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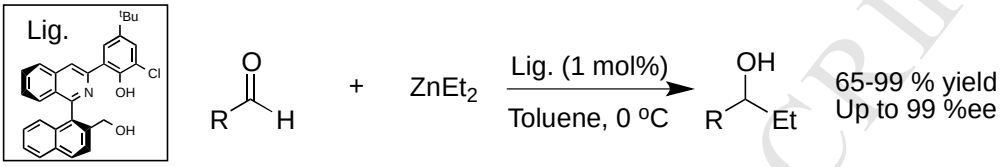

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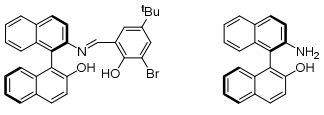
ABSTRACT

The synthesis and resolution of new tridentate isoquinoline-derived ligands has been developed. The key steps in the synthetic sequence include successive, chemo-selective Suzuki-Miyaura cross-couplings of 1,3-dichloroisoquinoline with suitable arylboronic acids. The new ligands prepared in this manner were resolved either *via* molecular complexation with *N*-benzylcinchonidinium chloride as with 1-[3-(2-hydroxyphenyl)isoquinolin-1-yl]naphthalen-2-ol or via chromatographic separation of its epimeric camphorsulfonates as for 1,3-bis-(2-hydroxynaphthalen-1-yl)isoquinoline. 4-*tert*-Butyl-2-chloro-6-[1-(2-hydroxymethylnaphthalen-1-yl)isoquinolin-3-yl]phenol was resolved by chiral semi-preparative HPLC. The application of these ligands in the diethylzinc addition to aldehydes was investigated. In certain cases, the desired secondary alcohols were obtained in high yield with excellent enantiomeric excess (ee > 99%) at low catalyst loading (1 mol%).

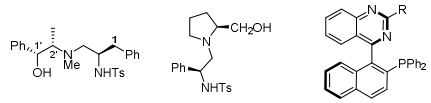
1. Introduction

The development of chiral tridentate ligands suitable for application in a variety of catalytic asymmetric processes has received much attention in recent years,[1-3] including examples from our own group.[4-11] Of these ligands, Carreira's imine **1** derived from NOBIN[12] (**2**) (Figure 1) has proven extremely effective in the Ti(IV)-catalyzed enantioselective Mukaiyama aldol reaction of various ketene acetals with aldehydes as well as the addition of 2-methoxypropene to aldehydes.[13] More recently, Mao *et al.* have described the synthesis of sulfamide-amine alcohols **3** and **4** (Figure 2) for the highly efficient enantioselective addition of diethylzinc to aldehydes.[14] We have recently reported a series of bidentate ligands, Quinazolinaps **5**, which give excellent results in a number of catalytic asymmetric reactions.[15-25] Encouraged by these results, a research program into the design, synthesis, and resolution of a series of ligands related to the previously reported tridentate ligands and our Quinazolinaps was initiated.



1 2

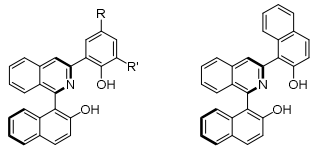
Figure 1. Carreira's ligand **1** derived from NOBIN **2**.



(1*R*,1'*R*,2'*S*)-**3** (*S*,*S*)-**4** **5**: R = H, Me, ^{i}Pr, ^{t}Bu, Ph, Bn

Figure 2. Mao's ligands **3** and **4** and Guiry's Quinazolinaps **5**

Our initial ligand design sought to combine the effective 6-chelate about the biaryl axis of the Quinazolinaps **5** while maintaining the tridentate binding mode of ligand **1**. Structural analysis of **1** shows a 6-membered and 7-membered chelate between the imine nitrogen and, respectively, the phenolic hydroxyl and the naphthol. The phenol is substituted with a 4-*tert*-butyl group and a 2-bromo substituent, with the latter increasing phenol acidity. We therefore reasoned that **6** would be a suitable synthetic target as the key design principle was to incorporate the nitrogen donor into an isoquinoline ring and to leave the remainder of the ligand mostly unchanged. Simplifying further, in our preliminary investigations, we decided to concentrate on the synthesis of analogues **7** and **8** (Figure 3).[26]



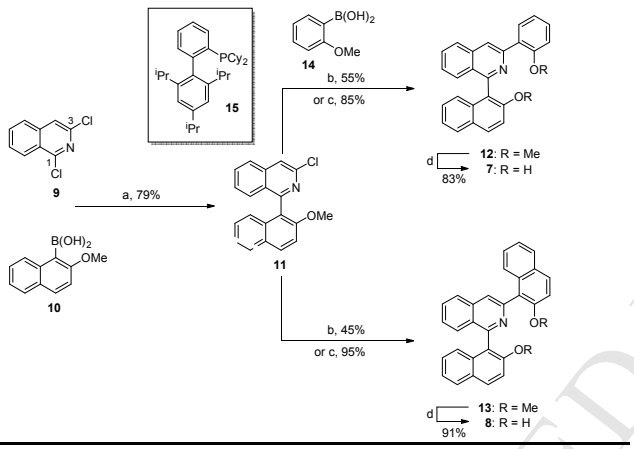
6: R = ^{t}Bu, R' = Cl
7: R = H, R' = H
8

Figure 3. Original design **6** and its simpler analogues **7** and **8**

Synthesis and Resolution

The synthesis of ligands **7** and **8** commenced with the Suzuki-Miyaura cross-coupling of 1,3-dichloroisoquinoline (**9**) and arylboronic acid **10** to yield biaryl **11** (Scheme 1). The regioselectivity of this cross-coupling reaction has previously been reported and rationalised by Woodward *et al.*[27] The preparation of aryl ethers **12** and **13** was completed *via* Suzuki-Miyaura cross coupling of **11** with arylboronic acids **14** and **10**, respectively, (Scheme 1). The 3-chloro substituent is generally a poor electrophilic partner for cross-coupling reactions, however, when $Pd(PPh_3)_4$ was employed as the catalyst, both coupled products **12** and **13** were obtained in moderate yields of 55% and 45%, respectively, even when forcing conditions were employed (110 °C in DMF). The emergence of XPhos (**15**) as an excellent ligand for the Suzuki-Miyaura cross-coupling reaction of aryl chlorides and tosylates has greatly expanded the scope of this useful process.[28] Therefore, by heating biaryl **11** with $Pd(OAc)_2$, XPhos and K_3PO_4 in THF with the requisite boronic acid at 80 °C for 18 h, the required aryl methyl ethers **12** and **13** were isolated in excellent yields of 85% and 95%, respectively.

Scheme 1. Synthesis of Ligands **7** and **8**



Reagents and conditions: (a) $Pd(PPh_3)_4$ (cat.), DME, $ArB(OH)_2$, Na_2CO_3, 90°C, 5 d (b) $Pd(OAc)_2$ (cat.), **15**, $ArB(OH)_2$, K_3PO_4, THF, 80°C, 18 h (c) 48% HBr, AcOH, 140 °C, 18 h.

Compounds **12** and **13** obtained from the Suzuki-Miyaura reaction were subsequently exhaustively demethylated with HBr to afford the desired tridentate ligands **7** and **8** in good yield.[29] Subsequently, various resolution methods were investigated. Ding *et al.* reported the optical resolution of ligand **2** by molecular complexation with *N*-benzylcinchonidinium chloride (**16**) (Figure 4).[30]

The stereoview of the crystal structure of the (*R*)-(+)-**2·16** shows that hydrogen bonding between the amino alcohol and the chlorine atom is crucial to formation of the molecular crystal - a fact that is best illustrated by the failure of biaryl **17**, to form an analogous molecular crystal.

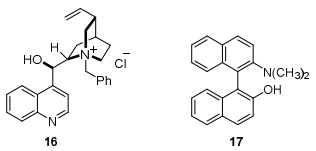
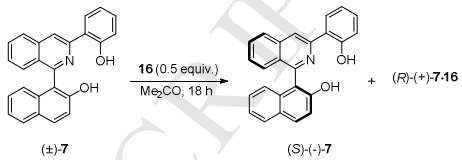


Figure 4. *N*-Benzylcinchonidinium chloride (**16**) and the dimethyl derivative of NOBIN **17**

We reasoned that, although our ligands **7** and **8** have no NH moiety available to form the analogous hydrogen bond, the existence of a second OH with a proton capable of occupying a similar region in space might facilitate formation of the molecular crystal. Gratifyingly, ligand **7** could be resolved by employing a modified procedure. Therefore, stirring racemic **7** with 0.5 equiv. of **16** in acetone for 18 h produced a white precipitate of (*R*)-**7·16** that was isolated and converted further to afford (*R*)-**7** in 36% yield with 90% ee. The mother liquor was also processed to give the opposite enantiomer in 56% yield and 88% ee. The resolution could be repeated with the enantioenriched (*R*)-**7** and (*S*)-**7** to furnish each enantiomer in 99% and 98% ee, respectively, (Scheme 2).[26]

Scheme 2. Optical resolution of ligand **7**



X-ray crystal analysis revealed formation of an intramolecular hydrogen bond between the phenol hydrogen and the isoquinoline nitrogen of (*R*)-**7** and an intermolecular bond between the naphthol hydrogen and the chloride anion (Figure 5).

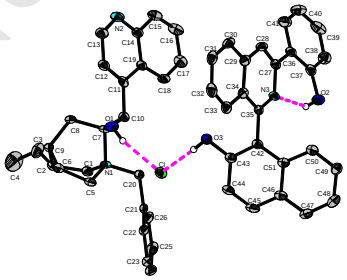


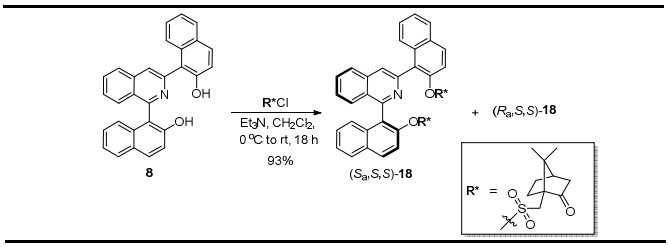
Figure 5. X-ray crystal structure of (*R*)-(+)-**7·16** (Hydrogen atoms and solvent molecules are omitted for clarity).[26]

Table 1. Selected bond lengths and angles for (*R*)-(+)-**7·16**

Length/Å			Angle/deg
H(3O)…Cl	2.22	N(3)-C(35)-C(42)-C(51)	074.5
H(2O)…N(3)	1.84	C(34)-C(35)-C(42)-C(43)	076.3
H(2O)…N(3)	2.22	O(3)-H(3O)...Cl	172.9
		O(2)-H(2O)…N(3)	144.9
		O(1)-H(1O)…Cl	166.2

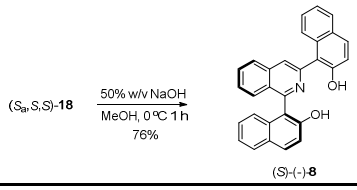
Unfortunately, ligand **8** could not be resolved using this method. Therefore, racemic **8** was converted to its camphor sulfonates using the procedure of Chow *et al.* (Scheme 3).[31]

Scheme 3. Synthesis of epimeric bis(sulfonates) (S_a,*S*,*S*)-**18** and (R_a,*S*,*S*)-**18** and conversion of (S_a,*S*,*S*)-**18** to (*S*)-(-)-**8**



The epimers were then converted to enantiomerically enriched (+)-**8** and (-)-**8**, by stirring in 50% w/v NaOH at 0 °C, followed by acidic work-up and extraction into CH_2Cl_2 (Scheme 4). Racemic **8** was also resolved *via* chiral semi-preparative HPLC, (see Supporting Information).

Scheme 4. Synthesis of Ligand (*S*)-**8**



Racemisation Studies

Ligands **7** and **8** are classed as tri-*ortho* substituted biaryls and these compounds are known to readily racemise when at least one of the *ortho* groups is small such as OMe or F.[32] However, Brown and co-workers have reported the synthesis of phenol **19** (Figure 6) the half-life of which they calculated to be 455 days at room temperature.[33] This compares favourably with the unsubstituted derivative **20**, an intermediate in the synthesis of Quinap (**21**), which has a half-life to racemisation of just 29 days at room temperature, Figure 6. We envisaged that our compounds, which are structurally close to Brown's intermediate **19**, might display a higher barrier to racemisation due to the similarity of the substitution pattern on the isoquinoline ring.

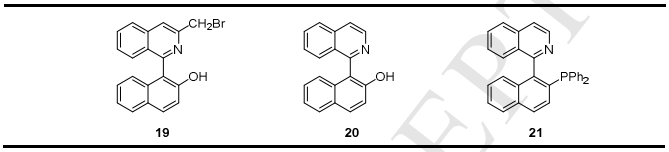


Figure 6. Brown's intermediates **19** and **20** and Quinap (**21**)

Spivey *et al.* have reported the atropisomerisation studies of a series of axially chiral biaryl derivatives of DMAP.[34,35] Following the method of Eyring and Cagle, they studied the atropisomerisation of individual enantiomers of these ligands in sealed-tube experiments followed by CSP HPLC analysis.[36] We therefore applied this method in our investigations into the racemisation of ligands **7** and **8**. Arrhenius and Eyring plots were graphed and kinetic parameters for the racemisation of **7** and **8** were obtained (Tables 3-4, Figures 8-9).

