme 3).[11] *tert*-Butyl groups were introduced into β-naphthol by Friedel-Crafts reaction to give **8** which was protected as its methyl ether **9**. Thereafter the synthesis parallels that of **3** but with reduced yields owing to the buttressing effect of the bulky *tert*-butyl group at $C_{3'}$. An improved synthesis of the 1-bromo-substituted ether **10** was developed which allowed the reaction to be performed on a large scale without the need for a difficult chromatographic separation. The derived boronic acid **11** was then coupled to **6** under standard Suzuki conditions. Use of caesium carbonate as base had a marked effect on the yield of this reaction. The coupled product **12** was obtained in 64% yield compared to the 30% previously reported when potassium carbonate was used.

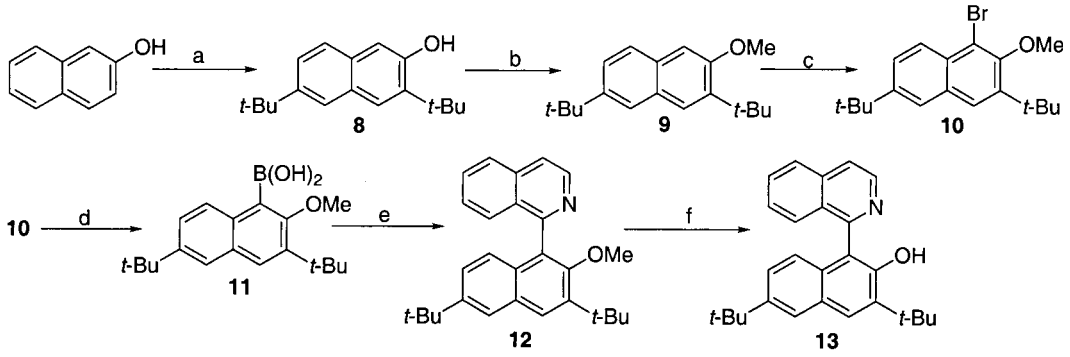


"*trans*" path for racemisation



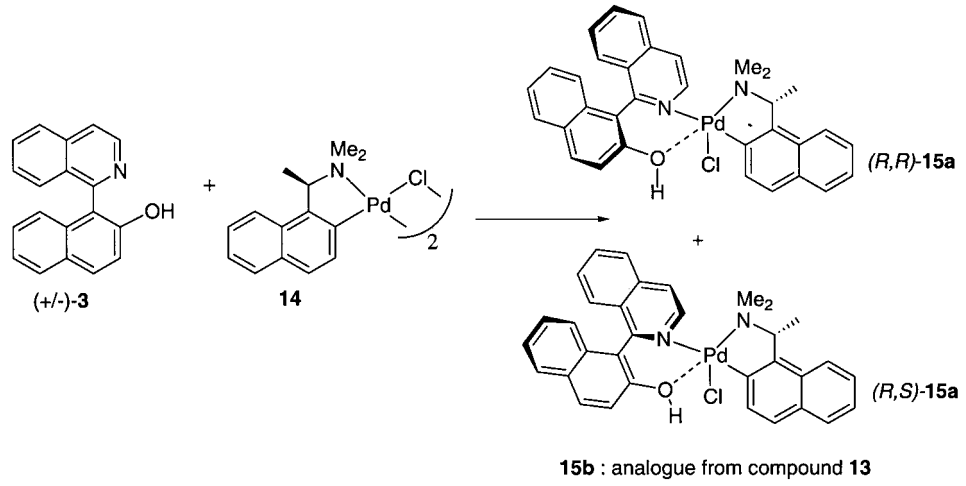
"*cis*" path for racemisation

Scheme 2. Analysis of the racemisation pathways for the series of biaryls.



Key (a) triflic acid, CF_3SO_3H. (b) MeI, KOH, DMSO. (c) Br_2, $CHCl_3$. (d) i) BuLi, ii) $B(OMe)_3$, iii) H_2O. (e) 1-chloroisoquinoline, $Pd(PPh_3)_4$, aq. Cs_2CO_3, DME. (f) BBr_3, CH_2Cl_2.

Scheme 3. Synthetic route to compound **13**.



Scheme 4. The resolution protocol for racemic **3** and **13**.

2.2. Resolution procedure

A direct comparison between the optical stabilities of **3** and **13** could be made using chloro-bridged palladium dimer **14** as a resolving agent (Scheme 4).[12] Although this methodology has been extensively used for the resolutions of diphosphines, phosphinamines and more occasionally for other chelating reactants including amino-acids,[13] it has not previously been employed in aminoalcohol resolution. When a $CDCl_3$ solution of **3** was treated with 0.5 equiv. of Pd-dimer the ^1H NMR of the resulting solution indicated conversion to two diastereomers, (*R*,*R*)-**15a** and (*R*,*S*)-**15a** in comparable amounts. Repeating the experiment using 0.25 equiv. of dimer led to selectivity in the formation of the two diastereomers (87:13). The uncomplexed ligand was recovered by crystallisation and the specific rotation of a sample dissolved in chloroform was observed over a period of time. A similar procedure was followed with biaryl **13**. In this latter case, it was possible to recover the free ligand by column chromatography, and also to isolate the major palladium diastereomer of **15b**, which was characterised by ^1H, ^{13}C NMR and electrospray MS. Fig. 1 shows the decline of specific rotation with time fitted to an exponential decay for the two biaryls. Thus it was possible to derive half-lives and rate constants for the racemisation process under ambient conditions. Values of $k_{rac}=2.77\times10^{-7}\ s^{-1}$ for **3** and $k_{rac}=9.55\times10^{-7}\ s^{-1}$ for *tert*-butylated analogue **13**, were obtained, corresponding to half-lives of ca. 700 and 200 h, respectively. It was immediately apparent that the introduction of a bulky group at $C_{3'}$ did not have the desired effect of preventing racemisation. Indeed, the rate of racemisation was increased by an approximate factor of four. As in the parent series, where 1-(1′-naphthyl)isoquinoline is far more stereochemically labile than 1,1′-binaphthyl,[14] the racemisation rates are high. For comparison, 2-hydroxy-1,1′-binaphthyl racemises in benzene solution with a half-life of about two days.[15]

2.3. Synthesis of bis-biaryls

The unpredicted result that substitution at $C_{3'}$ increased the rate of racemisation (vide infra) prompted questions about the consequence of introducing substituents at C_3 of the isoquinoline, necessary for the construction of a bridge between two biaryls. The achievement of a route to a bis-biaryl where the two biaryl units are linked by a CH_2–S–CH_2 bridge provided a situation where the effect of such substitution on racemisation could be followed by ^1H NMR. Two such ligands were synthesised as shown in Scheme 5.

