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New chiral tridentate ligands for asymmetric catalysis*

Kevin Murtagh, Brian A. Sweetman, and Patrick J. Guiry‡

Centre for Synthesis and Chemical Biology, Conway Institute for Biomedical and Biomolecular Research, School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland

Abstract: The synthesis of new tridentate, isoquinoline-derived ligands, involving successive Suzuki cross-coupling reactions, is described. We were able to resolve 1-[3-(2-hydroxyphenyl)-isoquinolin-1-yl]-naphthalen-2-ol via molecular complexation with *N*-benzylcinchonidinium chloride, whereas 1,3-bis(2-hydroxy-naphthalen-1-yl)-isoquinoline was resolved by chromatographic separation of its epimeric camphorsulfonates. Their barrier to rotation about the central biaryl axis was evaluated via racemization studies. Application of enantiopure 1,3-bis(2-hydroxynaphthalen-1-yl)-isoquinoline in the addition of diethylzinc to aldehydes proceeded in moderate yield but without asymmetric induction. A new tridentate ligand, 4-*tert*-butyl-2-chloro-6-[1-(2-hydroxymethyl-naphthalen-1-yl)-isoquinolin-3-yl]-phenol, was prepared in good yield and resolved by semipreparative high-performance liquid chromatography (HPLC). Its application in the addition of diethylzinc to a range of aromatic aldehydes proceeded in near perfect enantioselectivities at low ligand loadings of 1 mol %.

Keywords: atropisomerism; biaryls; Suzuki cross-coupling; resolution; racemization.

The preparation of enantiomerically pure compounds is an important and challenging area of contemporary synthetic organic chemistry [1,2]. Asymmetric synthesis using metal catalysts is one approach to such compounds [3–5]. Recently, a number of tridentate ligands have been disclosed which have proven to form excellent catalysts for a range of asymmetric processes [6–8]. We have recently reported a series of bidentate ligands, Quinazolinaps **1** (Fig. 1), which give excellent enantioselectivities in a number of catalytic reactions [9]. We therefore initiated a research program into the design, synthesis, and resolution of a series of ligands related to the previously reported tridentate ligands and our Quinazolinaps. The first examples we prepared, resolved, and tested were the 2-(2-pyridyl)- and 2-(2-pyrazinyl)-Quinazolinaps **2a**–**b** which we successfully applied to palladium-catalyzed allylic substitution of 1,3-diphenyl-propenyl acetate with dimethyl malonate in enantioselectivities of up to 81 % [10]. The related ligand class **3**–**4** was identified as a potential candidate for a wide range of asymmetric transformations, including Ti(IV)-catalyzed asymmetric aldol reaction, due to its structural similarity to Carreira's ligand **5**, [11] and diethylzinc addition to aldehydes. It was of interest to determine whether the change in chelate ring size (from 6.7 in **5** to 6.6 in **3**–**4**) had any beneficial effects on reactivity and enantioselectivity. We now wish to present our work on the synthesis, attempted resolution, and application in asymmetric catalysis of ligand class **3**–**4**.

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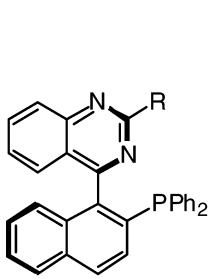
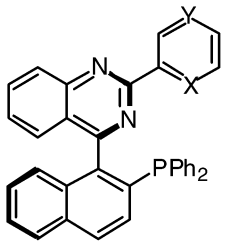
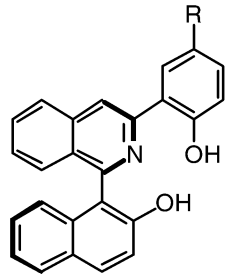
‡Corresponding author



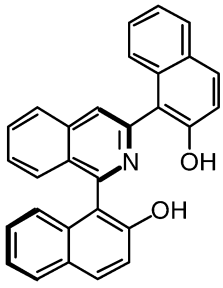
1: R = H, Me, Ph, Bn, *i*-Pr, *t*-Bu



2a: X = N, Y = H
2b: X, Y = N



3a: R = H
3b: R = t-Bu
3c: R = CF_3



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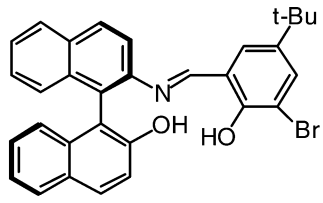