From these data it can be calculated that for ligand **7** the half-life to racemisation at room temperature is 97 days and that an enantiomerically homogeneous sample would lose 1% of its optical purity after 34 h. For ligand **8** these values are 105 days and 37 h, respectively. The barriers to atropisomerisation for these two ligands are arguably too low to render them useful for application in asymmetric catalysis at room temperature.

Table 3. The kinetic parameters for the racemisation of **7**

T (K)	$10^6 k_{racem}/s^{-1}$	Eyring Functions	
328	008.3 (0.5)[a]	$\Delta H^{\#}$/kJmol^{-1}	99 (24)
338	022 (1.3)	$\Delta S^{\#}$/J mol^{-1}K^{-1}	-43 (68)
348	05700(1.7)	$\Delta G^{\#}$/kJmol^{-1}	112 (20)
363	300 (13.0)		
		Arrhenius Parameters	
		E_a/kJ mol^{-1}	102 (24)
		ln(A/s^{-1})	260 (8)

[a]Figures in parentheses are errors calculated for 95% confidence level

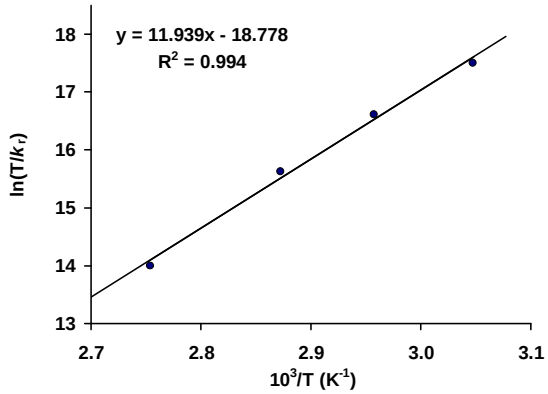


Figure 8. The Eyring plot for the racemisation of **7** in benzene

Table 4. The kinetic parameters for the racemisation of **8**

T (K)	$10^6 k_{racem}/s^{-1}$	Eyring Functions	
313	007.5 (0.4)[a]	$\Delta H^{\#}$/kJmol^{-1}	86 (10)
328	041 (4)	$\Delta S^{\#}$/Jmol^{-1}K^{-1}	-88 (29)
348	230 (3)	$\Delta G^{\#}$/kJmol^{-1}	112 0(9)
363	860 (13)		
		Arrhenius Parameters	
		E_a/kJ mol^{-1}	89 (10)
		ln(A/s^{-1})	020 (4)

[a]Figures in parentheses are errors calculated for 95% confidence level

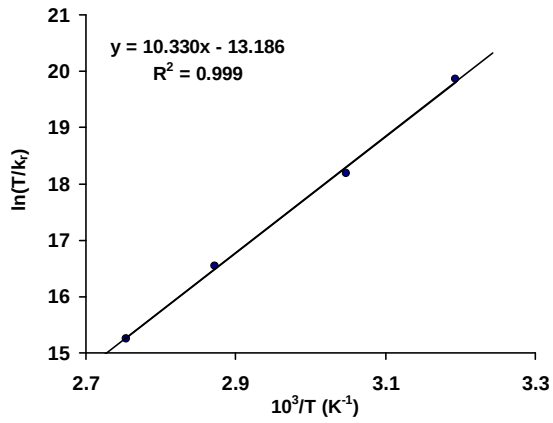
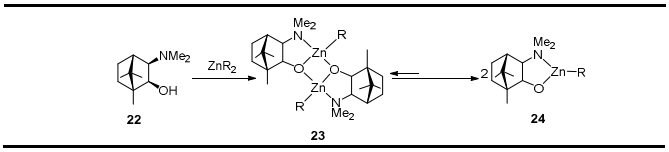


Figure 9. The Eyring plot for the racemisation of **8** in benzene

However, their use at temperatures below ambient might still be possible although not practical. Ligand **8** was therefore applied in the diethylzinc addition to benzaldehyde at –20 °C with varying catalyst loadings to afford the desired product as a racemate in only moderate yield. In order to explain the moderate yields and racemic nature of the product it is worthwhile investigating the mechanism of the diethylzinc addition. It has been proposed that the mechanism for the bidentate ligand **22** in the diethylzinc

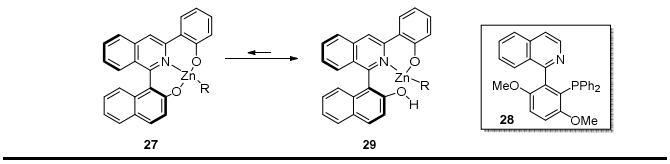
addition proceeds through an alkoxide dimer **23** which then dissociates into a reactive monomer **24** which ensures high reactivity (Scheme 5).

Scheme 5. The mechanism for bidentate ligands in the diethylzinc addition



However, with a potentially tridentate system the key design feature is to create a more rigid structure that might better discriminate between the two enantiotopic faces of benzaldehyde within the transition-state complex. If one considers the momomeric tridentate binding mode of ligand **7**, i.e., complex **27**, (Scheme 6). It has been shown that such monomers, in the case of bidentate ligands, are the reactive components in the addition process.[37,38]

Scheme 6. Monomeric tridentate binding mode of ligand **7**



However, it has previously been shown that the $PdCl_2$ complex of the structurally related compound **28** contains a palladium-nitrogen bond which is 26° out of the isoquinoline ring plane. This distortion is required to accommodate the constraints of the chelate unit. It may be reasoned therefore that, based on this observation and on molecular models of the monomer **27**, that the ligand may not form the desired complex but may instead bind the zinc ion in a bidentate fashion preferably adopting a six-chelate binding mode as in **29** (Scheme 6). This bidentate binding mode would have little influence on the level of enantioselectivity of zinc addition, as chiral information would not be efficiently transferred from the chiral axis. We therefore proposed ligand **30** as a suitable candidate to offset all the difficulties encountered with ligands **7** and **8** and which still incorporates key features of the successful Carreira ligand **1** (Figure 10). Interestingly, Baker and co-workers have previously described the synthesis and resolution of ligand **31** and its application in the diethylzinc addition to benzaldehyde producing the desired alcohol in 91% yield and 68% ee.[39]

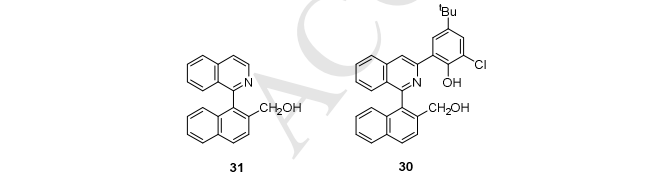
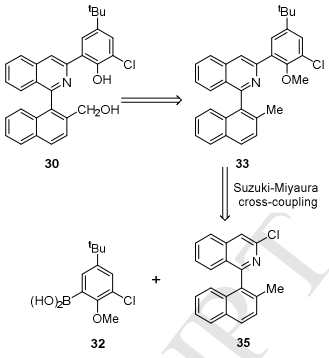


Figure 10. Baker's ligand **31** and our proposed tridentate ligand **30**

Synthesis and Resolution

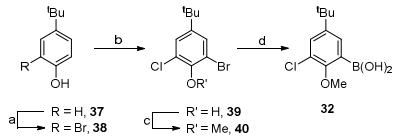
Our initial strategy involved the synthesis of ligand **30** *via* selective cross-coupling of 1,3-dichloroisoquinoline and arylboronic acid **9** followed by a cross-coupling with arylboronic acid **32**. The resulting cross-coupled product may then be converted to **30** (Scheme 7).

Scheme 7. Retrosynthetic Analysis of ligand **30**



The preparation of boronic acid **32** began with the bromination of 4-*tert*–butyl-phenol **37** to produce the desired *ortho*-brominated product **38** in 99% yield. This compound was then chlorinated following the procedure of Sheldon *et al*. to yield phenol **39** in 95% yield.[40] Methylation of **39** following a modification of the procedure of Cram and co-workers afforded aryl ether **40** in 92% yield.[41] The synthesis of the desired boronic acid **32** was then completed by formation of the Grignard reagent and subsequent quenching with trimethylborate, followed by hydrolysis (Scheme 8).

Scheme 8. Synthesis of boronic acid **32**

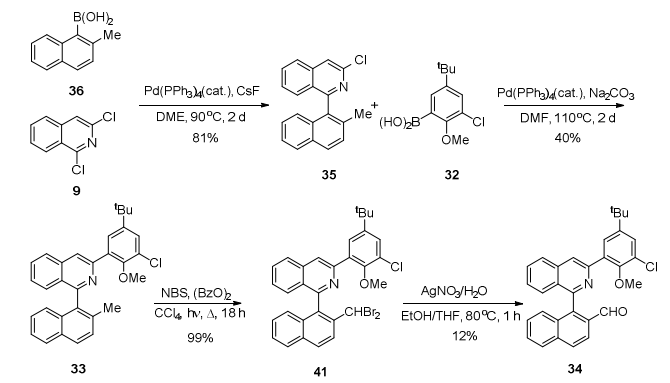


Reagents and conditions: (a) Br_2, 0 °C, CH_2Cl_2, 1 h, 99%. (b) SO_2Cl_2, diisobutylamine, toluene, 70 °C, 95%. (c) K_2CO_3, MeI, Me_2CO, 70 °C, 24 h, 92%. (d) (i) Mg, THF; (ii) $B(OMe)_3$, -78 °C, 18 h; (iii) H_2O.

Compound **35** was synthesised in 81% yield by Suzuki-Miyaura cross-coupling between aryl chloride **9** and arylboronic acid **36** (Scheme 9). The synthesis of intermediate **33** was completed by a similar coupling of aryl chloride **35** and boronic acid **32**. As with the analogous aryl chloride used in the synthesis of ligands **7** and **8**, this compound reacted to produce the desired compound in only a moderate yield of 40% even under forcing conditions of DMF at 110 ºC. Attempts to offset this poor reactivity by the use of XPhos (**15**) were unsuccessful due to its poor selectivity in the cross-coupling reaction. The resulting compound **33** was then dibrominated to yield compound **41** in near quantitative yield. This compound was subsequently converted to aldehyde **34** in a very disappointing 12% yield.

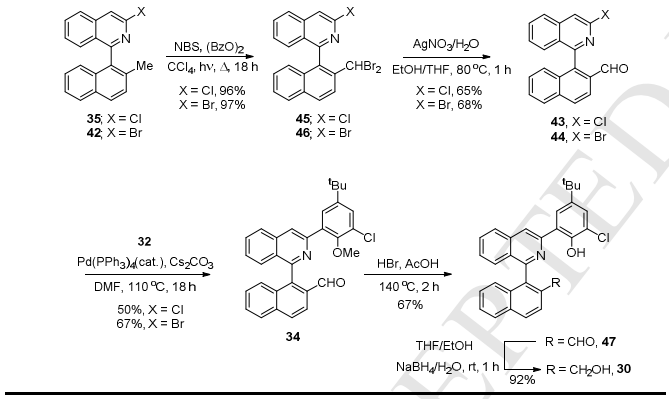
Due to the moderate yield of the cross-coupling reaction and the poor yield in the synthesis of the aldehyde **34**, we decided to investigate an alternative approach, by functionalising the methyl substituent on the naphthyl ring prior to cross-coupling. The 2-bromo-biaryl **42** was synthesised in 72% yield in an identical manner to its 3-chloro substituted analogue **35** as we envisage that the aryl bromide **42** would be more reactive in the proposed Suzuki-Miyaura cross-coupling than aryl chloride **35**. To this end, the synthetic strategy (Scheme 10) was developed where compounds **43** and **44** are key intermediates.

Scheme 9. Synthesis of aldehyde **34**



The synthesis of **43** and **44** was achieved following an identical procedure to that previously described for aldehyde **34**. Dibromination of **35** was completed in 96% yield, followed by conversion of the dibromide **45** to aldehyde **43** in 65% yield. The related 3-bromo derivative **46** was synthesized in 97% yield whilst the aldehyde **44** was prepared in 68% yield. The Suzuki-Miyaura cross-coupling of compound **43** proceeded in a moderate yield of 50% whereas the brominated derivative **44** gave the desired product in an improved yield of 67%. The resulting aryl ether **34** was demethylated using HBr/AcOH to afford the desired phenol **47** in 67% yield. The synthesis was completed by reduction of the aldehyde to give the desired ligand **30** in 92% yield.

Scheme 10. Synthesis of ligand **30**



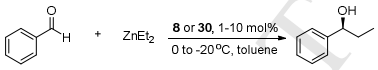
Various attempts at resolving ligand **30** *via* complexation with *N*-benzylcinchonidinium chloride **16** were unsuccessful. Fortunately, ligand **30** proved resolvable *via* chiral semi-preparative HPLC. The absolute configuration of ligand **30** was assigned tentatively based on analogy between the signs of the optical rotation of both hands of ligand **30** with the sign of the optical rotation of the (*R*)- and (*S*)-enantiomers of Baker's ligand **31**.