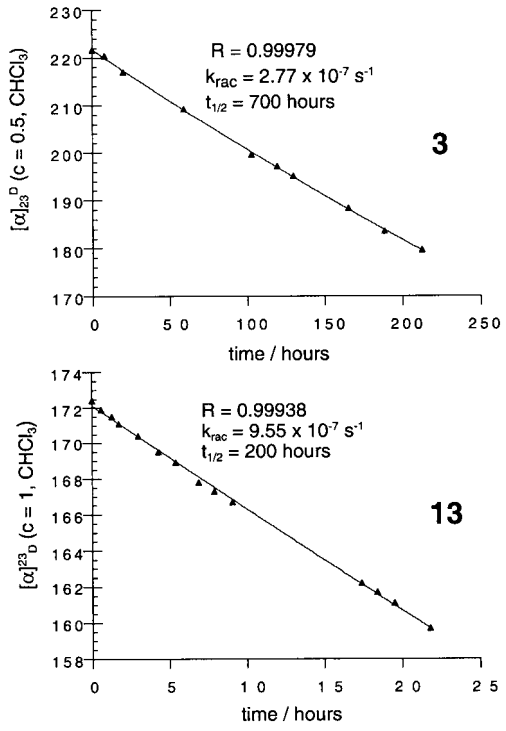
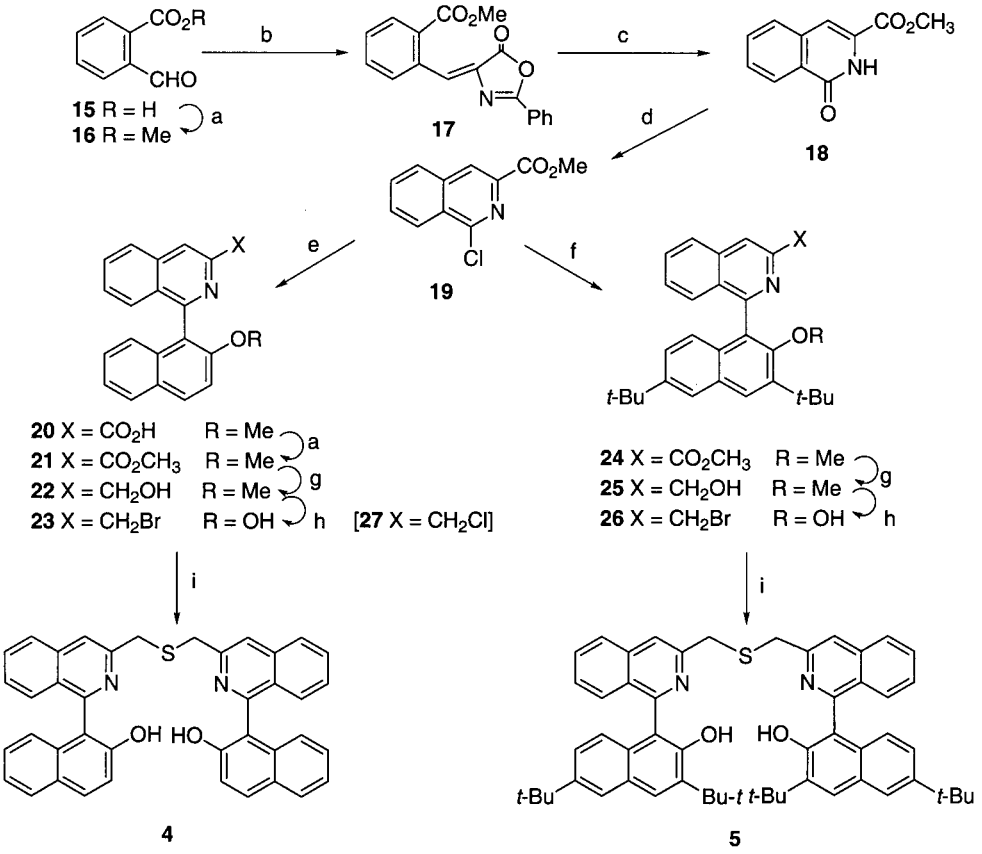


Figure 1. Decline in specific rotation with time for compounds **3** and **13** at 25°C in $CHCl_3$ measured by polarimetry.

2-Carbomethoxybenzaldehyde **16** was condensed with hippuric acid to give oxazolone **17** according to a literature procedure.[16] Cyclisation with KOH in MeOH gave substituted isocarbostyril **18**,[17] which on treatment with $POCl_3$ underwent both chlorination and aromatisation to give the required substituted isoquinoline **19**. The product was separately coupled to boronic acids **7** and **11** under Suzuki conditions. With the unhindered boronic acid **7** the coupling was carried out using $Pd(PPh_3)_4$ as catalyst and aq. K_2CO_3 as base, and gave biaryl **20** in 88% yield. Under these conditions the ester functionality was hydrolysed but could be readily converted into ester **21** on treatment with methyl iodide. As expected, the coupling with *tert*-butylated boronic acid **11** was initially more difficult to achieve. Optimisation of the reaction conditions, particularly in the choice of the palladium phosphine ligands, allowed the reaction to be performed on a large scale with satisfactory yields. Use of a $Pd_2dba_3{\cdot}CHCl_3$/tri-2-furylphosphine catalyst system[18] gave biaryl **24** in 75% (as determined by ^1H NMR), a notable improvement on the 19% yield obtained with $Pd(Ph_3)_4$ as catalyst. Triphenylarsine was also an effective palladium ligand; in this case a yield of 59% was achieved. It was also found convenient to use the base, K_2CO_3, as a fine suspension in DME.

Methyl esters **21** and **24** were reduced in turn to alcohols **22** and **25**. Under demethylation conditions the bromides **23** and **26** were formed in good yield. Reaction of **26** with



Key (a) MeI, K_2CO_3, acetone; (b) $PhC(O)NHCH_2CO_2H$, Ac_2O, NaOAc; (c) KOH, MeOH; (d) $POCl_3$; (e) (**7**), $Pd(PPh_3)_4$, aq. K_2CO_3, DME; (f) (**11**), $Pd_2(dba)_3.CHCl_3$, tri-2-furylphosphine, K_2CO_3, DME; (g) $LiBH_4$, THF; (h) BBr_3, CH_2Cl_2; (i) Na_2S, DMF.

Scheme 5. Coupling routes to compounds **4** and **5** via biaryl precursors

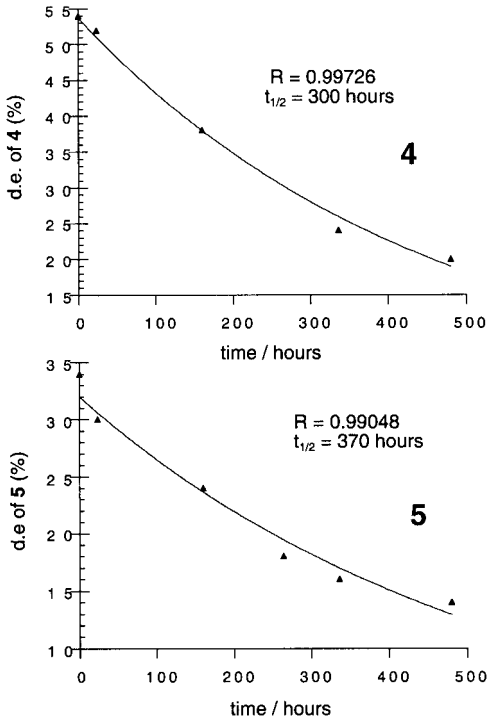


Figure 2. Interconversion of diastereomers of compounds **4** and **5** in $CDCl_3$ at 25°C.

0.5 equiv. of sodium sulphide in DMF resulted in complete conversion to two major products. These were separated by column chromatography and shown to have identical masses corresponding to that expected for the sulphur bridged dimer **5**, and were thus assigned as the (*R*,*R*)/(*S*,*S*) pair and the *meso* (*R*,*S*) diastereomer. This was confirmed by ^{1}H NMR which showed nine distinct resonances for the aromatic protons and two doublets for the CH_2 protons in each case.

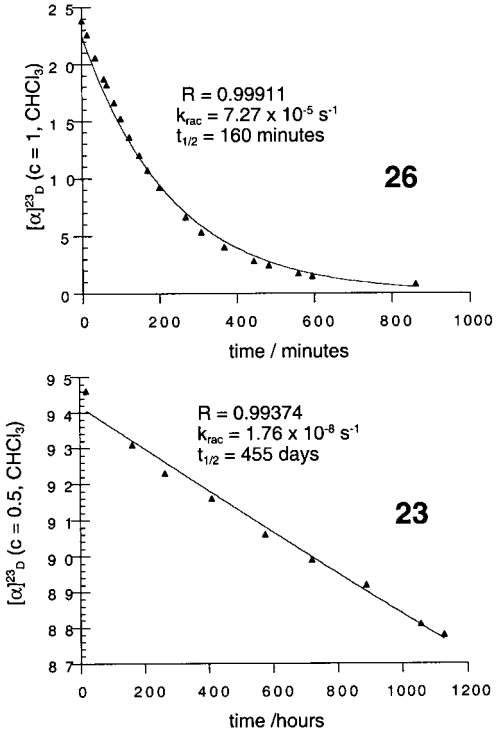


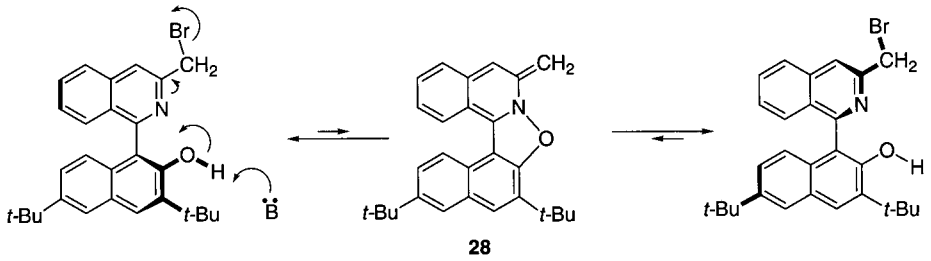
Figure 3. Decline in specific rotation with time for compounds **23** and **26** at 25°C in $CHCl_3$ measured by polarimetry.