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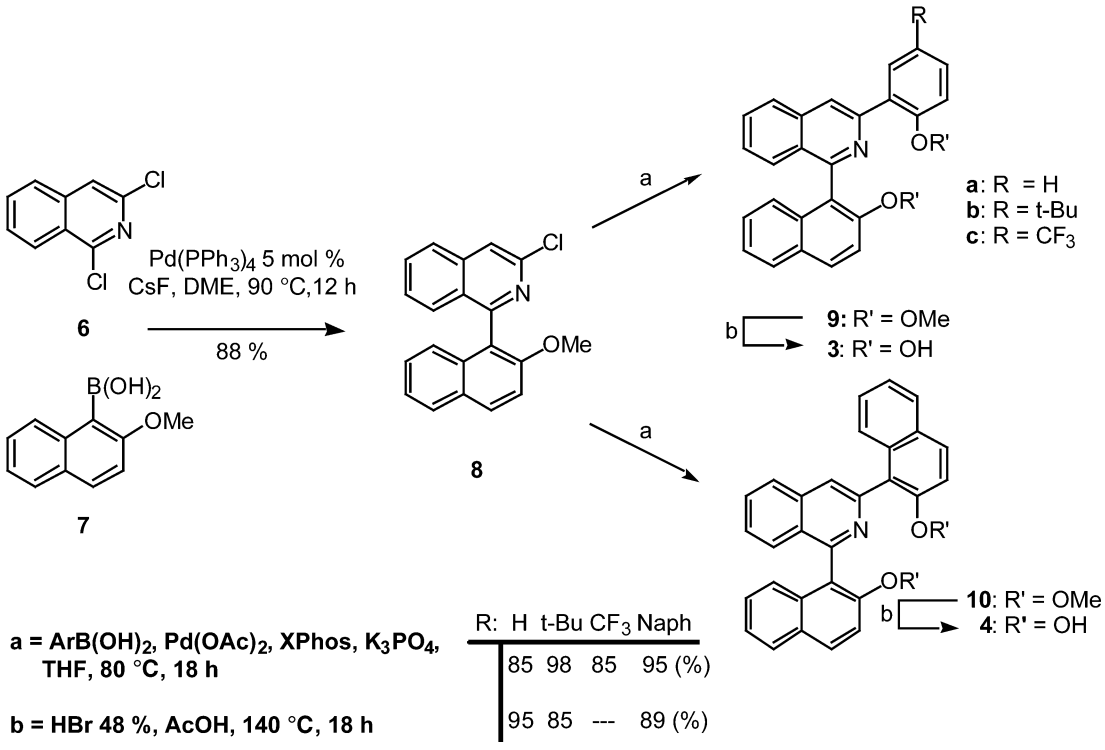
Fig. 1

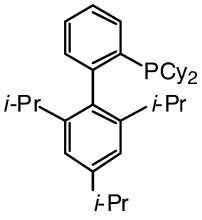
The synthesis of ligands **3** and **4** began with Suzuki cross-coupling of 1,3-dichloroisoquinoline **6** and 2-methoxynaphthylboronic acid **7** to yield biaryl **8** in a satisfactory 88 % yield (Scheme 1). This regioselectivity of oxidative addition in palladium-catalyzed processes at the 1-position of 1,3-dichloroisoquinoline **6** has previously been reported by Woodward [12]. However, subsequent reactions at the 3-position employing palladium catalysis does require a change from tetrakis(triphenylphosphine)palladium as initial reactions using it as the catalyst for Suzuki reactions with arylboronic acids to form the 1,3-diaryl-substituted products **9** and **10** proceeded in poor to moderate yields (5–20 %) and only then when they were performed under forcing conditions (110 °C in DMF). Recently, Buchwald's ligand Xphos **11** has emerged as an excellent ligand for the Suzuki cross-coupling of aryl chlorides and tosylates [13]. By heating biaryl **8** with Pd(OAc)2, XPhos and K_3PO_4 in THF with the appropriately substituted arylboronic acids at 80 °C for 18 h, the required aryl methyl ethers **9** and **10** were isolated in excellent yields (85 to 95 %). Thereafter, double demethylation is required to prepare the O,N,O ligands of interest and, after employing boron tribromide in initial studies but without success, treatment of **9** and **10** with aqueous HBr in acetic acid provided **3a–b** and **4** in good overall yield (85–95 %) [14–16]. Interestingly, the 4-triflouromethylphenyl-substituted ether **9c** proved to be inert to these and other demethylation procedures attempted.

It was then necessary to determine conditions for the resolution of the ligands thus prepared prior to application in asymmetric catalysis. A number of examples for the resolution of racemic compounds via derivatization to their diastereomers, which may then be separated by either crystallization or chromatography, have been reported [17–18]. Recently, Ding et al. reported the optical resolution of Kocovsky's NOBIN **12,** by molecular complexation with *N*-benzylcinchonidinium chloride **13** [19,20].