Racemisation Study

The racemisation study of phenol **30** was first attempted using the same procedure as outlined for the first two ligands **7** and **8**. Interestingly, even at 120 °C overnight no racemisation was observed. By increasing the temperature to 180 °C, however, the enantioenriched ligand began to racemise at an appreciable rate. Due to the high barrier to rotation about the chiral axis of compound **30** at 180°C it is evident that its racemisation at room temperature would be exceedingly slow. It was therefore decided not to examine the racemisation of **30** at other, higher than 180 °C temperatures. By making a simple approximation ($\Delta S^{\#} = 0$), it is possible to estimate the Gibbs free energy for this ligand, which is calculated as $\Delta G^{\#} = 164.6$ kJ·mol^{-1}. The half-life to racemisation at room temperature may be estimated using this value to be around 777 million years!

Diethylzinc Addition

Scheme 11. General scheme for the addition of diethylzinc to benzaldehyde



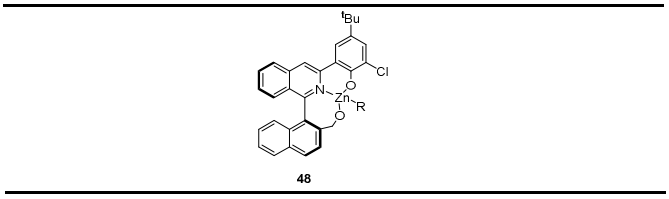
In order to study the effectiveness of the two classes of ligands (**8** and **30**), they were employed initially in the diethylzinc addition to benzaldehyde (Scheme 11).[42] A number of factors influencing the effectiveness of both ligands were of interest, including the catalyst loading and the reaction temperature (Table 5).

Table 5[a,b] Diethylzinc addition to benzaldehyde catalysed by ligands **8** and **30**

Entry	Temp (°C)	Ligand	Mol (%) of Ligand	Yield of 47 (%)	ee of 47 (%)	Config.
1	-20	*S*-(**8**)	10	50	0	-
2	-20	*S*-(**8**)	5	60	0	-
3	-20	*S*-(**8**)	1	60	0	-
4	-20	*S*-(**30**)	10	85	98	*S*
5	-20	*S*-(**30**)	5	99	>99	*S*
6	-20	*S*-(**30**)	1	99	99	*S*
7[b]	0	*R*-(**30**)	5	98	98	*R*
8	rt	*S*-(**30**)	0.1	99	91	*S*
9	rt	*S*-(**30**)	0.0001	91	0	-

[a]All reactions carried out in toluene for 40 to 45 h. [b]Configuration assigned by comparison with literature values. Enantiomeric excesses were determined using chiral HPLC.

Unlike ligand **8**, the related ligand **30** gave excellent results even at 1 mol%. At -20 °C, the catalyst loading was varied from 10 mol% to 1 mol%, with excellent enantioselectivities in each case (entries 4-6). Even at 0.1 mol% the ligand produces the desired alcohol in nearly quantitative yield with the enantiomeric excess reduced to 91% (entry 8). At 0 °C with 5 mol% of **30**, the yield and enantiomeric excess were 98% (entry 7). The decrease of enantiomeric excess to 91% in the case of the 0.1 mol% reaction at room temperature may be due to competition between the background process and the catalytic asymmetric pathway. It is known that at 0 °C this non-catalytic pathway is "shut down" although at room temperature it may be active. This suggestion is reinforced when only 0.001 mol% of the ligand was employed at room temperature. In this instance the desired alcohol is produced in 91% yield but without asymmetric induction, entry 9. By analogy to the mechanism outlined for **8** it may be reasoned that the incorporation of a methylene unit permits the formation of a rigid tridentate monomeric complex of the form **48**, Figure 11.



48

Figure 11. Tridentate monomeric complex **48**

As a result of the effectiveness of **30** at low loadings and low temperature we decided to perform a substrate scope by variation of the aldehydic substrates (**49**-**57**), Table 6. The isomeric naphthaldehydes **49** and **50**, entries 1 and 2, and 4-chlorobenzaldehyde **51**, entry 3 gave good yields and excellent enantioselectivities (95-98 %ee). In the case of 1-naphthaldehyde **49** and 4-chlorobenzaldehyde **51**, lowering the temperature, and increasing the catalyst loading gave higher yield and enantiomeric excess (99 and 98%ee, respectively), entries 8 and 9. *trans*-Cinnamaldehyde **52**, gave both high yield (86%) and enantiomeric excess (88%). For the more electron-rich substrates, 4-methoxybenzaldehyde **54** and ferrocenealdehyde **53**, the enantioselectivities dropped to 70% and 82% ee, respectively, entries 5 and 6. Interestingly, the electron poor pentafluorobenzaldehyde **55**, entry 7, gave the desired product in a moderate yield of 60% and an enantiomeric excess of 62%. The aliphatic aldehyde 3-phenylpropanal **56**, entry 10. gave the product in a good yield of 81% and an excellent enantiomeric excess of 97%. This is quite an impressive result since aliphatic aldehydes generally give poorer levels of enantioselectivities in the diethylzinc addition. The propargyl aldehyde **57**, entry 2, gave an excellent yield of product albeit with poor enantioselectivity (20 %ee). This is not uncommon for linear aldehydes where differentiation between the two enantiotopic faces of the aldehyde is difficult.

Table 6[a] Diethylzinc addition to various aldehydes catalysed by **30**

Entry	Aldehyde	Ligand	Time (h)	Yield (%)	ee (%)	Config.
1	1-naphthaldehyde (**49**)	(*S*)-**30**	36	74	95	*S*
2	2-naphthaldehyde (**50**)	(*S*)-**30**	36	95	98	*S*
3	4-chlorobenzaldehyde (**51**)	(*S*)-**30**	40	65	95	*S*
4	*trans*-cinnamaldehyde (**52**)	(*S*)-**30**	36	86	88	*S*
5 [b,c]	ferrocenealdehyde (**53**)	(*R*)-**30**	40	65	82	*R*
6	4-methoxybenzaldehyde (**54**)	(*R*)-**30**	40	82	70	*R*
7[c]	pentafluorobenzaldehyde (**55**)	(*R*)-**30**	40	60	62	*R*
8[d]	1-naphthaldehyde (**49**)	(*R*)-**30**	48	91	99	*R*
9[d]	4-chlorobenzaldehyde (**51**)	(*R*)-**30**	48	99	98	*R*
10[d]	3-phenylpropanal (**56**)	(*R*)-**30**	48	81	97	*R*
11[d]	phenylpropargyl aldehyde (**57**)	(*R*)-**30**	48	90	20	*R*

[a]All reactions carried out in toluene with 1mol% of **30**, at 0 °C. Enantiomeric excess determined by HPLC analysis using an OD or OD-H chiralcel column. [b]Enantiomeric excess determined using an AD chiralpak column. [c]No literature values for configuration available and product configuration assigned by analogy to other aryl aldehydes. [d]Reactions carried out with 2 mol% of **30** at -20 ºC.

Conclusion

The synthesis and resolution of three tridentate ligands has been described. All three ligands were synthesized using selective, successive Suzuki-Miyaura cross-coupling reactions. Resolution was achieved by a range of techniques including molecular complexation for ligand **7** as well as conversion of the ligand to its epimeric camphor sulfonates as in the case of ligand **8**. Ligands **8** and **30** were also resolved *via* semi-preparative HPLC. The barrier to racemisation about the chiral axis of the three ligands was investigated *via* racemisation studies and Arrhenius and Eyring plots were graphed. The half-life to racemisation at room temperature was extrapolated from these graphs. Ligand **8** was applied in the diethylzinc addition to benzaldehyde to produce the secondary alcohol in moderate yield but without asymmetric induction. In contrast, the application of ligand **30** in the diethylzinc addition to benzaldehyde was investigated and afforded the desired alcohol in excellent yield with near perfect enantioselectivities at low catalyst loadings. Ligand **30** was also applied in the diethylzinc addition to a variety of other aldehydes, providing the desired secondary alcohols in good yields with moderate to excellent enantiopurity.

Experimental Section

All commercially available solvents were purified and dried before use. Diethyl ether and tetrahydrofuran were distilled from

sodium/benzophenone and dichloromethane was distilled from calcium hydride. Ammonium hydroxide was purchased as a 28% solution of NH_3 in H_2O. 1-Bromo-2-methylnaphthalene was purchased as 90% technical grade and was used without any further purification. Where necessary other solvents and reagents used were purified according to known procedures.[43] DMF and DME were degassed using three freeze-thaw cycles prior to use. Oxygen-free nitrogen was obtained from BOC gases. Flash chromatography was performed using Merck Kieselgel 60 (Art. 9385) and aluminium oxide 90, standardised (activity II-III). Merck precoated Kieselgel 60F_{254} and alumina (neutral, type E) were used for thin layer chromatography. High-resolution mass spectrometry (HRMS) measurements are valid to ±5 ppm.

*1,3-Dichloroisoquinoline (**9**)*

Method 1

Phenylphosphonic dichloride (7.0 mL, 48 mmol) was added drop-wise with stirring to homophthalimide (0.94 g, 5.8 mmol). The mixture was then heated to 130 °C for 2 h during which time the initial aggregate turned to a dark brown solution. The solution was allowed to cool and water (35 mL) was added drop-wise [**Caution!**] with stirring. Diethyl ether (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 30 mL). The ether layers were combined, washed with 1 M NaOH (2 × 20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to yield the title compound **9** as an off-white solid (0.91 g, 79%). R_f = 0.70, (CH_2Cl_2); m.p. 121-123 °C (lit.[44] 120-121 °C); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.27 (dd, 1H, J_1 = 8.4 Hz, J_2 = 0.9 Hz), 7.77-7.75 (m, 2H), 7.69-7.64 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) 151.1 (4°), 143.3 (4°), 139.4 (4°), 132.4, 129.0, 126.8, 126.5, 125.9 (4°), 120.0; IR (KBr) ν_{max} 2918, 1553, and 746 cm^{-1}.

Method 2

To homophthalic acid (12.50 g, 69.4 mmol) was added ammonium hydroxide (15.8 mL, 0.16 mol). This mixture was vacuum distilled until a brown solid remained and then heated gently at normal pressure with a Bunsen burner until an orange oil resulted. The flask was allowed to cool and phenylphosphonic dichloride (30 mL, 0.21 mol) was added and the mixture heated to 160 °C for 3 h after which time the resultant solution was cooled and poured onto ice water [**Caution!**]. The solution was extracted with dichloromethane (3 × 100 mL) and the organic layer was washed sequentially with 20% NaOH (2 × 50 mL), water (50 mL), brine (50 mL), and then dried over $MgSO_4$. The organic layer was filtered and evaporated *in vacuo* to yield the crude product which was purified by column chromatography over silica gel (CH_2Cl_2) to give the title compound **9** (10.3 g, 75%), which was identical to a sample prepared according to method 1.

*2-Methoxy-1-naphthaleneboronic acid (**10**)*

Method 1

Magnesium (5.00 g, 0.21 mol) was activated by heating and stirring *in vacuo* for 1 h at 80 °C after which time it was allowed to cool to room temperature. Dry THF (20 mL) was added under an atmosphere of nitrogen. A solution of 1-bromo-2-methoxynaphthalene (10.9 g, 46.3 mmol) in THF was then added slowly *via* cannula to give a black suspension. The mixture was heated with a heat gun at regular intervals during the addition period. The solution was then allowed to stir for 1 h at room temperature. The resulting mixture was added slowly *via* cannula to a solution of triisopropylborate (14.6 mL, 63.3 mmol) in THF (20 mL) at -78 °C. The reaction mixture was allowed to warm to room temperature while stirring overnight (18 h). Water (40 mL) was added and the suspension was allowed stir for a further 1 h. The reaction mixture was evaporated *in vacuo* and dichloromethane (100 mL) was added. The organic layer was separated, and the aqueous layer was washed with dichloromethane (4 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a brown solid, which was stirred in pentane overnight producing the title compound **10** (8.04 g, 86%) as a white powder. m.p. 116-118 °C (lit.[45] m.p. 117-119 °C); ^{1}H NMR (300 MHz; d_6-DMSO) δ = 8.27 (s, 2H, $B(OH)_2$), 7.89-7.81 (m, 2H), 7.69 (d, 1H, J = 8.3 Hz), 7.44-7.28 (m, 3H), and 3.85 (s, OCH_3); ^{13}C NMR (75 MHz; d_6-DMSO) 159.0 (4°), 136.2 (4°), 129.8, 128.9 (4°), 128.4, 127.8 (2C), 126.3, 123.5, 114.1, 56.6 (OMe); IR (KBr) ν_{max} 3350, 1589, 1512, 1333, 1244, and 1063 cm^{-1}.