The related non *tert*-butylated compound **4** was also prepared. The two diastereomers were easily distinguishable by their CH_2 peaks; one appears as a very distinct AB quartet centred at 4.12 ppm, the other as two coalesced doublets at 4.00 ppm. These diastereomers could not be separated by chromatography, although recrystallisation from ethyl acetate gave a diastereomeric mixture with a d.e. of 54%.

For both **4** and **5** interconversion between the diastereomers could be observed by recording at intervals the ^{1}H NMR spectra of samples with an initial diastereomeric excess. The results are displayed graphically in Fig. 2. A fairly slow loss of d.e. is indicated for both compounds. The accuracy of the half-lives obtained from the graphs ($t_{1/2}$=300 h for **4** and 370 h for **5**) is limited by the method of determining d.e. from relative integrals in the ^{1}H NMR spectrum, but it is clear that both compounds stereomutate with half lives of the same order of magnitude as one another, and similar to those derived for the racemisation of the simple monomer ligands **3** and **13**. This is in marked contrast to the situation that exists for the bromide precursors **23** and **26** to be discussed in the following section.

2.4. Anomalous behaviour of bromides 23 and 26

Resolution experiments similar to those described previously were carried out on biaryls **23** and **26**. The complexation step was shown by ^{1}H NMR to proceed quite slowly in either case, compared to biaryls **3** and **13**, and so reactions were stirred overnight prior to recovery of the free ligand. With the *tert*-butylated biaryl **26** only one diastereomer was seen after stirring for 24 h. The uncomplexed ligand was separated by column chromatography and further elution of the column afforded the palladium complex, albeit of the other hand. The decline in specific rotation of the recovered biaryl was followed and the rapidity with which this occurred ($t_{1/2}$=160 min) was quite startling (Fig. 3). This result was reproducible, and the stereochemical lability of **26** further demonstrated by the observation that if a slight excess of resolving agent was used complete conversion of the racemate to a single palladium diastereomer occurred, identical to the one previously observed. The dramatic effect that the CH_2Br substituent exerted on the rate of racemisation led to the expectation that biaryl **23** would also racemise at a much higher rate than its non C_3-substituted analogue. However, when the experiment in question was carried out the opposite result was obtained. The racemisation rate of the uncomplexed ligand was very slow; indeed a decline in specific rotation could only be observed in larger scale assays. The prolonged period of observation required rendered the results less reliable than for the other three biaryls, but a half-life of the order of a year at ambient temperature could be extrapolated from the data (Fig. 3). The results in this case were slightly complicated by the presence (ca. 5%) in the recovered material of what was identified as the chloro-substituted biaryl **27**. A peak of the correct mass was seen



Scheme 6. A possible pathway for the easy racemisation of the bromomethyl compound **26**.

in the mass spectrum and the ^{1}H NMR showed two doublets in the methylene region, very close to the doublets assigned to the bromo-substituted compound. Thus the decline in optical rotation could not be attributed entirely to racemisation of **23**.

With the high stability of bromide **26** to racemisation established and the procedure for its conversion, under very mild conditions, to a tetradentate ligand already in place the synthesis of a single stereoisomer seemed possible. Accordingly a sample of resolved ligand **26** was stirred for 1 h in DMF with 0.5 equiv. of sodium sulphide. The usual work-up procedure (removal of DMF in vacuo, followed by column chromatography) was used. Most surprisingly two diastereomers in equal proportions were observed in the ^{1}H NMR. The reaction was repeated on an NMR scale in d^7 DMF. This showed that conversion to products was very fast. No starting material was seen by the time the acquisition was complete and two diastereomers were indicated in the product. The optical stability of **23** in DMF was confirmed by polarimetry, as was the stability of product **4** towards the interconversion of its diastereomers. These observations indicated that the loss of stereochemical integrity in the product was associated with the course of the substitution reaction.

2.5. Discussion of racemisation experiments

The two possible racemisation pathways for a biaryl are depicted in Scheme 2, with the planar transition state shown for each case. In the *trans* pathway the biggest interactions as the two arms pass each other are between H_8 and the hydroxy group. In the *cis*pathway the passing position results in severe interactions between H_8 and $H_{8'}$. Despite the potential for stabilisation by hydrogen bonding in this case, such unfavourable interactions were thought to effectively preclude this pathway from contributing to the racemisation process. In the discussion that follows the *trans* pathway will be assumed.

The rationale behind the introduction of the *tert*-butyl groups in **3** was that a bulky substituent at $C_{3'}$ would distort the C–O bond of the hydroxyl group and sufficiently increase the crowding in the transition state so as to prevent racemisation. That the *tert*-butyl group exerted such a buttressing effect on the hydroxyl group was evident from a number of prior observations. For example, the reversible bromination of the *tert*-butylated methoxynaphthol **9** and the instability of the subsequently derived boronic acid **11** both indicated destabilisation of $C_{1'}$.[11]

The increase in the rate of racemisation on going to **13** was, therefore, initially surprising. However, inspection of the literature revealed several precedents whereby bulky substituents on biaryls apparently facilitated racemisation. Some years ago a series of papers was published dealing with the unexpectedly facile racemisation of several 8,8′ disubstituted binaphthyls[19] and more recently Fuji and co-workers reported on the optical liability of 8-diphenylphosphinoyl-8′-methoxy-1,1′-binaphthyl as compared to the enantiomerically stable 2,2′ substituted analogue.[20] Meyers and co-workers have observed the easy racemisation of an 8,8′-disubstituted-bis-oxazolinylbinaphthyl.[21] In both of the recent cases unfavourable ground-state effects were invoked to explain the easy rotation about the axial biaryl bond; in the first case due to steric destabilisations and in the second to lone pair repulsion operating specifically in one diastereomer. A related argument could in principle apply to biaryls **3** and **13**. Crystal structures of bulky di-*ortho*-substituted aromatic rings have been recorded, and the bonds to the substituents shown to be both splayed out in the main arene plane and also displaced from it.[22] In order to test this view, preliminary molecular modelling on was carried out and a conformational search for the global energy minima revealed various small but significant differences in bond angles between the biaryls that could lead to destabilisation of the ground state. However, the size of the effect for the *tert*-butylated bromide **26** would indicate that other more important factors are involved. The inferred rapid rotation about the biaryl axis during the course of the coupling reaction with Na_2S points towards pH dependence and/or solvent interactions as playing a role. The intervention of a cyclised intermediate like **28** is sheer speculation at this stage, but would account for the enhanced rapidity of racemisation observed with an adjacent *tert*-butyl substituent at the 3′-position[23] (Scheme 6).

3. Experimental

3.1. General methods

Reactions involving air-sensitive reagents were conducted under a dry argon atmosphere, using standard vacuum line techniques in Schlenk glassware. Melting points were recorded on a Reichert–Koffler block and are uncorrected. Elemental microanalyses were performed using a Carlo Erba 1106 elemental analyser. Specific rotations were recorded on a thermostatically controlled Perkin–Elmer 241 polarimeter with a path length of 1 dm, using the 589.3 nm D-line of sodium. Infrared spectra were recorded

on a Perkin–Elmer 1750 Fourier Transform spectrometer. Samples were prepared as thin films on NaCl plates or as KCl discs. ^{1}H NMR spectra were recorded on Varian Gemini 200 (200), Bruker AM 250 (250 MHz), Bruker WH 300 (300 MHz), Bruker AMX 500 (500 MHz), or Bruker AM 500 (500 MHz) spectrometers. Mass spectra were recorded on a Trio 1, a Hewlett Packard series 1050 (atmospheric pressure chemical ionisation), ZAB1F or BIO-Q spectrometer. High-resolution mass spectra (HRMS) were run on a V.G. Autospec spectrometer operating in positive electrospray mode.

3.1.1. Preparation of 1-bromo-3,6-di-*tert*-butyl-2-methoxynaphthalene 10. A solution of bromine (11.6 , 73.0 mmol) in chloroform (50 ml) was placed in a pressure-equalising addition funnel, and added over a period of 5 min to a stirred ice cold solution of **9** (19.6 g, 73.0 mmol) in chloroform (300 ml). The reaction mixture was basified by addition of 2 M sodium hydroxide (1 l) with vigorous stirring, then the organic layer separated, and the solvent evaporated to give a yellow oil. Crystallisation from methanol gave the title compound as white needles (19.7 g, 60%), data as Ref. 7.

3.1.2. Preparation of 3-carbomethoxyisocarbostyril 18. Compound **17** as in Ref. 14; bright yellow powder (58.1 g, 61%) mp 165–168°C (lit.[14] 171°C); δH (300 MHz; $CDCl_3$) 8.65 (1H, d, J=8.6 Hz), 8.20–8.15 (3H, m), 8.02 (1H, d, J=8.5 Hz), 7.70–7.45 (5H, m), 3.95 (3H, s); δC (50.3 MHz; $CDCl_3$) 167.6, 164.5, 134.8, 133.9, 133.8, 133.1, 132.2, 131.6, 131.0, 130.3, 129.7, 129.2, 128.7, 125.5, 52.5; *m/z* ($APCI^+$; NH_3) 308 (M+1, 60%). From 9.18 g **17** proceeding as Ref. [15]15: white needles of compound **18** (4.98 g, 79%) mp 163–165°C (lit.[15] 161–162°C) (Found: C, 64.94; H, 4.37; N, 6.91. $C_{11}H_9NO_3$ requires C, 65.02; H, 4.46; N, 6.89%); δH (300 MHz; $CDCl_3$) 9.24 (1H, br s, NH), 8.46 (1H, d, J=7.9 Hz, H_8), 7.77–7.60 (3H, m, H_5, H_6, H_7), 7.38 (1H, s, H_4), 3.99 (3H, s, OCH_3); δC (125.8 MHz; $CDCl_3$) 162.5 162.4, 136.1, 133.2, 132.2, 129.5, 128.4, 128.0, 111.5, 53.1; *m/z* (NH_3; $APCI^+$) 204 (M+1, 100%).

3.1.3. Preparation of 3-carbomethoxy-1-chloroisoquinoline 19. Phosphoryl chloride (20.0 ml, 21.5 mol) was added to **18** (2.35 g, 21.5 mol), and the resulting white suspension brought to reflux. Dissolution occurred and the pale yellow solution was stirred at reflux for a further 1.5 h. After cooling to room temperature the solution was poured slowly, with external cooling, into a 2 l beaker containing water (100 ml). A white precipitate was formed and heat and HCl gas evolved. The mixture was neutralised by careful addition of 2 M sodium hydroxide (600 ml) and the product extracted with diethyl ether (3×200 ml). The combined organics were dried ($MgSO_4$), filtered and the solvent evaporated to give the title compound as a white solid (4 g, 84%) mp 118–119°C (Found: C, 59.23; H, 3.8; N, 6.16. $C_{11}H_8O_2NCl$ requires C, 59.61; H, 3.64; N, 6.32%); δH (300 MHz; $CDCl_3$) 8.54 (1H, s), 8.43–8.40 (1H, m), 8.02–7.81 (3H, m), 4.05 (3H, s); δC (50.3 MHz; $CDCl_3$) 165.3, 152.0, 140.4, 137.3, 132.2, 131.0, 128.7, 128.4, 126.8, 124.3, 53.0; *m/z* ($APCI^+$; NH_3) 222 (M+1, 100%).

3.1.4. Preparation of 1-(3,6-di-*tert*-butyl-2-methoxy-1-naphthyl)-3-carbomethoxyisoquinoline 24. Dry degassed DME (10 ml) was added to $Pd_2(dba)_3{\cdot}CHCl_3$ (373 mg, 0.360 mol) and tri-2-furylphosphine (334 mg, 1.44 mmol), and stirred for 10 min under an argon atmosphere. The bright yellow solution was transferred via cannula to a Schlenk containing **11** (2.20 g, 7.00 mmol), **19** (1.55 g, 7.00 mmol) and powdered potassium carbonate (1.90 g, 14 mmol), and heated at 100°C for 24 h. The mixture was then cooled and the solvent evaporated. The residue was taken into diethyl ether (200 ml) and filtered. The solid residue was washed with more diethyl ether and evaporated to leave a brown oil which was stirred overnight with 2 M sodium hydroxide (50 ml), thus hydrolysing unreacted **19**. The desired product was extracted with diethyl ether (2×25 ml), dried ($MgSO_4$), filtered and the solvent evaporated to give a yellow oil. Purification by flash chromatography on silica gel (dichloromethane, R_f=0.21) gave the title compound as a white crystalline solid (1.79 g, 56%) mp 111°C (Found: C, 78.99; H, 7.39; N, 3.03. $C_{30}H_{33}NO$ requires C, 79.09; H, 7.30; N, 3.07%); δH (500 MHz; $CDCl_3$) 8.73 (1H, s, H_4), 8.06 (1H, d, J=8.2 Hz, H_5), 7.91 (1H, s, $H_{4'}$), 7.78 (1H, d, J=2.0 Hz, $H_{5'}$), 7.76 (1H, ddd, J=8.2, 6.7, 0.9 Hz, H_6), 7.64 (1H, d, J=8.4 Hz, H_8), 7.55 (1H, ddd, J=8.3, 6.7, 1.0 Hz, H_7), 7.34 (1H, dd, J=8.9, 2.0 Hz, $H_{7'}$), 7.10 (1H, d, J=8.9 Hz, $H_{8'}$), 4.05 (3H, s, CO_2CH_3), 3.22 (3H, s, OCH_3), 1.54 (9H, s, *t*-butyl), 1.37 (9H, s, *t*-butyl); δC (125.8 MHz; $CDCl_3$) 166.7, 159.4 156.4, 147.3, 142.2, 141.1, 136.0, 131.1, 130.8, 130.4, 129.9, 129.7, 128.2, 127.8, 127.0, 126.0, 125.0, 123.9, 123.7, 122.8, 62.0, 52.9, 35.4, 34.6, 31.2, 30.7; *m/z* ($APCI^+$; NH_3); 456 (M+1, 100%).