Method 2[46]

n-Butyllithium (7.0 mL, 2.5 M in hexanes, 18 mmol) was added dropwise to a stirred solution of 1-bromo-2-methoxynaphthalene (3.78 g, 15.9 mmol) in dry Et_2O (60 mL) at -78 °C under an atmosphere of nitrogen. The solution was warmed to room temperature and stirred for 1 h. After this time, the flask was re-cooled to -78 °C and trimethylborate (2.3 mL, 21 mmol) was added drop-wise. The mixture was allowed warm to room temperature overnight (18 h) under nitrogen. 1M HCl (50 mL) was added dropwise and the solution was stirred for an additional 1 h. The reaction mixture was evaporated *in vacuo* and extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. The solution was filtered and concentrated *in vacuo* to produce a light brown solid that was stirred in pentane for 2 h, filtered and dried *in vacuo* to give the title compound **10** (2.64 g, 82%) as an off-white powder which was identical to a previously prepared sample.

*3-Chloro-1-(2-methoxynaphthalen-1-yl)isoquinoline (**11**)*[15]

1,3-Dichloroisoquinoline **9** (6.85 g, 34.6 mmol) was added to a dry Schlenk tube under nitrogen followed by $Pd(PPh_3)_4$ (2.00 g, 0.73 mmol) and stirred under vacuum. Anhydrous, degassed DME (150 mL) was added and the mixture was stirred for 15 min. Arylboronic acid (**10**) (7.00 g, 34.6 mmol), dissolved in the minimum amount of degassed ethanol (50 mL), was then added. Sodium carbonate solution (35 mL, 2 M) was added and a white precipitate was formed instantly. The yellow mixture was refluxed at 90 ºC for 5 d. The reaction mixture was cooled to room temperature and water (100 mL) and dichloromethane (100 mL) were added. The organic layer was separated and concentrated *in vacuo* to give a brown oil which was re-dissolved in dichloromethane (100 mL), washed with water (50 mL), brine (30 mL), and then dried over $MgSO_4$. The solution was filtered and evaporated *in vacuo* to give a dark brown solid which was stirred in diethyl ether (50 mL) for 1 h and filtered to give the title compound **11** as an off-white solid (9.5 g, 86%). This material was used without any further purification. R_f = 0.30, 2:1 (CH_2Cl_2:pentane); m.p. 172-173 °C (lit.[15] m.p. 159-160 °C); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.00 (d, 1H, J = 8.9 Hz), 7.86-7.81 (m, 3H), 7.66 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.3 Hz), 7.48 (d, 1H, J = 8.5 Hz), 7.42-7.24 (m, 4H), 7.04 (d, 1H, 8.1 Hz), 3.76 (s, 3H, OCH_3); ^{13}C NMR (75 MHz; $CDCl_3$) 159.10 (4°), 154.9 (4°), 145.1 (4°), 138.3 (4°), 133.6 (4°), 131.1, 130.9, 129.0 (4°), 128.0, 127.7, 127.3, 127.01 (4°), 127.02, 126.1, 124.6, 123.8, 120.6 (4°), 119.3, 113.3, 56.5 (OMe); IR (KBr) ν_{max} 1621, 1576, 1547, 1510, 1264, and 1069 cm^{-1}; HRMS (ES^+): calculated mass 320.0842, found 320.0840; $C_{20}H_{14}ClNO$: calculated C, 75.12; H, 4.41; N, 4.38, found, C, 75.12; H, 4.44; N, 4.28

*2-Methoxyphenylboronic acid (**14**)*

Method 1

Magnesium (5.30 g, 0.22 mol), was activated by heating and stirring under nitrogen for 1 h at 90 °C after which time it was allowed to cool to room temperature and dry THF (30 mL) was added. A solution of 2-bromoanisole (5.0 mL, 42 mmol) in dry THF (50 mL) was added slowly *via* syringe to give a black suspension. The solution was allowed to stir for 1 h at room temperature. The reaction mixture was then added slowly, *via* cannula filtration, to a solution of triisopropylborate (15 mL, 43 mmol) in THF (15 mL) at -78 °C. The reaction mixture was allowed to warm to room temperature while stirring overnight (18 h). Water (60 mL) was added and the suspension was allowed to stir for a further 1 h. The reaction mixture was evaporated *in vacuo* and dichloromethane (100 mL) was added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (4 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a light green solid, which was stirred in pentane producing the title compound **14** (4.40 g, 69%) as a white powder. m.p. 109-111 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.87 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.9 Hz), 7.45 (ddd, 1H, J_1 = 11.7 Hz, J_2 = 4.5 Hz, J_3 = 2.5 Hz), 7.03 (app t, 1H, J = 7.2 Hz), 6.91 (d, 1H, J = 8.4 Hz), 6.63 (s, 2H, $B(OH)_2$), 3.90 (s, 3H, OCH_3); ^{13}C NMR (75 MHz; $CDCl_3$) 164.5 (4°), 136.9, 132.9, 121.3, 110.0, 55.5 (OMe); IR (KBr) ν_{max} 3384, 1601, 1412, 1229, 1164, 1055, 1024, 756, and 658 cm^{-1}.

Method 2

n-Butyllithium (10.6 mL, 2.5 M in hexanes, 26.5 mmol), was added drop-wise to a stirred solution of 2-bromoanisole (3.0 mL, 24 mmol) in dry diethyl ether (20 mL) at -78 °C under an atmosphere of nitrogen. The solution was warmed to 0 °C and stirred for 1 h after which time it was re-cooled to -78 °C and trimethylborate (3.5 mL, 31 mmol) was added drop-wise. The mixture was allowed to warm to room temperature overnight (18 h) under nitrogen. 1 M HCl (30 mL) was added drop-wise and the solution was stirred for 1 h. The reaction mixture was evaporated *in vacuo* and then extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The solution was filtered and evaporated *in vacuo* to produce a light green solid. The solid was stirred in pentane for 2 h, filtered and the resulting white powder was dried *in vacuo* to give the title compound **14** (2.25 g, 69%), which was identical to a previously prepared sample.

*1-(2-Methoxynaphthalen-1-yl)-3-(2-methoxyphenyl)isoquinoline (**12**)*

Method 1[15]

Biaryl **11** (0.60 g, 1.88 mmol) was added to a dry Schlenk tube under nitrogen followed by $Pd(PPh_3)_4$ (0.143 g, 0.124 mmol) and stirred under vacuum. Anhydrous, degassed DMF (20 mL) was added under nitrogen and the mixture was stirred for 15 min. Arylboronic acid **14** (286 mg, 1.88 mmol), dissolved in the minimum amount of degassed ethanol (3 mL), was then transferred to the Schlenk tube. Sodium carbonate (1.9 mL, 2 M) was added and the mixture was heated at 110 ºC for 3 d. The mixture was cooled to room temperature and water (30 mL) and diethyl ether (50 mL) were added. The organic layer was separated and concentrated *in vacuo* to give a brown oil which was re-dissolved in diethyl ether (50 mL), washed with water (20 mL), brine (20 mL), and then dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give a dark brown oil which was then purified by column chromatography over silica gel (CH_2Cl_2) to yield the title compound **12** (0.40 g, 55%) as a white solid. R_f = 0.40, (CH_2Cl_2); m.p. 146-148 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.28 (s, 1H, H_4), 8.00-7.91 (m, 3H), 7.85 (d, 1H, J = 7.7 Hz), 7.62 (app t, 1H, J = 7.9 Hz), 7.50 (d, 1H, J = 8.3 Hz), 7.42 (d, 1H, 9.0 Hz), 7.36-7.23 (m, 5H), 7.03 (app t, 2H, J = 7.5 Hz), 3.92 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) 157.4 (4°), 157.2 (4°), 154.9 (4°), 149.0 (4°), 136.7 (4°), 134.1 (4°), 131.9, 130.3, 129.9, 129.6 (4°), 129.3(2C), 127.9, 127.5 (4°), 127.4, 127.3, 126.8, 126.6, 125.3, 123.6, 122.6 (4°), 121.1, 120.7, 113.8, 111.4, 56.8 (OMe), 55.7 (OMe); IR (KBr) ν_{max} 1621, 1598, 1267, 1250, 1023, and 760 cm^{-1}; HRMS (ES^+): calculated for $C_{27}H_{21}NO_2$, 392.1651; found, 392.1667; $C_{27}H_{21}NO_2$: calculated C, 82.84; H, 5.41; N, 3.58, found, C, 82.60; H, 5.43; N, 3.48.

Method 2[27]

Biaryl **11** (320 mg, 1.00 mmol) was added to a dry Schlenk tube under nitrogen followed by $Pd(PPh_3)_4$ (58 mg, 50 μmol) and stirred under vacuum. Anhydrous, degassed DMF (10 mL) was added under nitrogen and the mixture was heated to 55 °C to form a yellow solution. Arylboronic acid **14** (0.167 g, 1.1 mmol) and Cs_2CO_3 (489 mg, 1.50 mmol) were then added sequentially and the mixture heated to 100 °C for 39 h. The mixture was cooled to room temperature and water (10 mL) and diethyl ether (30 mL) were added. The organic layer was extracted and concentrated *in vacuo* to give a brown oil which was re-dissolved in diethyl ether (30 mL), washed with water (20 mL), brine (20 mL), and then dried over $MgSO_4$. The solution was filtered and evaporated *in vacuo* to give a dark brown oil. The oil was then purified by column chromatography over silica gel (CH_2Cl_2) to yield the title compound **12** (0.175 g, 45%) as a white solid which was identical to a previously prepared sample.

Method 3[28]

Biaryl **11** (0.20 g, 0.63 mmol), $Pd(OAc)_2$ (2.8 mg, 1.3 μmol), XPhos (11.9 mg, 31 μmol), **14** (0.19 g, 1.25 mmol) and K_3PO_4 (0.40 g, 1.88 mmol) were placed in a 20 mL Schlenk tube which was then evacuated and backfilled with nitrogen. This process was repeated an additional two times. Dry THF (1.5 mL) was added and the mixture was heated overnight (18 h) with stirring at 80 °C. Water (5 mL) and ethyl acetate (20 mL) were added and the phases were separated and the aqueous layer was extracted with additional portions of ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered and evaporated under reduced pressure to yield the crude product which was purified by column chromatography over silica gel (5:1, pentane:EtOAc) to yield the title compound **12** (234 mg, 96%) as a white solid which was identical to a previously prepared sample.

*1,3-Bis-(2-methoxynaphthalen-1-yl)isoquinoline (**13**)*

Method 1

Biaryl **11** (0.32 g, 1 mmol) was added to a dry Schlenk tube under nitrogen followed by $Pd(PPh_3)_4$ (58 mg, 50 μmol) and stirred under vacuum. Anhydrous, degassed DMF (10 mL) was added under nitrogen and the mixture was heated to 55 °C to form a yellow solution. Arylboronic acid **10** (0.17 g, 1.1 mmol) and Cs_2CO_3 (0.49 g, 1.5 mmol) were then added sequentially to the Schlenk tube and the mixture was heated to 100 °C for 39 h. The mixture was cooled to room temperature and water (10 mL) and diethyl ether (30 mL) were added. The organic layer was extracted and concentrated *in vacuo* to give a brown oil which was re-dissolved in diethyl ether (30 mL), washed with water (20 mL), brine (20 mL), and then dried over $MgSO_4$. The solution was filtered and evaporated *in vacuo* to give a dark brown oil.

The oil was purified by column chromatography over silica gel (CH_2Cl_2) to yield the title compound **13** (0.175 g, 45%) as a white solid. R_f = 0.20, (3:1 pentane:EtOAc); m.p. 208-210 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.97-7.75 (m, 6H), 7.71-7.65 (m, 2H), 7.59 (d, 1H, *J* = 8.3 Hz), 7.43-7.25 (m, 8H), 3.86 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) 157.8, 155.1, 154.7, 148.8, 136.8, 134.1, 133.9, 130.3, 130.1, 129.8, 129.3, 129.2, 127.9, 127.8, 127.6, 127.4, 127.2, 127.1, 126.6, 126.4, 125.3, 125.2, 124.9, 123.6, 123.5, 122.5, 122.4, 114.3, 113.9, 57.1 (OMe), 56.9 (OMe); IR (KBr) ν_{max} 1621, 1593, 1511, 1268, 1251, 1084, 807, and 748 cm^{-1}; HRMS (ES$^+$): calculated for $C_{31}H_{23}NO_2$, 442.1807, found 442.1821; $C_{31}H_{23}NO_2$: calculated C, 84.33; H, 5.25; N, 3.17, found, C, 83.83; H, 5.17; N, 3.08.

Method 2

Biaryl **11** (0.20 g, 0.63 mmol), $Pd(OAc)_2$ (2.8 mg, 1.3 μmol), XPhos (11.9 mg, 31 μmol), **10** (0.253 g, 1.25 mmol) and K_3PO_4 (0.40 g, 1.9 mmol) were placed in a 20 mL Schlenk tube which was then evacuated and backfilled with nitrogen. This process was repeated an additional two times. Dry THF (1.5 mL) was added and the mixture was heated overnight (18 h) with stirring at 80 °C. Water (5 mL) and ethyl acetate (30 mL) were added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The organic layer was filtered and concentrated *in vacuo* to yield the crude product which was purified by column chromatography over silica gel (CH_2Cl_2) to yield the title compound **13** (0.236 g, 86%) as a white solid which was identical to a previously prepared sample.