3.1.5. Preparation of 1-(3,6-di-*tert*-butyl-2-methoxy-1-naphthyl)-3-hydroxymethylisoquinoline 25. 24 (2.19 g, 4.81 mmol) was dissolved in dry THF (20 ml) and a suspension of lithium borohydride (209 mg, 9.62 mmol) in THF (40 ml) added. The mixture was stirred at room temperature overnight, then quenched by addition of water (20 ml) and 1 M hydrochloric acid (15 ml). The solvent was evaporated and the product extracted into dichloromethane (30 ml), washed with water (2×20 ml), dried ($MgSO_4$), filtered and concentrated. The residue was triturated with pentane (20 ml) to give the title compound as a pale yellow solid (1.89 g, 92%) mp 146–148°C; δH (500 MHz; $CDCl_3$) 7.94 (1H, s, H_4), 7.93 (1H, d, J=8.2 Hz, H_5), 7.80 (1H, d, J=2.0 Hz, $H_{5'}$), 7.79 (1H, s, $H_{4'}$), 7.44 (1H, dd, J=8.3, 7.9 Hz, H_6), 7.59 (1H, d, J=8.3 Hz, H_8), 7.35 (1H, dd, J=8.3, 7.9 Hz, H_7), 7.34 (1H, dd, J=8.9, 2.0 Hz, $H_{7'}$), 7.07 (1H, d, J=8.9 Hz, $H_{8'}$), 5.05 (1H, d, J=13.9 Hz, OCH_2), 5.02 (1H, d, J=13.9 Hz, OCH_2), 3.19 (3H, s, OCH_3), 1.54 (9H, s, *t*-butyl), 1.37 (9H, s, *t*-butyl); δC (125.8 MHz; $CDCl_3$) 158.2, 156.7, 151.4, 147.5, 142.3, 137.2, 131.2, 130.6, 130.2, 127.8, 127.5, 127.2, 126.8, 125.1, 123.8, 123.0, 116.8; *m/z* ($APCI^+$; NH_3) 428 (M+1, 100%), HRMS, 428.2591; Calcd 428.2590.

3.1.6. Preparation of 3-bromomethyl-1-(3,6-di-*tert*-butyl-2-hydroxy-1-naphthyl)isoquinoline 26. Compound **25** (250 mg, 0.585 mmol) was dissolved in dry dichloromethane (10 ml) and stirred overnight with boron tribromide (0.11 ml, 1.2 mmol). Water (10 ml) was added to quench the reaction, then 1 M sodium hydroxide (15 ml) and the mixture stirred for 4 h. More dichloromethane (10 ml) was added and the organic layer was separated,

dried ($MgSO_4$), filtered and evaporated to give a solid. Purification by column chromatography on silica gel (dichloromethane, R_f=0.7) gave the title compound as a yellow crystalline solid (226 mg, 81%) mp 109–110°C (Found: C, 70.01; H, 6.19; N, 2.81. $C_{28}H_{30}BrNO$ requires C, 70.58; H, 6.35; N, 2.94%); δH (500 MHz; $CDCl_3$) 8.82 (1H, br s, OH), 7.92 (1H, d, *J*=8.3 Hz, H_5), 7.88 (1H, s, H_4), 7.86 (1H, s, $H_{4'}$), 7.77 (1H, d, *J*=1.9 Hz, $H_{5'}$), 7.72 (1H, dd, *J*=8.3, 7.2 Hz, H_6), 7.62 (1H, d, *J*=8.5 Hz, H_8), 7.41 (1H, dd, *J*=8.5, 7.2 Hz, H_7), 7.25 (1H, dd, *J*=8.9, 1.9 Hz, $H_{7'}$), 6.99 (1H, d, *J*=8.9 Hz, $H_{8'}$), 4.89 (1H, d, *J*=10.3 Hz, CH_2Br), 4.78 (1H, d, *J*=10.3 Hz, CH_2Br), 1.58 (9H, s, *t*-butyl), 1.39 (9H, s, *t*-butyl); δC (125.8 MHz; $CDCl_3$) 158.8, 153.0, 148.8, 145.8, 139.2, 137.7, 131.2, 129.5, 128.8, 128.2, 127.8, 127.6, 127.5, 127.2, 124.6, 124.2, 123.2, 119.7, 116.5, 35.5, 34.5, 34.3, 31.3, 29.9; *m/z* ($APCI^+$; NH_3) 477 (M+1, 85%).

3.1.7. Preparation of bis[3-(1-(3,6-di-*tert*-butyl-2-hydroxy-1-naphthyl)isoquinolyl)methyl] sulphide 5. Compound **26** (25 mg, 0.47 mmol) was stirred overnight with sodium sulphide nonahydrate (6.0 mg, 2.5 mmol) in DMF (2 ml). The DMF was removed in vacuo and ^1H NMR analysis of the residue showed 85% conversion to the diastereomeric mix of products. Purification and separation of the diastereomers was achieved by preparative tlc (dichloromethane, R_f=0.40(a) and 0.36(b));

3.1.8. Diastereomer (a). δH (500 MHz; $CDCl_3$) 7.85 (1H, s, H_4), 7.77 (1H, d, *J*=8.4 Hz, H_5), 7.75 (1H, d, *J*=2.1 Hz, $H_{5'}$), 7.73 (1H, s, $H_{4'}$), 7.61 (1H, dd, *J*=8.4, 8.4 Hz, H_6), 7.53 (1H, d, *J*=8.4 Hz, H_8), 7.29 (1H, dd, *J*=8.4, 8.4 Hz, H_7), 7.21 (1H, dd, *J*=8.9, 2.1 Hz, $H_{7'}$)., 6.99 (1H, d, *J*=8.9 Hz, $H_{8'}$), 4.18 (1H, d, *J*=14.1 Hz, CH_2S), 4.11 (1H, d, *J*= 14.1 Hz, CH_2S), 1.57 (9H, s, *t*-butyl), 1.38 (9H, s, *t*-butyl); δC (125.8 MHz; $CDCl_3$) 158.4, 153.2, 150.2, 145.6, 139.1, 137.7, 130.7, 129.5, 128.6, 128.1, 127,4, 127.0, 126.8, 127.4, 127.0, 126.8, 124.4, 123.1, 119.1, 116.5, 37.6, 35.5, 34.5, 31.2, 29.9; *m/z* ($APCI^+$; NH_3) 826 (M+1, 60%), 398 (100%), HRMS, 825.4454; Calcd 825.4454.

3.1.9. Diastereomer (b). δH (500 MHz; $CDCl_3$) 7.88 (1H, s, H_4), 7.76 (1H, d, *J*=2.1 Hz, $H_{5'}$), 7.72 (1H, d, *J*=8.4 Hz, H_5), 7.72 (1H, s, $H_{4'}$), 7.26 (1H, dd, *J*=8.4, 7.3 Hz, H_6), 7.45 (1H, d, *J*=8.5 Hz, H_8), 7.20 (1H, dd, *J*=8.5, 7.5 Hz, H_7), 7.19 (1H, dd, *J*=8.9, 2.1 Hz, $H_{7'}$), 6.96 1H, d, *J*=8.9 Hz, $H_{8'}$), 4.14 (1H, d, *J*=14.3 Hz, CH_2S), 4.11 (1H, d, *J*= 14.3 Hz, CH_2S), 1.64 (9H, s, *t*-butyl), 1.37 (9H, s, *t*-butyl); *m/z* ($APCI^+$; NH_3) 826 (M+1, 70%), 398 (100%).