*1-[3-(2-Hydroxyphenyl)isoquinolin-1-yl]naphthalen-2-ol (**7**)*[29]

Aryl ether **12** (0.13 g, 0.33 mmol) was placed in a 20 mL Schlenk tube, 48% HBr (1.2 mL) and acetic acid (1.5 mL) were added sequentially and the resultant solution was heated to 140 °C overnight (18 h). The Schlenk tube was allowed to cool and water (5 mL) was added followed by dichloromethane (20 mL). The organic layer was separated and the aqueous layer was washed with dichloromethane (2 × 5 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The organic layer was filtered and evaporated *in vacuo* to yield the crude product which was purified by column chromatography over silica gel (3:1 pentane:EtOAc) to yield the title compound **7** (0.10 g, 83%) as a yellow solid. R_f = 0.20, (3:1 pentane:EtOAc); m.p. 223-227 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.67 (s, 1H, H_4), 8.19 (d, 2H, *J* = 8.1), 8.07-7.94 (m, 2H), 7.82 (app t, 1H, *J* = 7.0 Hz), 7.62 (d, 1H, *J* = 8.4 Hz), 7.55-7.44 (m, 2H), 7.37-7.25 (m, 3H), 7.09 (d, 1H, *J* = 8.0 Hz), 6.97 (app t, 1H, *J* = 7.3 Hz), 6.86 (d, 1H, *J* = 8.3 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) 159.6, 155.5, 152.9, 150.9, 137.9, 133.8, 131.4, 130.8, 130.7, 128.7, 128.2, 127.7, 127.6, 127.5, 127.3, 127.0, 126.5, 123.9, 123.2, 119.8, 118.9, 118.4, 118.2, 117.4, 115.4; IR (KBr) ν_{max} 3246, 2925, 1591, 1505, 1436, 1348, 1262, 883, 816, and 758 cm^{-1}; HRMS (ES$^+$): calcd. for $C_{25}H_{17}NO_2$, 364.1338, found 364.1347; $C_{25}H_{17}NO_2$: calculated C, 82.63; H, 4.72; N, 3.85, found C, 82.22; H, 4.75; N, 3.90; HPLC OD-H Column, 1 ml/min, 80:20 pentane:IPA, 40 °C, t_R(*R*) = 7.3 min, t_R(*S*) = 11.7 min.

*1,3-Bis-(2-hydroxynaphthalen-1-yl)-isoquinoline (**8**)*

Biaryl **13** (0.13 g, 0.29 mmol) was placed in a 20 mL Schlenk tube. To this were added 8% HBr (1.1 mL) and acetic acid (1.5 mL) and the resultant solution heated to 140 °C overnight (18 h). The resulting mixture was allowed to cool and water (5 mL) was added followed by dichloromethane (20 mL). The organic layer was separated and the aqueous layer was washed with dichloromethane (2 × 5 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The organic layer was filtered and evaporated *in vacuo* to yield the crude product which was purified by column chromatography over silica gel (5:1 pentane:EtOAc) to yield the title compound **8** (111 mg, 91%) as a yellow solid. R_f = 0.20, (3:1 pentane:EtOAc); m.p. 226-228 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.37 (d, 1H, *J* = 8.6 Hz), 8.27 (s, 1H, H4), 7.98 (d, 1H, *J* = 8.2 Hz), 7.86-7.70 (m, 5H), 7.63 (d, 1H, *J* = 8.4 Hz), 7.52-7.16 (m, 8H); ^{13}C NMR (75 MHz; $CDCl_3$) 156.1 (4°), 154.7 (4°), 152.4 (4°), 148.9 (4°), 137.7 (4°), 133.1 (4°), 131.9 (4°), 131.5, 131.3, 131.2, 129.5 (4°), 128.84 (4°), 128.81, 128.3, 128.1, 127.8, 127.6, 127.04, 127.00, 126.8 (4°), 124.7, 123.8, 123.6, 123.2, 122.7, 119.5, 118.5, 117.3 (4°), 115.7 (4°); IR (KBr) ν_{max} 3222, 1620, 1589, 1494, 1436, 1346, 1262, 1242, 882, 816, 756, and 738 cm^{-1}; HRMS (ES$^+$): calculated for $C_{29}H_{19}NO_2$, 414.1494, found 414.1512; $C_{29}H_{19}NO_2$: calculated C, 84.24; H, 4.63; N, 3.39, found C, 83.75; H, 4.69; N, 3.31; HPLC AD semi-preparative column, 4.7 mL/min, pentane:IPA 70:30, 40 °C, t_R(*S*) 8.7 min, t_R(*R*) 14.0 min.

*Resolution of 1-[3-(2-hydroxyphenyl)isoquinolin-1-yl]naphthalen-2-ol (**7**)*[30]

Racemic biaryl **7 (**93 mg, 0.26 mmol) was placed in a 50 mL flask and acetone (2 mL) was added, followed by *N*-benzylcinchonidinium chloride **16** (54 mg, 0.19 mmol). The mixture was allowed to stir overnight (18 h) at room temperature producing a white precipitate (*R*)-(+)-**7**·**16**. The precipitate was filtered, washed with acetone and then stirred in a 3M HCl/EtOAc biphasic mixture (10 mL) until all the precipitate had dissolved. The organic layer was then separated, washed with brine (5 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to yield (*R*)-(+)-**7** (33.5 mg, 36% yield, 90% ee). The mother liquor was worked up in an identical manner to yield (*S*)-(-)-**7** (52.1 mg, 56% yield, 88% ee). This entire process was repeated with enantioenriched **7** to yield (*R*)-(+)-**7** and (*S*)-(-)-**7** in 98% and 99% ee respectively. α_D = (*R*) +48.0, (*S*) –47.0, ($CHCl_3$, c=1.0); HPLC AD semi-preparative column, 4.7 ml/min, pentane:IPA, 70:30, 40 °C t_R(*S*) = 8.7 min, t_R(*R*) = 14.0 min.

*Epimeric bis(sulfonates) (**R**$_a$,S,S)-**18** and (**S**$_a$,S,S)-**18***[31]

To a solution of diol **8** (100 mg, 0.242 mmol) in dry dichloromethane (2 mL) was added dry triethylamine (84 μL, 0.61 mmol) at 0 °C. After 15 min at this temperature camphorsulfonyl chloride (151 mg, 0.61 mmol) was added and the resultant solution was allowed to warm to room temperature with stirring overnight (18 h). Water (5 mL) was added and the reaction mixture was extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. This crude material was purified by column chromatography over silica gel (5:1 to 1:1 pentane:EtOAc) to yield a mixture of the epimeric bis(sulfonates) **18** (190 mg, 93%). The epimers were separated by column chromatography over silica gel (pentane-EtOAc 3:1) to afford four main fractions, the yields and diastereomeric excesses for which are shown in Table 2.

Table 2. Yields and diastereomeric excesses for (S_a,*S*,*S*)-**18** and (R_a,*S*,*S*)-**18**

Fraction	Yield (%)	de (%)
1	17	98 (S_a,*S*,*S*)-**18**
2	24	79 (S_a,*S*,*S*)-**18**
3	14	84 (R_a,*S*,*S*)-**18**
4	21	95 (R_a,*S*,*S*)-**18**

[a]Absolute configuration was tentatively assigned by analogy between the sign of the optical rotation of (*S*)-(-)-**7** and (-)-**8** which was obtained from fraction 1 by removal of the auxiliaries.

(S_a,S,S)-18

R_f = 0.20, (3:1 pentane-EtOAc); m.p. 240-243 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.10-7.88 (m, 7H), 7.81-7.71 (m, 3H), 7.52-7.32 (m, 7H), 3.59-3.45 (m, 2H), 2.99 (d, 1H, *J* = 12.7 Hz), 2.63 (d, 1H, *J* = 13.9 Hz), 2.26-2.02 (m, 4H), 1.96-1.72 (m, 6H), 1.41-1.23 (m, 4H), 0.61 (s, 3H), 0.46 (s, 3H), 0.32 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) 213.6, 213.3, 156.1, 147.3, 146.0, 145.4, 136.7, 133.7, 133.6, 132.4, 132.1, 131.1, 130.9, 130.5, 130.4, 128.5, 128.3, 128.3, 128.0, 127.9 (2C), 127.8, 127.7, 127.6, 127.5, 126.6, 126.5, 126.4, 123.9, 120.6, 114.3, 58.1, 57.9, 48.5 (2C) (CH_2), 47.9, 47.8, 43.0 (CH_2), 42.9 (CH_2), 42.6, 42.5, 27.0 (2C) (CH_2), 25.4 (CH_2), 25.2 (CH_2), 19.5 (CH_3), 19.4 (CH_3), 19.4 (CH_3), 19.2 (CH_3); HPLC AD semi-prep column, 4.7 ml/min, 80:20 Pentane:IPA, 40 °C, t_R = 22.7 min; α_D = + 80.0 ($CHCl_3$, c=1.0); IR (KBr) ν_{max} 2958, 1747, 1371, 1169, 955, 823 and 754 cm^{-1}; HRMS (ES^+): calculated for $C_{49}H_{47}NO_8S_2$, 842.2821, found 842.2833; $C_{49}H_{47}NO_8S_2$: calculated C, 69.89; H, 5.63; N, 1.66, found C, 69.23; H, 5.73; N, 1.54.

(R_a,S,S)-18

R_f = 0.20, (3:1 pentane-EtOAc); m.p. 145-150 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ = 8.10 (s, 1H), 8.02 (dd, 2H, J_1 = 9.2 Hz, J_2 = 4.8 Hz), 7.94 (app t, 2H, *J* = 8.9 Hz), 7.89 (dd, 1H, J_1 = 6.0 Hz, J_2 = 3.2 Hz), 7.81 (d, 1H, *J* = 8.9 Hz), 7.74 (dt, 2H, J_1 = 12.0 Hz, J_2 = 7.0 Hz, J_3 = 3.0 Hz), 7.56 (d, 1H, *J* = 8.6 Hz), 7.51-7.48 (m, 4H), 7.40 (dd, 2H, J_1 = 14.9 Hz, J_2 = 8.6 Hz), 3.55 (d, 1H, *J* = 14.2 Hz), 3.12 (d, 1H, *J* = 14.9 Hz), 2.97 (d, 1H, *J* = 14.6 Hz), 2.86 (d, 1H, *J* = 14.0 Hz), 2.24-2.12 (m, 3H), 1.98-1.73 (m, 7H), 1.33-1.22 (m, 4H), 0.84 (s, 3H), 0.73 (s, 3H), 0.45 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) 213.6, 213.2, 156.0, 147.1, 145.9, 145.3, 136.7, 133.6, 133.5, 132.4, 132.1, 131.1, 130.8, 130.5, 130.4, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.8, 127.6, 127.6, 126.7, 126.6, 126.5, 126.4, 124.0, 121.3, 121.1, 58.2 (CH_2), 58.0 (CH_2), 48.7 (2C), 47.9, 47.8, 43.0 (2C), 42.5 (2C, CH_2), 26.9 (2C, CH_2), 25.6 (CH_2), 25.5 (CH_2), 19.8 (CH_3), 19.6 (CH_3), 19.4 (CH_3), 19.3 (CH_3); HPLC AD semi-prep column, 4.7 ml/min, 80:20 pentane:IPA, 40 °C, t_R = 30.1 min; α_D = -32.0 ($CHCl_3$, c=1.0); R (KBr) ν_{max} 2959, 1748, 1373, 1168, 954, 823, and 754 cm^{-1}; HRMS (ES^+): calculated for $C_{49}H_{47}NO_8S_2$, 842.2821, found 842.2807.

(-)-1,3-Bis-(2-hydroxynaphthalen-1-yl)-isoquinoline (-)-(8)

(S_a,*S*,*S*)-**18** (56 mg, 66 μmol) was dissolved in methanol (5 mL) and 50% w/v NaOH (1 mL) was added at 0 °C. Stirring was continued for a further 1 h at this temperature. The mixture was then acidified with HCl (10 mL, 2 M) and extracted with dichloromethane (3 × 10 mL). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. This crude material was purified by column chromatography over silica gel (3:1, pentane:EtOAc) to yield the title compound (-)-**8** (21.2 mg, 76%) which was identical to a previously prepared sample. Racemic **8** was also resolved *via* semi-preparative HPLC using a CHIRALPAK AD column to yield both (-)-**8** and (+)-**8** in >99% ee each. Absolute configuration was assigned based on analogy with **7**; α_D = (*R*)-**8** +103, (*S*)-**8** –103 ($CHCl_3$, c=1.0).