3.1.10. Preparation of 3-carboxy-1-(2-methoxy-1-naphthyl)isoquinoline 20. A solution of tetrakis(triphenylphosphine)palladium(0) (1.80 g, 1.56 mmol) in DME (150 ml) was added to a 1 l, three-necked round bottomed flask, containing **19** (13.8 g, 62.2 mmol), and stirred under argon for 20 min. Solutions of **7** (12.6 g, 62.2 mmol) in ethanol (100 ml), and potassium carbonate (25.8 g, 18.6 mmol) in water (100 ml) were added and the mixture heated at 100°C overnight. On cooling, the reaction mixture was filtered and the solvents evaporated. Water (150 ml) was added to the residue and the solution was washed with dichloromethane (3×100 ml). The aqueous layer was then acidified with 1 M hydrochloric acid and the resultant precipitate isolated by suction filtration and dried in a dessicator over phosphorous pentoxide to yield the title compound as a pale yellow powder (18.0 g, 88%) mp 165–167°C; δH (500 MHz; DMSO) 8.76 (1H, s, H_4), 8.31 (1H, d, *J*=8.2 Hz, H_5), 8.21 (1H, d, *J*=9.1 Hz, $H_{4'}$), 8.02 (1H, d, *J*=8.1 Hz, $H_{5'}$), 7.88 (1H, dd, *J*=8.2, 7.4 Hz, H_6), 7.69 (1H, d, *J*=9.1 Hz, $H_{3'}$), 7.65 (1H, dd, *J*=8.4, 7.4 Hz, H_7), 7.44 (1H, d, *J*=8.4 Hz, H_8), 7.38 (1H, dd, *J*=8.1, 7.9 Hz, $H_{7'}$), 7.10 (1H, d, *J*=8.1 Hz, $H_{8'}$), 3.76 (3H, s, OCH_3); δC (125.8 MHz; DMSO) 166.8, 157.9, 154.6, 141.8, 135.8, 133.2, 131.3, 130.8, 130.1, 129.5, 128.8, 128.6, 128.2, 127.1, 126.7, 124.3, 123.8, 123.3, 120.6, 113.9, 56.4;

3.1.11. Preparation of 3-carbomethoxy-1-(2-methoxy-1-naphthyl)isoquinoline 21. 20 (8.46 g, 25.7 mmol) was refluxed overnight with potassium carbonate (14.2 g, 103 mmol) and methyl iodide (14.6 g, 103 mmol) in acetone (500 ml). On cooling the reaction mixture was filtered and the solvent evaporated. The residue was taken into chloroform, filtered and the filtrate concentrated to ca. 20 ml. Pentane (200 ml) was added and the resulting solid isolated by suction filtration to give the title compound as a yellow powder (7.24 g, 82%) mp 199–201°C; δH (500 MHz; $CDCl_3$) 8.71 (1H, s, H_4), 8.06 (1H, d, *J*=8.2 Hz, H_5), 8.01 (1H, d, *J*=9.1 Hz, $H_{4'}$), 7.86 (1H, d, *J*=8.2 Hz, $H_{5'}$), 7.77 (1H, ddd, *J*=8.2, 6.5, 1.6 Hz, H_6), 7.54–7.49 (2H, m, H_7, H_8), 7.44 (1H, d, *J*=9.1 Hz, $H_{3'}$), 7.34 (1H, ddd, *J*=8.2, 7.0, 1.1 Hz, $H_{6'}$), 7.26 (1H, ddd, *J*=8.5, 7.2, 1.1 Hz, $H_{7'}$), 7.03 (1H, d, *J*=8.5 Hz, $H_{8'}$), 4.05 (3H, s, CO_2CH_3), 3.78 (3H, s, OCH_3); δC (125.8 MHz; $CDCl_3$) 166.8, 158.8, 155.0, 141.6, 135.9, 130.8, 130.7, 130.3, 129.4, 129.2, 128.3, 127.9, 127.6, 126.8, 124.7, 123.8, 123.7, 121.5, 113.5, 56.6, 52.8; *m/z* ($APCI^+$; NH_3) 344 (M+1, 100%); HRMS, 344.1291; Calcd 344.1287.

3.1.12. Preparation of 3-hydroxymethyl-1-(2-methoxy-1-naphthyl)isoquinoline 22. 21 (8.60 g, 25.0 mmol) was dissolved in dry THF (250 ml) and lithium borohydride (1.09 g, 50.0 mmol) was added in solid portions over 10 min. The reaction mixture was stirred for 4 h, then quenched by the sequential addition of water (50 ml) and 1 M hydrochloric acid (25 ml). The THF was removed on the rotary evaporator, then the product extracted into chloroform (2×75 ml), dried ($MgSO_4$) and the solvents evaporated to give the title compound as a pale yellow solid (7.88 g, 95%) mp 213–214°C; δH (500 MHz; $CDCl_3$) 8.06 (1H, d, *J*=9.1 Hz, $H_{4'}$), 7.95 (1H, d, *J*=8.3 Hz, H_5), 7.88 (1H, d, *J*=8.2 Hz, $H_{5'}$), 7.82 (1H, s, H_4), 7.75 (1H, dd, *J*=8.3, 8.3 Hz, H_6), 7.55 (1H, d, *J*=8.4 Hz, H_8), 7.46 (1H, d, *J*= 9.1 Hz, $H_{3'}$), 7.44 (1H, dd, *J*=8.4, 8.3 Hz, H_7), 7.35 (1H, dd, *J*=8.2, 8.2 Hz, $H_{6'}$), 7.27 (1H, dd, *J*=8.5, 8.3 Hz, $H_{7'}$), 6.99 (1H, d, *J*=8.5 Hz, $H_{8'}$), 5.03 (2H, s, OCH_2), 3.82 (3H, s, OCH_3); δC (125.8 MHz; $CDCl_3$) 157.4, 155.1, 151.1, 137.3, 133.5, 131.6, 131.4, 128.9, 128.1, 128.0, 127.9, 127.6, 127.2, 127.1, 124.4, 123.9, 117.5, 113.4, 64.2, 56.7; *m/z* ($APCI^+$; NH_3) 315 (M+1, 100%); HRMS, 316.1329; Calcd 316.1338.

3.1.13. Preparation of 3-bromomethyl-1-(2-hydroxy-1-naphthyl)isoquinoline 23. To a solution of 3-hydroxymethyl-1-(2-methoxy-1-naphthyl)isoquinoline (6.67 g, 21.2 mmol) in dry dichloromethane (150 ml) was added boron

tribromide (4.00 ml, 42.4 mmol) dropwise with stirring. The resulting black solution was stirred overnight, then the reaction mixture quenched by the careful addition of water (50 ml) and 0.5 M sodium hydroxide solution (25 ml). The dichloromethane layer was separated and the aqueous layer extracted with ethyl acetate (2×75 ml). The combined organics were dried ($MgSO_4$), filtered and the solvents evaporated, to give a residue which on trituration with pentane gave the title compound as a bright yellow powder (5.95 g, 77%) mp decomp >240°C; δH (500 MHz; $CDCl_3$) 7.94 (1H, d, J=8.2 Hz, H_5), 7.93 (1H, d, J=8.9 Hz, $H_{4'}$), 7.88 (1H, s, H_4), 7.87 (1H, d, J=8.3 Hz, $H_{5'}$), 7.74 (1H, ddd, J=8.2, 7.0, 0.9 Hz, H_6), 7.63 (1H, d, J=8.5 Hz, H_8), 7.43 (1H, ddd, J=8.5, 7.1, 1.0 Hz, H_7), 7.39 (1H, d, J=8.9 Hz, $H_{3'}$), 7.35 (1H, ddd, J=8.3, 7.1, 1.1 Hz, $H_{6'}$), 7.26 (1H, ddd, J=8.4, 7.1, 1.3 Hz, $H_{7'}$), 7.20 (1H, d, J=8.4 Hz, $H_{8'}$), 4.89 (1H, d, J=10.3 Hz, CH_2Br), 4.75 (1H, d, J=10.3 Hz, CH_2Br); δC (125.8 MHz; $CDCl_3$) 157.9, 153.6, 149.0, 137.7, 132.8, 131.4, 131.2, 128.9, 128.4, 128.3, 127.9, 127.3, 126.5, 125.1, 123.4, 119.8, 119.1, 116.5; m/z ($APCI^+$; NH_3) 365 (M+1, 100%).