2-Methyl-1-naphthaleneboronic acid (36)

Method 1

Magnesium (4.50 g, 0.19 mol) was activated by heating and stirring *in vacuo* for 1 h at 80 °C after which time it was allowed to cool to room temperature and dry THF (20 mL) was added under an atmosphere of nitrogen. A solution of 1-bromo-2-methylnaphthalene (5.5 mL, 32 mmol) in dry THF (20 mL) was slowly added *via* cannula to give a black suspension. The solution was heated with a heat gun at regular intervals during the addition period. The solution was allowed to stir for 1 h at room temperature. The Grignard solution was then added slowly, *via* cannula filtration, to a solution of triisopropylborate (11.0 mL, 47.6 mmol) in THF (20 mL) at -78 °C. The reaction mixture was allowed to warm to room temperature while stirring overnight (18 h). Water (30 mL) was added and the suspension was allowed stir for a further 1 h. The reaction mixture was reduced *in vacuo* to remove the THF and dichloromethane (100 mL) was added. The organic layer was separated, and the aqueous layer was washed with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and filtered and the solvent was removed *in vacuo* to give a yellow oil. Conc. HCl (1 mL) was added and the mixture was stirred in pentane overnight producing a white powder which was filtered and dried *in vacuo* to yield the title compound **36** (4.8 g, 81%). m.p. 128-131 °C (lit.[47] m.p. 125-128 °C); ^{1}H NMR (300 MHz; d_6-DMSO) δ = 8.45 (s, 2H, $B(OH)_2$), 7.81 (ddd, 3H, J_1 = 4.0 Hz, J_2 = 7.8 Hz, J_3 = 12.2 Hz), 7.50-7.40 (m, 2H), 7.33 (d, 1H, *J* = 8.5 Hz), and 2.49 (s, CH_3); ^{13}C NMR (75 MHz; d_6-DMSO) 136.8 (4°), 135.3 (4°), 131.3 (4°), 128.6, 128.5, 128.3, 127.63, 127.62 (4°), 125.9, 125.0, 22.8 (CH_3); IR (KBr) ν_{max} 3301, 1427, 1397, 1356, 1333, 1307, 1066, and 810 cm^{-1}.

Method 2

n-Butyllithium (19.3 mL, 2.5 M in hexanes, 48 mmol), was added dropwise to a stirred solution of 1-bromo-2-methylnaphthalene (7.3 mL, 47 mmol) in dry THF (80 mL) at -78 °C under an atmosphere of nitrogen. The solution was warmed to room temperature and stirred for 1 h. After this time the flask was re-cooled to -78 °C and trimethylborate (7.9 mL, 70 mmol) was added dropwise. The mixture was allowed warm to room temperature overnight (18 h) under nitrogen. HCl (50 mL, 1 M) was added dropwise and the solution was stirred for 1 h. The reaction mixture was reduced *in vacuo* and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. The solution was filtered and evaporated *in vacuo* to produce a yellow oil. Conc. HCl (1 mL) was added and the mixture was stirred in pentane overnight producing a white suspension. The precipitate was filtered and dried *in vacuo* to yield the title compound **36** (4.52 g, 52%), which was identical to a previously prepared sample.

3-Chloro-1-(2-methylnaphthalen-1-yl)isoquinoline (35)

Method 1

$Pd(PPh_3)_4$ (0.80 g, 0.67 mmol) was added to a dry Schlenk tube containing anhydrous, degassed DME (100 mL) followed by 1,3-dichloroisoquinoline **9** (4.45 g, 22.5 mmol) and the mixture stirred under nitrogen for 10 min. Arylboronic acid **36** (4.6 g, 25 mmol) was then added as a solid followed by Cs_2CO_3 (7.5 g, 50 mmol). The mixture was then refluxed at 90 °C for 2 d after which time it was cooled to room temperature and water (100 mL) and dichloromethane (100 mL) were added. The organic

layer was extracted and concentrated *in vacuo* to give a brown oil which was re-dissolved in dichloromethane (100 mL), washed with water (30 mL), brine (30 mL), and then dried over Na_2SO_4. The solution was filtered and evaporated *in vacuo* to give an oil which was purified by column chromatography over silica gel (2:1, pentane:CH_2Cl_2) to yield the title compound **35** (5.54 g, 81%). R_f = 0.50, (3:1 pentane:EtOAc); m.p. 129-131 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.91-7.83 (m, 4H), 7.68 (dt, 1H, J_1 = 1.9 Hz, J_2 = 6.0 Hz, J_3 = 14.0 Hz), 7.47-7.32 (m, 4H), 7.24 (dd, 1H, J_1 = 7.0 Hz, J_2 = 8.2 Hz), 6.98 (d, 1H, J = 8.6 Hz), 2.16 (s, 3H, CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) 161.5 (4°), 145.2 (4°), 138.4 (4°), 134.5 (4°), 133.4 (4°), 132.7 (4°), 132.0 (4°), 131.3, 128.8, 128.6, 128.0, 127.7, 127.4, 127.2 (4°), 126.4, 126.3, 125.4, 125.1, 119.2, 20.2 (CH_3); IR (KBr) ν_{max} 3054, 1547, 1310, 1146, 1093, 965, 865, 812, and 742 cm^{-1}; HRMS (ES$^+$): calculated for $C_{20}H_{14}ClN$, 304.0893, found 304.0892; $C_{20}H_{14}ClN$: calculated C, 79.07; H, 4.65; N, 4.61, found C, 78.79; H, 4.39; N, 4.53.

*3-Chloro-1-(2-dibromomethylnaphthalen-1-yl)isoquinoline (**45**)*[48]

To biaryl **35** (3.80 g, 12.5 mmol) was added *N*-bromosuccinimide (4.60 g, 26.3 mmol), dibenzoyl peroxide (70%, 0.44 g, 1.3 mmol) and CCl_4 (100 mL). The mixture was heated to reflux while being irradiated with a UV lamp overnight (18 h). The resultant mixture was filtered and the precipitate washed with benzene (2 x 20 mL). The mother liquors were combined and washed sequentially with water (20 mL) saturated $NaSO_3$ (20 mL) and brine (20 mL) and then dried over $MgSO_4$. The organic layer was filtered and evaporated *in vacuo* to yield the title compound **45**, (5.5 g, 96%) a brown solid, which was used without any further purification. R_f = 0.50, (2:1 CH_2Cl_2:pentane); m.p. 186-187 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.10 (d, 1H, J = 8.9 Hz), 8.01 (d, 1H, J = 8.9 Hz), 7.83-7.84 (m, 3H) 7.6 (ddd, 1H, J_1 = 1.9 Hz, J_2 = 6.6 Hz, J_3 = 10.3 Hz), 7.40 (ddd, 1H, J_1 = 1.2 Hz, J_2 = 6.79 Hz, J_3 = 9.1 Hz), 7.34-7.16 (m, 4H), 6.86 (dd, 1H, J_1 = 0.70 Hz, J_2 = 8.42 Hz), 6.17 (s, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) 157.9, (4°) 145.4 (4°), 138.4 (4°), 137.4 (4°), 133.6 (4°), 131.9, 131.2 (4°), 130.6, 130.0 (4°), 128.09, 128.14, 127.5, 127.4, 127.2 (4°), 126.8, 126.4, 126.1, 120.4 and 38.8 (1C obscured); IR (KBr) ν_{max} 1549, 1314, 1140, and 748 cm^{-1}; HRMS (ES$^+$): calculated for $C_{20}H_{12}Br_2ClN$; 459.9103, found 459.9118; $C_{20}H_{12}Br_2ClN$: calculated C, 52.04; H, 2.62; N, 3.03, found C, 51.74; H, 2.54; N, 2.82.

*1-(3-Chloroisoquinolin-1-yl)naphthalene-2-carbaldehyde (**43**)*[48]

To compound **45** (1.85 g, 4.0 mmol) was added EtOH (20 mL) and THF (12 mL) and the solution was heated to reflux. $AgNO_3$ (2.00 g, 11.7 mmol) in water (5.6 mL) was added drop-wise with stirring to produce a yellow precipitate. The reaction was refluxed for a further 1 h and filtered hot. The precipitate was washed with hot THF (20 mL), the filtrates were combined and concentrated, dichloromethane (50 mL), was added followed by water (20 mL), and the organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 20 mL). The organic layers were combined, washed with brine (20 mL) and dried over Na_2SO_4. The organic layer was filtered and evaporated *in vacuo* to yield the crude product which was purified by column chromatography over silica gel (10:1 pentane:EtOAc) to yield the title compound **43** (0.82 g, 65%); R_f = 0.40, (5:1 pentane:EtOAc); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 9.66 (s, 1H, COH), 8.15 (d, 1H, J = 8.6 Hz), 8.08 (d, 1H, J = 8.6 Hz), 7.97 (d, 1H, J = 8.2 Hz), 7.91 (app d, 2H, J = 8.8 Hz), 7.71 (app dt, 1H, J_1 = 0.9 Hz, J_2 = 7.6 Hz), 7.60 (app t, 1H, J = 7.0 Hz), 7.42-7.33 (m, 3H), 7.22 (d, 1H, J = 8.5 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) 190.8, 157.8 (4°), 145.0 (4°), 141.1 (4°), 138.0 (4°), 136.2 (4°), 132.3 (4°), 132.2 (4°), 131.8, 129.9, 129.1, 128.4, 128.3, 127.5, 127.1 (2C), 126.4, 122.53, 122.49 (4°), 120.2; IR (KBr) ν_{max} 3062, 1693, 1618, 1549, 1311, 1227, 1093, and 750 cm^{-1}; HRMS (ES$^+$): calculated for $C_{20}H_{12}ClNO$; 318.0686, found 318.0690.

1,3-Dibromisoquinoline

To homophthalic acid (12.0 g, 66.3 mmol) was added ammonium hydroxide (30 mL, 0.31 mol) and the mixture was vacuum distilled until a brown solid remained. The solid was heated gently at ambient pressure with a Bunsen burner until an orange oil remained. The flask was allowed to cool and PBr_3 (6.3 mL, 66 mmol) was added and the mixture was heated at 160 °C with stirring overnight (18 h). The resultant solution was cooled and poured onto ice water [**Caution!**]. The solution was extracted with dichloromethane (3 × 100 mL) and the organic layer was washed sequentially with 20% NaOH (2 × 50 mL), water (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to yield crude product that was purified by column chromatography over silica gel (CH_2Cl_2) to yield the title compound (6.0 g, 31%). R_f = 0.70, (CH_2Cl_2); m.p. 151.0-153.0 °C (lit.[49] 147.0-147.5 °C); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.26 (m, 1H), 7.85 (s, 1H, H4), 7.77-7.67 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) 144.1 (4°), 138.9 (4°), 132.7 (4°), 132.1, 129.1, 128.9, 128.0 (4°), 126.2, 124.2 (4°); IR (KBr) ν_{max} 1569, 1544, 1483, 1432, 1288, 1247, 1078, 965, 818 and 747 cm^{-1}; HRMS (ES$^+$): calculated for $C_9H_5Br_2N$; 285.8867, found 285.8869; $C_9H_5Br_2N$: calculated C, 37.67; H, 1.76; N, 4.88, found C, 37.67; H, 1.56; N, 4.70.

*3-Bromo-1-(2-methylnaphthalen-1-yl)isoquinoline (**42**)*

$Pd(PPh_3)_4$ (1.09 g, 0.94 mmol) was added to a dry Schlenk tube containing anhydrous, degassed DME (100 mL) followed by 1,3-dibromoisoquinoline (4.45 g, 22.5 mmol) and the mixture stirred under nitrogen for 15 min at 70 °C to give a pale yellow solution. Arylboronic acid **36** (3.85 g, 20.7 mmol) was then added as a solid followed by Cs_2CO_3 (6.29 g, 41.4 mmol). The orange mixture was then refluxed at 90 ºC for 2 d after which time it was cooled to room temperature and water (100 mL) and diethyl ether (100 mL) were added. The organic layer was separated and concentrated *in vacuo* to give a brown oil which was re-dissolved in diethyl ether (100 mL), washed with water (20 mL), brine (20 mL), and then dried over $MgSO_4$. The solution was filtered and evaporated *in vacuo* to give the crude product which was purified by column chromatography over silica gel (1:1 CH_2Cl_2:pentane) to yield the title compound **42** (4.75 g, 72%). R_f = 0.2, (1:1 CH_2Cl_2:pentane); m.p. 138.0-140.0 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.00 (s, 1H. H4), 7.90-7.82 (m, 3H), 7.65 (m, 1H), 7.45 (d, 1H, J = 8.4 Hz), 7.40-7.30 (m, 1H), 7.23 (m, 1H), 6.99 (d, 1H, J = 8.4 Hz), 2.11 (s, 3H, CH_3); ^{13}C NMR (75 MHz; $CDCl_3$) 161.7 (4°), 138.4 (4°), 135.4 (4°), 134.6 (4°), 133.5 (4°), 132.8 (4°), 132.0 (4°), 131.4, 123.9, 128.7, 127.9, 127.5, 127.4 (4°), 126.5, 126.2, 125.5, 125.1, 123.4, 20.2 (CH_3); IR (KBr) ν_{max} 3051, 1544, 1310, 1145, 1089, 962, 841, 812 and 754 cm^{-1}; HRMS (ES$^+$): calculated for $C_{20}H_{14}BrN$; 348.0388, found 348.0398; $C_{20}H_{14}BrN$: calculated C, 68.98; H, 4.05; N, 4.02, found C, 68.58; H, 4.02; N, 3.95.

*3-Bromo-1-(2-dibromomethylnaphthalen-1-yl)isoquinoline (**46**)*

To biaryl **42** (4.66 g, 13.4 mmol) was added *N*-bromosuccinimide (5.0 g, 28.1 mmol) and dibenzoyl peroxide (70%, 0.46 g, 1.3 mmol) followed by CCl_4 (100 mL). The mixture was heated to reflux while being irradiated with a UV lamp overnight (18 h). The resultant mixture was filtered and the precipitate washed with benzene (2 × 20 mL). The mother liquors were combined, washed sequentially with water (20 mL), saturated $NaSO_3$ (20 mL) and brine (20 mL) and then dried over $MgSO_4$. The organic layer was filtered and evaporated *in vacuo* to yield the title

compound **46** (6.60 g, 97%) as a brown solid, which was used without any further purification. R_f = 0.55, (2:1 CH_2Cl_2:pentane); m.p. 191-193 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.18 (d, 1H, *J* = 8.8 Hz), 8.10-8.07 (m, 2H), 7.92-7.87 (m, 2H), 7.72 (ddd, 1H, J_1 = 1.3 Hz, J_2 = 6.7 Hz, J_3 = 8.2 Hz), 7.49 (ddd, 1H, J_1 = 1.2 Hz, J_2 = 7.0 Hz, J_3 = 8.2 Hz), 7.44-7.25 (m, 3H), 6.95 (d, 1H, *J* = 7.9 Hz), 6.26 (s, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) 158.0 (4°), 138.4 (4°), 137.4 (4°), 135.4 (4°), 133.6 (4°), 131.9, 131.2 (4°), 130.7, 129.9 (4°), 128.3, 128.2, 127.5, 127.5 (2C), 127.4 (4°), 126.9, 126.3, 126.2, 124.5, 38.9; IR (KBr) ν_{max} 1544, 1142, and 750 cm^{-1}; HRMS (ES$^+$): calculated for $C_{20}H_{12}Br_3N$; 503.8598, found 503.8596; $C_{20}H_{12}Br_3N$: calculated C, 47.47; H, 2.39; N, 2.77, found C, 47.07; H, 2.12; N, 2.55.

*1-(3-Bromoisoquinolin-1-yl)naphthalene-2-carbaldehyde (**44**)*

To dibromide **46** (0.6 g, 1.2 mmol) was added EtOH (6 mL) and THF (4 mL) and the solution was heated to reflux. $AgNO_3$ (0.59 g, 3.5 mmol) in water (1.7 mL) was added drop-wise with stirring to produce a yellow precipitate. The reaction was refluxed for a further 1 h and the hot mixture was filtered and the precipitate was washed with hot THF (2 × 20 mL). The filtrate was concentrated and dichloromethane (50 mL) was added followed by water (20 mL), the organic layer was separated and the aqueous layer washed with dichloromethane (2 × 20 mL). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to yield the crude product which was purified by column chromatography over silica gel (2:1 CH_2Cl_2:Pentane) to yield the title compound **44** (0.29 g, 68%) as a white solid. R_f = 0.45, (3:1 pentane:EtOAc); m.p. 145-146 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 9.66 (s, 1H, CHO), 8.17-8.07 (m, 3H), 7.98 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 8.3 Hz), 7.73 (app t, 1H, *J* = 7.6 Hz), 7.61 (app t, 1H, *J* = 7.8 Hz), 7.45-7.32 (m, 3 H), 7.22 (d, 1H *J* = 8.56 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) 190.8, 157.9, 141.0, 137.9, 136.1, 135.0, 132.3, 132.2, 131.7, 129.9, 129.1, 128.5, 128.4, 127.5, 127.1, 126.3, 124.2, 122.52, 122.47, 122.45; IR (KBr) ν_{max} 1693, 1544, 1316, 1227, 1088, 823, and 748 cm^{-1}; HRMS (ES$^+$): calculated for $C_{20}H_{12}BrNO$; 362.0181, found 362.0163; $C_{20}H_{12}BrNO$: calculated C, 66.32; H, 3.34; N, 3.87, found C, 66.38; H, 3.35; N, 3.83.

*2-Bromo-4-tert-butylphenol (**38**)*

To 4-*tert*-butyl-phenol **(37)** (20.1 g, 0.134 mol) was added dichloromethane (200 mL) and the mixture stirred until all of the substrate had dissolved. The reaction mixture was then cooled to 0 °C and bromine (7.0 mL, 0.14 mol) in dichloromethane (50 mL) was added drop-wise over a period of 15 min. This solution was allowed to stir for another 40 min after which time saturated Na_2SO_3 (100 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL) and the combined organic layers were washed with Na_2SO_3 (50 mL), water (50 mL), brine (50 mL), and dried over Na_2SO_4. The organic layer was filtered and evaporated *in vacuo* to yield the title compound **38** (30.3 g, 99%) as a clear oil, which solidified upon standing and was used without any further purification. R_f = 0.20, (3:1 pentane:EtOAc); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.44 (d, 1H, *J* = 2.2 Hz), 7.23 (m, 1H), (m, 1H), 6.95 (d, 1H, *J* = 4.1 Hz), 1.28 (s, 9H, -$(CH_3)_3$); HRMS (ES$^-$): calculated for $C_{10}H_{13}BrO$; 227.0072, found 227.0067.

*2-Bromo-4-tert-butyl-6-chlorophenol (**39**)*[40]

To phenol **38** (30.2 g, 0.132 mol) was added toluene (100 mL) and diisobutylamine (183 µL, 1.05 mmol). The solution was heated to 70 °C and at this temperature sulfuryl chloride (10.6 mL, 0.132 mmol) was added. The solution was allowed to stir for an additional 30 min. Water (30 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 × 20 mL) and all organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to afford the title compound **39** (32.9 g, 95 %) as a yellow oil which was used without any further purification. R_f = 0.70, (3:1 pentane:EtOAc); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.39 (d, 1H, *J* = 2.1 Hz) 7.80 (d, 1H, *J* = 2.1 Hz), 5.72 (s, 1H, OH), 1.27 (s, 9H, C-$(CH_3)_3$); ^{13}C NMR (75 MHz; $CDCl_3$) 146.2 (4°), 145.5 (4°), 128.4, 126.1, 120.1 (4°), 109.8 (4°), 34.4 (4°), 31.2 -$(CH_3)_3$; IR (KBr) ν_{max} 3512, 2964, 1565, 1482, 1395, 1279, 1169, and 768 cm^{-1}; HRMS (ES$^-$): calculated for $C_{10}H_{12}BrClO$; 260.9682, found 260.9678.

*1-Bromo-5-tert-butyl-3-chloro-2-methoxybenzene (**40**)*

To phenol **39** (10.50 g, 39.9 mmol) was added anhydrous acetone (100 mL) followed by anhydrous K_2CO_3 (16.6 g, 138 mmol) and methyl iodide (7.5 mL, 120 mmol). The mixture was refluxed for 24 h and the solvent was removed *in vacuo*. Water (50 mL) and dichloromethane (100 mL) were added and the organic layer was separated. The aqueous layer was extracted again with dichloromethane (2 × 30 mL) and all organic layers were combined, washed with brine (30 mL) and dried over Na_2SO_4. The organic layer was filtered and evaporated *in vacuo* to yield the title compound **40** (10.2 g, 92%) as a yellow oil which was used without any further purification. R_f = 0.8, (3:1 pentane:EtOAc); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.44 (d, 1H, *J* = 2.4 Hz), 7.32 (d, 1H, *J* = 2.2 Hz), 3.87 (s, 3H, CH_3), 1.29 (s, 9H, -$(CH_3)_3$; ^{13}C NMR (75 MHz; $CDCl_3$) 150.7 (4°), 149.4 (4°), 129.0, 128.4 (4°), 126.9, 117.9 (4°), 60.6 (CH_3), 34.6 (4°), 31.1 (CH_3)$_3$; IR (KBr) ν_{max} 2964, 1546, 1479, 1275, 999, and 769 cm^{-1}

*5-tert-Butyl-1-chloro-2-methoxy-3-phenylboronic acid (**32**)*

Magnesium (5.00 g, 0.21 mol) was activated by heating and stirring *in vacuo* for 1 h at 80 °C after which time it was allowed to cool to room temperature and dry THF (20 mL) was added under an atmosphere of nitrogen. A solution of aryl bromide **40** (7.0 mL, 36 mmol) in dry THF (50 mL) was added slowly *via* cannula to give a black suspension. The solution was heated with the aid of a heat gun at regular intervals during the addition period. The solution was allowed to stir for 1 h at room temperature. The Grignard solution was then added slowly, *via* cannula filtration, to a solution of triisopropylborate (12.5 mL, 54.0 mmol) in THF (20 mL) at -78 °C. The reaction mixture was allowed to warm to room temperature while stirring overnight (18 h). Water (30 mL) was added and the suspension was allowed to stir for a further 1 h. The reaction mixture was reduced *in vacuo* to remove the THF and dichloromethane (100 mL) was added. The organic layer was separated, and the aqueous layer was washed with dichloromethane (3 × 30 mL), the combined organic extracts were evaporated *in vacuo* to give a yellow oil. NaOH (20% w/v) was added producing a white precipitate that was stirred in pentane overnight (18 h) and then filtered using a sintered glass funnel. The precipitate was washed with more pentane, removed from the funnel and stirred in an HCl (1 M)/CH_2Cl_2 biphasic mixture. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 50 mL). All organic layers were combined, washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. The organic layer was filtered and evaporated *in vacuo* to yield slightly crude product which was purified by column chromatography over silica gel 10:1 (pentane:EtOAc) to yield the title compound **32** (4.40 g, 50%) as an oil that solidified upon standing. R_f = 0.4, (3:1 pentane:EtOAc); m.p. 65-67 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.74 (d, 1H, *J* = 2.4 Hz) 7.49 (d, 1H, *J* =

2.4 Hz), 6.58 (s, 2H, $B(OH)_2$), 3.94 (s, 3H, (OMe)), 1.32 (s, 9H, $(CH_3)_3$); ^{13}C NMR (75 MHz; $CDCl_3$) 158.6 (4°), 148.8 (4°), 131.7, 131.1, 126.2 (4°), 61.9 (CH_3), 34.5 (4°), 31.2 $(CH_3)_3$ (1C obscured); IR (KBr) ν_{max} 3361, 2956, 1476, 1431, 1398, 1366, 1333, 1236, 1070, 987, 810 and 769 cm^{-1}; HRMS (ES^-): calculated for $C_{11}H_{16}BClO_3$; 241.0803, found 241.0792.

*3-(5-tert-Butyl-3-chloro-2-methoxyphenyl)-1-(2-methylnaphthalen-1-yl)isoquinoline (**33**)*

$Pd(PPh_3)_4$ (0.10 g, 86 μmol) was added to a dry Schlenk tube containing anhydrous, degassed DMF (25 mL) followed by biaryl **35** (0.88 g, 2.89 mmol) and the mixture was stirred under nitrogen for 10 min. Boronic acid **32** (0.70 g, 2.9 mmol) was then added as a solid followed by sodium carbonate (3 mL, 2.0 M). The mixture was then heated to 110 °C for 2 d after which time it was cooled to room temperature and water (50 mL) and dichloromethane (50 mL) were added. The organic layer was extracted and concentrated *in vacuo* to give a brown oil which was re-dissolved in dichloromethane (50 mL), washed with water (20 mL), brine (20 mL), and then dried over Na_2SO_4. The organic solution was filtered and evaporated *in vacuo* to give an oil which was purified by column chromatography over silica gel (1:1 pentane:CH_2Cl_2) to yield the title compound **33** (0.54 g, 40%) as a white solid. R_f = 0.25, (1:1 CH_2Cl_2:pentane); m.p. 135-136 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.21 (s, 1H, H4), 7.98-7.88 (m, 3H), 7.72-7.66 (m, 2H), 7.50 (d, 1H, *J* = 8.3 Hz), 7.45-7.36 (m, 4H), 7.25 (app t, 1H, *J* = 7.9 Hz), 7.15 (d, 1H, *J* = 8.5 Hz), 3.70 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3), 1.30 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz; $CDCl_3$) 160.1, 151.6, 149.2, 148.0, 136.8, 135.3, 134.9, 134.4, 133.0, 132.1, 130.5, 128.7, 128.4, 127.9, 127.8, 127.52 (2C), 127.48, 127.3, 127.2 (2C), 126.1, 125.8, 124.9, 120.4, 61.3 (OMe), 34.6 (4°), 31.3, $(CH_3)_3$, 20.3 (CH_3); IR (KBr) ν_{max} 2960, 1618, 1562, 1479, 1320, 1268, 996, 811, and 742 cm^{-1}; HRMS (ES^+): calculated for $C_{31}H_{28}ClNO$; 466.1938, found 466.1944; $C_{31}H_{28}ClNO$: calculated C, 79.90; H, 6.06; N, 3.01, found C, 79.70; H, 6.14; N, 2.98.