3.1.14. Preparation of bis[3-(1-(2-hydroxy-1-naphthyl)-isoquinolyl)methyl]sulphide 4. 23 (1.00 g, 2.75 mmol) was heated at 100°C with sodium sulphide nonahydrate (330 mg, 1.37 mmol) in DMF (10 ml) for 10 min. The DMF was removed in vacuo and the residue purified by column chromatography (1:1 ethyl acetate/pentane, R_f= 0.35) to yield the title compound as a bright orange crystalline solid (511 mg, 62%) mp 94–125°C; ν_{max} (KBr disc)/cm^{-1} 3500–3350s (O–H), 3057w (Ar C–H), 2360s (sp^3 C–H), 2341s (sp^3 C–H), 1622s (Ar C=N), 1587m (Ar C=C), 1558m (Ar C=C), 1512m (Ar C=C), 1347s, 1262s, 1245s, 816m, 749s; δH (500 MHz; $CDCl_3$) 7.85 (1H, d, J=8.1 Hz, $H_{4'}$), 7.84 (1H, d, J=8.3 Hz, $H_{4'}$), 7.81 (2H, s, H_4), 7.78 (1H, d, J=8.3 Hz, H_5), 7.71 (1H, d, J=8.2 Hz, H_5), 7.60–7.41 (6H, m, H_6, H_8, $H_{5'}$), 7.36–7.14 (8H, m, H_7, $H_{6'}$, $H_{7'}$, $H_{3'}$), 7.07 (1H, d, J=8.8 Hz, $H_{8'}$), 6.89 (1H, d, J=8.8 Hz, $H_{8'}$), 4.20 (1H, d, J=14.1 Hz, CH_2S), 4.04 (1H, d, J=14.1 Hz, CH_2S), 4.01 (1H, d, J=14.2 Hz, CH_2S), 3.98 (1H, d, J= 14.2 Hz, CH_2S); δC (125.8 MHz; $CDCl_3$) 157.6, 157.0, 153.7, 153.4, 150.7, 137.7, 137.4, 132.8, 131.1, 131.0, 130.8, 130.7, 129.0, 128.7, 128.2, 128.1, 127.0, 126.9, 126.8, 126.3, 125.3, 125.0, 124.6, 123.6, 123.3, 123.2, 120.1, 119.9, 119.1, 118.9, 118.3, 116.6, 38.5, 36.5; m/z ($APCI^+$; NH_3) 601 (M+1, 100%); HRMS, 601.1958; Calcd 601.1950.

3.1.15. Racemisation studies on compound 3. Compound **3** (200 mg, 0.740 mmol) and **14** (125 mg, 0.180 mmol) were stirred in chloroform (20 ml) for 2 h. ^{1}H NMR analysis of the solution indicated three species were present: uncomplexed starting material (60%), palladium complex (major diastereomer) (35%), and palladium complex (minor diastereomer) (5%). The solution was concentrated to ca. 5 ml, and on standing a white precipitate formed. This was filtered off to give a pure sample of uncomplexed **3** (46 mg, 30%) which was dissolved in chloroform (25 mg in 5 ml) and kept at 23°C. Its optical rotation was measured periodically.

3.1.16. Racemisation studies on 13. 13 (200 mg, 0.520 mmol) and **14** (89 mg, 0.13 mmol) were stirred in chloroform (5 ml) for 10 min. ^{1}H NMR analysis of the solution indicated three species were present: uncomplexed starting material (49%), palladium complex (major diastereomer) (38%), and palladium complex (minor diastereomer) (13%). The solvent was evaporated, and the residue purified by flash column chromatography on silica (dichloromethane) to give uncomplexed **13** (75 mg, 38%) which was dissolved in chloroform (50 mg in 5 ml) and kept at 23°C. Its optical rotation was measured over a period of time. Further elution of the column (CH_2Cl_2) gave the major diastereomer of the palladium complex; mp 190–192°C; δH (500 MHz; $CDCl_3$) 9.09 (1H, d, J=6.4 Hz), 8.00 (1H, d, J= 6.4 Hz), 7.99 (1H, d, J=8.2 Hz), 7.89 (1H, s, $H_{4'}$), 7.77 (1H, ddd, J=8.2, 7.9, 1.6 Hz), 7.66 (1H, d, J=7.2 Hz), 7.44–7.40 (3H, m), 7.24–7.19 (4H, m), 6.58 (1H, d, J=8.5 Hz), 6.25 (1H, dd, J=8.8, 1.7 Hz), 6.16 (1H, d, J=8.8 Hz), 3.73 (1H, q, J=6.4 Hz), 2.70 (3H, s), 2.48 (3H, s), 1.65 (9H, s), 0.80 (9H, s), 0.45 (3H, d, J=6.4 Hz); δC (125 MHz; $CDCl_3$) 162.8, 151.4, 146.4, 146.1, 145.5, 144.0, 142.9, 135.8, 132.2, 131.5, 131.0, 129.1, 128.9, 128.5, 128.1, 127.8, 127.0, 126.7, 125.2, 125.1, 124.3, 123.8, 123.4, 123.2, 122.6, 121.6, 73.9, 53.3, 49.1, 35.6, 33.9, 30.4, 30.4, 20.9; m/z (Electrospray)=687.6 (M+1).

3.1.17. Racemisation studies on 26. 26 (200 mg, 0.420 mmol) and **14** (71.0 mg, 1.05 mmol) were stirred overnight in chloroform (5 ml). ^{1}H NMR analysis of the solution indicated two species were present: uncomplexed starting material (50%), and a single palladium complex (50%). The solvent was evaporated, and the residue purified by flash column chromatography on silica (dichloromethane) to give uncomplexed starting material (81 mg, 41%) which was dissolved in chloroform (50 mg in 5 ml) and kept at 23°C. Its optical rotation was measured over a period of time. Further elution of the column gave the palladium complex; mp 165–167°C; δH (500 MHz; $CDCl_3$) 8.48 (1H, s), 8.02 (1H, d, J=8.3 Hz), 7.90 (1H, s), 7.77 (1H, ddd, J=8.3, 6.5, 1.5 Hz), 7.64 (1H, d, J=7.4 Hz), 7.42–7.35 (4H, m), 7.27–7.19 (3H, m), 7.17 (1H, d, J= 8.6 Hz), 6.33 (1H, d, J=8.6 Hz), 6.28 (1H, dd, J=8.9, 1.9 Hz), 6.25 (1H, d, J=13.1 Hz), 6.18 (1H, d, J=8.9 Hz), 5.70 (1H, d, J=13.1 Hz), 3.76 (1H, q, J=6.4 Hz), 2.78 (3H, s), 2.50 (3H, s), 1.64 (9H, s), 0.80 (9H, s), 0.43 (3H, d, J=6.4 Hz); δC (500 MHz; $CDCl_3$) 162.6, 151.4, 148.0, 146.3, 146.2, 142.9, 136.7, 132.5, 131.8, 131.5, 129.1, 129.0, 128.5, 128.3, 128.2, 128.1, 127.8, 127.3, 126.8, 125.3, 124.5, 124.2, 124.0, 123.6, 123.3, 122.6, 121.5, 73.9, 53.5, 49.1, 35.6, 33.9, 33.5, 30.5, 20.9; m/z (Electrospray)=781.4 (M+1).

3.1.18. Racemisation studies on 23. 23 (1.72 g, 4.73 mmol) and **14** (805 mg, 1.18 mmol) were stirred overnight in chloroform (50 ml). ^{1}H NMR analysis of the solution indicated three species were present: uncomplexed starting material (48%), palladium complex (major diastereomer) (50%) and another palladium complex (minor diastereomer) (2%). The solvent was evaporated and the residue purified by flash chromatography on silica gel (3:1 pentane/ethyl acetate) to give uncomplexed 3-bromomethyl-1-(2-hydroxy-1-naphthyl)isoquinoline (652 mg, 38%) which was dissolved in chloroform (250 mg in 50 ml) and kept at 23°C. Optical rotation measurements were made periodically. Further elution of the column (ethyl acetate) gave the