*3-(5-tert-Butyl-3-chloro-2-methoxyphenyl)-1-(2-dibromomethylnaphthalen-1-yl)isoquinoline (**41**)*

To compound **33** (1.50 g, 3.22 mmol) was added *N*-bromosuccinimide (1.20 g, 6.75 mmol) and dibenzoyl peroxide (70%, 0.11 g, 0.32 mmol) followed by CCl_4 (125 mL). The mixture was heated to reflux while being irradiated with a flood lamp for 7 h after which time *N*-bromosuccinimide (0.12 g, 0.68 mmol) was added and the mixture allowed to stir at reflux under irradiation overnight (18 h). The resultant mixture was filtered and the precipitate washed with benzene (2 × 20 mL). The mother liquors were combined, washed sequentially with water (20 mL), $NaHCO_3$ (20 mL), brine (20 mL) and then dried over $CaCl_2$. The organic layer was filtered and evaporated *in vacuo* to yield the title compound **41** (1.98 g, 99%) as a brown solid, which was used without any further purification. R_f = 0.65, (3:1 pentane:EtOAc); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.43 (s, 1H, H4), 8.22 (d, 1H, *J* = 8.8 Hz), 8.11 (d, 1H, *J* = 8.8 Hz), 8.01 (d, 1H, *J* = 8.4 Hz), 7.92 (d, 1H, *J* = 8.0 Hz), 7.85 (d, 1H, *J* = 2.4 Hz), 7.73 (m, 1 H), 7.51-7.25 (m, 5H), 6.47 (s, 1H), 3.72 (s, 3H, OCH_3), 1.30 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz; $CDCl_3$) 156.8, 151.6, 148.8, 148.3, 137.5, 136.8, 134.3, 133.6, 131.4, 131.0, 130.2, 128.1, 128.0, 127.8, 127.7 (2C), 27.5, 127.3, 127.21(2C), 127.18(2C), 127.05, 126.2, 121.6, 61.2 (OMe), 39.5 ($CHBr_2$), 34.7 (4°), 31.3 $(CH_3)_3$; IR (KBr) ν_{max} 2960, 1561, 1478, and 750 cm^{-1}; HRMS (ES^+): calculated for $C_{31}H_{26}Br_2ClNO$; 622.0148, found 622.0160.

*1-[3-(5-tert-Butyl-3-chloro-2-methoxyphenyl)isoquinolin-1-yl]naphthalene-2-carbaldehyde (**34**)*

Method 1

$Pd(PPh_3)_4$ (0.12 g, 0.10 mmol) was added to a dry Schlenk tube containing anhydrous, degassed DMF (25 mL) followed by aryl chloride **43** (0.64 g, 2 mmol) and the mixture was stirred under nitrogen for 10 min. Arylboronic acid **32** (0.73 g, 3.0 mmol) was then added as a solid followed by Cs_2CO_3 (1.34 g, 4.1 mmol). The mixture was then heated to 110 °C overnight (18 h) after which time it was cooled to room temperature and water (50 mL) and dichloromethane (50 mL) were added. The organic layer was separated and concentrated *in vacuo* to give a brown oil which was re-dissolved in dichloromethane (100 mL), washed with water (20 mL), brine (20 mL), and then dried over Na_2SO_4. The organic solution was filtered and evaporated *in vacuo* to give an oil which was purified by column chromatography over silica gel (10:1 pentane:EtOAc) to yield the title compound **34** (0.48 g, 50%) as a white solid. R_f = 0.60, (3:1 pentane:EtOAc); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 9.75 (s, 1H, COH), 8.33 (s, 1H, H4), 8.19 (d, 1H, *J* = 8.6 Hz), 8.09 (d, 1H, *J* = 8.6 Hz), 8.00 (dd, 1H J_1 = 6.3 Hz, J_2 = 7.32 Hz), 7.75-7.59 (m, 3H), 7.46-7.38 (m, 5H), 3.70 (s, 3H, OCH_3), 1.29 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz; $CDCl_3$) 191.5, 156.3 (4°), 151.7 (4°), 149.0 (4°), 148.2 (4°), 143.1 (4°), 136.5 (4°), 136.3 (4°), 134.6 (4°), 132.5 (4°), 130.9, 129.5, 128.9, 128.4 (2C), 128.1, 128.0 (4°), 127.9, 127.6, 127.4, 127.2 (2C), 127.0, 126.9, 122.4, 121.2, 61.2 (OMe), 34.6 (4°), 31.2 $(CH_3)_3$; IR (KBr) ν_{max} 1691, 1619, 1322, 770, and 702 cm^{-1}; HRMS (ES^+): calculated for $C_{31}H_{26}ClNO_2$; 480.1730, found 480.1748.

Method 2

$Pd(PPh_3)_4$ (0.58 g, 0.05 mmol) was added to a dry Schlenk tube containing anhydrous, degassed DMF (20 mL) followed by aryl bromide **44** (0.362 g, 1.0 mmol) and the mixture was stirred under nitrogen for 10 min. Arylboronic acid **32** (0.36 g, 1.5 mmol) was then added as a solid followed by Cs_2CO_3 (0.49 g, 1.5 mmol). The mixture was then heated to 110 ^oC overnight (18 h) and cooled to room temperature. Water (50 mL) and dichloromethane (50 mL) were added. The organic layer was separated and concentrated *in vacuo* to give a brown oil which was re-dissolved in dichloromethane (100 mL), washed with water (20 mL), brine (20 mL), and then dried over Na_2SO_4. The organic solution was filtered and evaporated *in vacuo* to give an oil which was purified by column chromatography over silica gel (10:1, pentane:EtOAc) to yield the title compound **34** (0.32 g, 67%) as white solid, identical to a previously prepared sample.

Method 3

To compound **41** (3.25 g, 5.21 mmol) was added ethanol (25 mL) and THF (15 mL) and the solution was heated to reflux. $AgNO_3$ (2.66 g, 15.6 mmol) in water (7.5 mL) was added drop-wise with stirring to produce a yellow precipitate. When all of the $AgNO_3$ solution had been added, the reaction was refluxed for a further 1 h. After this time, the hot mixture was filtered using a sintered glass funnel and the precipitate washed with more THF (2 × 20 mL). The mother liquors were combined concentrated and dichloromethane (100 mL) was added followed by water (30 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 20 mL). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to yield the crude product which was purified by column chromatography over silica gel (10:1 Pentane:EtOAc) to yield the title compound **34** as a white solid (0.3 g, 12%) which was identical to a previously prepared sample.

*1-[3-(5-tert-Butyl-3-chloro-2-hydroxyphenyl)isoquinolin-1-yl]naphthalene-2-carbaldehyde (**47**)*[29]

Aldehyde **34** (0.33 g, 0.69 mmol) was placed in a 50 mL Schlenk tube. HBr (48%, 3 mL) and AcOH (3 mL) were added at room temperature and the resultant solution heated to 140 °C for 2 h. After this time the solution was cooled to room temperature and water (10 mL) and dichloromethane (20 mL) were added. The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 10 mL). The combined organic layers were then washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to give the crude product which was purified by column chromatography over silica gel (5:1, pentane:EtOAc) to yield the title compound **47** (215 mg, 67%) as a pale yellow solid. R_f = 0.30, (5:1 pentane:EtOAc); m.p. 200-202 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 9.68 (s, 1H, COH), 8.45 (s, 1H, H4), 8.13-8.09 (m, 3H), 8.00 (d, 1H, *J* = 8.1 Hz), 7.95 (d, 1H *J* = 2.3 Hz), 7.77 (m, 1H), 7.62 (dd, 1H, J_1 = 7.3 Hz, J_2 = 14.5 Hz), 7.45-7.34 (m, 4H), 7.22 (d, 1H, *J* = 8.5 Hz), 1.41 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz; $CDCl_3$) 190.6, 154.7 (4°), 152.6 (4°), 150.4 (4°), 142.3 (4°), 140.5 (4°), 137.2 (4°), 136.3 (4°), 132.3 (4°), 132.2 (4°), 132.0, 130.2, 129.3, 128.9, 128.6, 128.5, 128.1 (4°), 127.9, 127.8, 127.2, 126.9, 122.8, 122.7 (4°), 121.4, 119.7 (4°), 116.3, 34.5 (4°), 31.6 -$(CH_3)_3$; IR (KBr) ν_{max} 3452, 2954, 1695, 1620, 1587, 1561, 1462, 1256, and 743 cm^{-1}; HRMS (ES^+): calculated for $C_{30}H_{24}ClNO_2$; 466.1574, found 466.1587.

*4-tert-Butyl-2-chloro-6-[1-(2-hydroxymethylnaphthalen-1-yl)isoquinolin-3-yl]-phenol (**30**)*

Aldehyde **47** (0.10 g, 0.22 mmol) was placed in a 25 mL round-bottomed flask to which THF (3 mL) and ethanol (3 mL) were added. The solution was allowed to stir at room temperature and (11.8 mg, 0.31 mmol) in water (220 μL) was added drop-wise and the mixture was allowed to stir for a further 1 h. Water (5 mL) was added, followed by 10% HCl (5 mL) and dichloromethane (50 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were then washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to yield the crude product which was purified by column chromatography over silica gel (5:1, pentane:EtOAc) to yield the title compound **30** (90 mg, 92%) as a yellow solid. Racemic **30** was resolved *via* semi-preparative HPLC using a CHIRALPAK AD column to yield both (-)-**30** and (+)-**30** in >99% ee. R_f = 0.40, (2:1 CH_2Cl_2:pentane); m.p. 205-207 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.37 (s, 1H, H4), 8.08-8.04 (m, 2H), 7.95-7.93 (m, 2H), 7.82-7.72 (m, 2H), 7.49-7.37 (m, 4H), 7.26 (ddd, 1H, J_1 = 1.2 Hz, J_2 = 6.9 Hz, J_3 = 9.6 Hz), 7.45-7.34 (m, 4H), 7.22 (d, 1H, *J* = 8.5 Hz), 7.00 (d, 1H, J = 8.57 Hz), 4.49 (d, 1H, *J* = 13.0 Hz), 4.38 (d, 1H, *J* = 13.0 Hz) 1.41 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz; $CDCl_3$) 156.8 (4°), 152.7 (4°), 150.3 (4°), 142.0 (4°), 137.4 (4°), 137.2 (4°), 132.9 (4°), 132.5 (4°), 132.2 (4°), 131.8, 129.7, 128.7, 128.2, 128.1, 127.6, 127.5, 127.2 (4°), 126.9, 126.1, 125.7, 125.6, 122.6 (4°), 121.2, 119.8 (4°), 115.6, 63.00 (CH_2), 34.4 (4°), 31.5 (CH_3)$_3$; HPLC AD semi-preparative column, 4.7 ml/min, 95:05 Pentane:IPA, 40 °C, t_R(-)-**30** = 27.9 min, t_R(+)-**30** = 37.1 min; α_D = +26.0, -30.0 ($CHCl_3$, c=1.0); IR (KBr) ν_{max} 3444, 2948, 1497, 1278, and 757 cm^{-1}; HRMS (ES^+) calculated for $C_{30}H_{24}ClNO_2$; 468.1730, found 468.1712; $C_{30}H_{24}ClNO_2$: calculated C, 76.99; H, 5.60; N, 2.99, found C, 76.76; H, 5.66; N, 2.91.

Racemization Studies

General procedure for racemisation study [35-37]

To benzene (3 mL), preheated to 90 °C was added (*R*)-(+)-**30** (2 mg, 4.27 μmol, 99.4% ee) in a sealed tube. The resulting solution was heated with stirring at this temperature for 60 min after which time it was placed in ice to cool. An aliquot was injected into the HPLC in order to determine the change in enantiomeric excess. This process was repeated at intervals of 30 min and a graph of ln (ee_0/ee) vs. time was plotted. This entire process was repeated at three other temperatures and the rate of racemisation at these temperatures was calculated. These rates were subsequently used to draw Arrhenius and Eyring plots from which the kinetic parameters for racemization were obtained.

General Procedure for the diethylzinc addition to aldehydes

Method A

To a solution of **30** (7 mg, 15 μmol) in toluene (1 mL) at room temperature was added $ZnEt_2$ (0.6 mL, 1 M in hexane, 0.6 mmol) and the solution was stirred for 30 min. After this time the solution was cooled to 0 °C and benzaldehyde (30 μL, 0.3 mmol) was added. The reaction was stirred for a further 48 h at 0 °C after which time 5% HCl (5 mL) and diethyl ether (20 mL) were added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 5 mL) and the organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product which was purified by column chromatography over silica gel (5:1 pentane/EtOAc) to give the pure alcohol.

Method B

To ligand **30** (40 mg, 85 mmol) was added toluene (4 mL) and the solution stirred at room temperature for 5 min. After this time 300 μL of this stock solution (3 mg, 6 μmol, 1 mol %) was transferred to a Schlenk tube and a further 1 mL of toluene added. To this solution at room temperature was added $ZnEt_2$ (1.2 mL, 1 M solution in hexane, 1.2 mmol) and the solution stirred for 30 min. After this time, the solution was cooled to -20 °C and benzaldehyde (58 μL, 0.6 mmol) was added. The reaction was stirred for a further 48 h at 0 °C, after which time 5% HCl (5 mL) and diethyl ether (20 mL) were added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 5 mL) and the organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product which was purified by column chromatography over silica gel (5:1, pentane/EtOAc) to give the pure product.

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