major palladium diastereomer; δH (500 MHz; $CDCl_3$) 8.52 (1H, s), 8.05 (1H, d, *J*=8.3 Hz), 7.97 (1H, d, *J*=8.7 Hz), 7.81 (1H, dd, *J*=8.3, 7.5 Hz), 7.74 (1H, s), 7.66 (1H, d, *J*=7.7 Hz), 7.59 (1H, d, *J*=8.1 Hz), 7.56 (1H, d, *J*=8.7 Hz), 7.41 (1H, dd, *J*=8.2, 7.5 Hz), 7.30–7.24 (5H, m), 7.17 (1H, d, *J*=8.5 Hz), 6.84 (1H, ddd, *J*=8.0, 5.3, 2.7 Hz), 6.45 (1H, d, *J*=8.0 Hz), 6.36 (1H, d, *J*=8.5 Hz), 6.18 (1H, d, *J*=13.0 Hz), 5.71 (1H, d, *J*=13.0 Hz), 3.82 (1H, q, *J*=6.4 Hz), 2.84 (3H, s), 2.56 (3H, s), 0.49 (3H, d, *J*=6.4 Hz); δC (125.8 MHz; $CDCl_3$) 161.4 (C_{10}), 152.3 (ArC), 148.4 (ArC), 146.9 (ArC), 144.2 (ArC), 136.8 (ArC), 132.7 (ArC), 131.7 (ArC), 131.5 (ArCH), 131.5 (ArCH), 131.4 (ArCH), 131.4 (ArC), 129.3 (ArC), 129.2 (ArCH), 128.5 (ArCH), 128.2 (ArC), 128.1 (ArCH), 127.9 (ArC), 127.0 (ArCH), 126.9 (ArCH), 125.5 (ArCH), 125.4 (ArCH), 124.7 (ArCH), 124.2 (ArCH), 123.8 (ArCH), 123.7 (ArCH), 122.9 (ArCH), 122.8 (ArCH), 74.0 ($CHCH_3$), 53.4 (NCH_3), 49.1 (NCH_3), 33.3 (CH_2Br), 21.1 ($CHCH_3$); *m*/*z* (FAB) 669 (M^+).

Acknowledgements

We thank Unilever Research (Port Sunlight) for a CASE award to S. C. T., and EPSRC for support. Mrs E. McGuinness was very helpful in the acquisition of NMR spectra, and Dr R. T. Aplin in the acquisition of MS. Mrs V. Lambourn is thanked for combustion analyses. We thank Dr D. J. Bayston for a first synthesis of compound **19**.

References

1. Calligaris, M.; Randaccio, L. In *Comprehensive Coordination Chemistry*, Pergamon: Oxford, 1987; Vol. 2, pp 727. Bottcher, A.; Elias, H.; Jager, E. G.; Langfelderova, H.; Mazur, M.; Muller, L.; Paulus, H.; Pelikan, P.; Rudolph, M.; Valko, M. *Inorg. Chem.* **1993**, *32*, 4131–4138. Leung, W. H.; Chan, E. Y. Y.; Chow, E. K. F.; Williams, I. D.; Peng, S. M. *J. Chem. Soc., Dalton Trans.* **1996**, 1229–1236.
2. Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH Publishers: New York, 1993; pp 159.
3. Kokubo, C.; Katsuki, T. *Tetrahedron* **1996**, *52*, 13895–13900. Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245–9248. Nishikori, H.; Ohta, C.; Oberlin, E.; Irie, R.; Katsuki, T. *Tetrahedron* **1999**, *55*, 13937–13946. Sevvel, R.; Rajagopal, S.; Srinivasan, C.; Alhaji, N. I.; Chellamani, A. *J. Org. Chem.* **2000**, *65*, 3334–3340.
4. Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403–405.
5. Belokon, Y. N.; North, M.; Parsons, T. *Org. Lett.* **2000**, *2*, 1617–1619. Belokon, Y. N.; Caveda Cepas, S.; Green, B.; Ikonnikov, N. S.; Krustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968–3973. Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett.* **1999**, *40*, 8147–8150. Flores Lopez, L. Z.; Parra Hake, M.; Somanathan, R.; Walsh, P. *J. Organometal.* **2000**, *19*, 2153–2160.
6. Fukuda, T.; Katsuki, T. *Tetrahedron* **1997**, *53*, 7201–7208. Uchida, T.; Irie, R.; Katsuki, T. *Synlett* **1999**, 1163–1165. Uchida, T.; Irie, R.; Katsuki, T. *Synlett* **1999**, 1793–1795.
7. Ho, C. M.; Lau, T. C.; Kwong, H. L.; Wong, W. T. *J. Chem. Soc.-Dalton Trans.* **1999**, 2411–2413. Li, Z.; Fernandez, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611–1613. Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245–9248.
8. Larrow, J. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 12129–12130. Hamada, T.; Irie, R.; Mihara, J.; Hamachi, K.; Katsuki, T. *Tetrahedron* **1998**, *54*, 10017–10028. Miyafuji, A.; Katsuki, T. *Synlett* **1997**, 836. Miyafuji, A.; Katsuki, T. *Tetrahedron* **1998**, *54*, 10339–10348. Punniyamurthy, T.; Katsuki, T. *Tetrahedron* **1999**, *55*, 9439–9454. Punniyamurthy, T.; Miyafuji, A.; Katsuki, T. *Tetrahedron Lett.* **1998**, *39*, 8295–8298.
9. Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924–10925. Kamada, M.; Satoh, T.; Kakuchi, T.; Yokota, K. *Tetrahedron: Asymmetry* **1999**, *10*, 3667–3669. Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420–7421. Lebel, H.; Jacobsen, E. N. *Tetrahedron Lett.* **1999**, *40*, 7303–7306. Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897–5898. Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086–6087. Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197–4199. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938. Wu, M. H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 5252–5254.
10. Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743–756. Badr, M. Z. A.; Aly, M. M. *Tetrahedron* **1972**, *28*, 3401–3406.
11. Braddock, D. C.; Tucker, S. C.; Brown, J. M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 399.
12. He, G. S.; Mok, K. F.; Leung, P. H. *Organometallics* **1999**, *18*, 4027–4031. Hockless, D. C. R.; Gugger, P. A.; Leung, P. H.; Mayadunne, R. C.; Pabel, M.; Wild, S. B. *Tetrahedron* **1997**, *53*, 4083–4094. Alcock, N. W.; Hulmes, D. I.; Brown, J. M. *J. Chem. Soc. Chem. Commun.* **1995**, 395–397.
13. Hockless, D. C. R.; Mayadunne, R. C.; Wild, S. B. *Tetrahedron: Asymmetry* **1995**, *6*, 3031–3037. Navarro, R.; Garcia, J.; Urriolabeitia, E. P.; Cativiela, C.; Diaz-de-Villegas, M. D. *J. Organometal. Chem.* **1995**, *490*, 35–43.
14. Pedersen, J. R. *Acta. Chem. Scand. A* **1974**, *28*, 213–216. Pedersen, J. R. *Acta. Chem. Scand. A* **1975**, *29*, 285–288.
15. Berson, J. A.; Greenbaum, M. A. *J. Am. Chem. Soc.* **1958**, *80*, 653–656.
16. Bain, D.; Perkin, W. H.; Robinson, R. *J. Chem. Soc.* **1914**, 2392–2396.
17. Stiller, E. T. *J. Chem. Soc.* **1937**, 473–478.
18. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
19. Cooke, A. S.; Harris, M. M. *J. Chem. Soc.* **1963**, 2365–2373. Badar, Y.; Cooke, A. S.; Harris, M. M. *J. Chem. Soc.* **1965**, 1412–1418.
20. Fuji, K.; Sakurai, M.; Kinoshita, T.; Tada, T.; Kuroda, A.; Kawabata, T. *Chem. Pharm. Bull.* **1997**, *45*, 1524–1526. Fuji, K.; Sakurai, M.; Tohkai, N.; Kuroda, A.; Kawabata, T.; Fukazawa, Y.; Kinoshita, T.; Tada, T. *Chem. Commun.* **1996**, 1609–1610.
21. Meyers, A. I.; Price, A. *J. Org. Chem.* **1998**, *63*, 412–413.
22. Ashton, P. R.; Brown, G. R.; Foubister, A. J.; Smith, D. R.; Spencer, N.; Stoddart, J. F.; Williams, D. *J. Tetrahedron Lett.* **1993**, *34*, 8333–8336.
23. Kirby, A. *J. Adv Phys Org. Chem.* **1980**, *19*, 183–278 esp. Table 12, Table B2.