Scheme 1

We envisaged that our structurally related compounds might be suitable candidates for resolution by this method. Pleasingly, ligand **3a** could be resolved by employing a modified procedure. Therefore, stirring racemic ligand **3a** with 0.5 equiv of *N*-benzylcinchonidinium chloride **13** in acetone for 18 h produced a white precipitate, (*R*)-(+)-**3a**~**13**. The initial resolution afforded (*R*)-**3a** in 36 % yield with 90 % ee and the mother liquor contained (*S*)-**3a** in 56 % yield and 88 % ee. This resolution process could be repeated with the enantioenriched (*R*)-**3a** and (*S*)-**3a** to yield each enantiomer in 99 and 98 % ee, respectively. We were able to unambiguously assign the configuration through X-ray crystallographic analysis [21].



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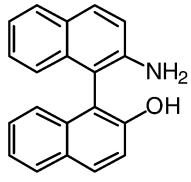

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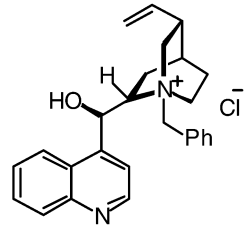

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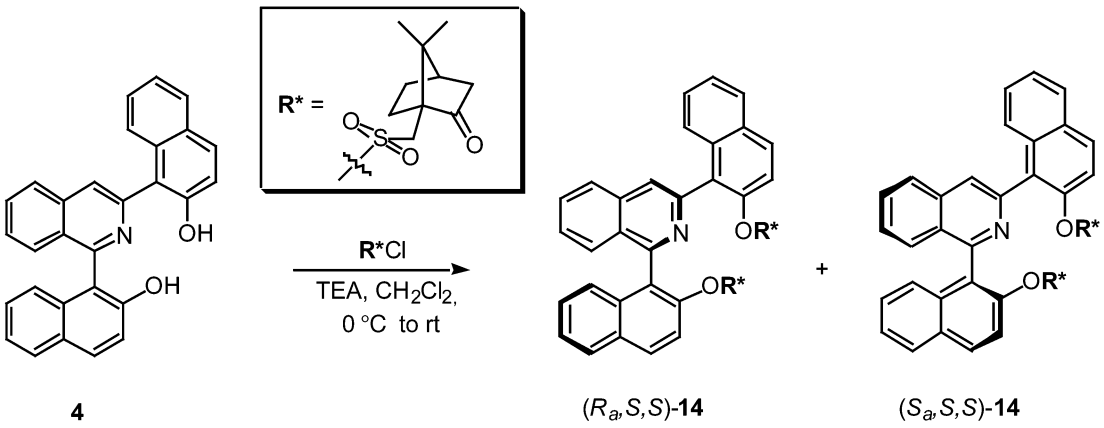
Unfortunately, ligands **3b** and **4** could not be resolved using this method as no precipitate formed when they was stirred in acetone in the presence of *N*-benzylcinchonidinium chloride. Racemic **4** was converted to its bis[(1*S*)-camphor-10-sulfonates] **14** in 93 % yield using the procedure of Chow, Scheme 2 [22]. The epimers formed were separated by column chromatography using pentane:ethyl ac-



4 (R_a,*S*,*S*)-**14** (S_a,*S*,*S*)-**14**

Scheme 2

etate (3:1) to yield four batches of products; the yields and diastereomeric excesses for which are shown in Table 1. The epimers were then converted to enantiomerically enriched **4** by stirring in 50 % w/v NaOH at 0 °C, followed by acidic work-up and extraction into dichloromethane. Despite being able to successfully form the corresponding bis[(1*S*)-camphor-10-sulfonate] derivatives of ligand **3b**, we were unable to find conditions for their separation.

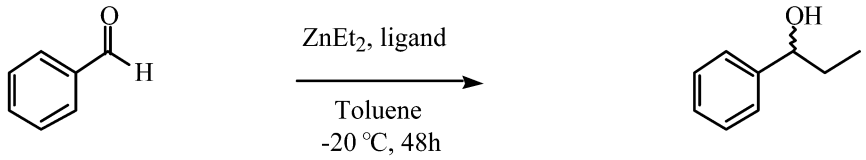
Table 1

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

Prior to applying ligands **3a** and **4** in asymmetric catalysis we were interested in determining their susceptibility to racemization. The study of the kinetics of racemization of axially chiral biphenyls has received much attention by, among others, Adams [23]. The rotational energy barrier about the biaryl axis of **3a** and **4** was determined employing high-performance liquid chromatography (HPLC), a technique first studied in kinetic studies of interconverting stereoisomers by Horváth [24]. Following the protocol of Eyring and Cagle [25], the racemization of an individual enantiomer of **3a** was studied in benzene at a range of temperatures, and we calculated that an enantiomerically pure of **3a** would lose 1 % of its optical purity after 33.6 h at room temperature. In a similar fashion, the rotational energy barrier in **4** was calculated to be 88 kJ/mol, meaning that it loses 1 % ee every 37 h. These values are arguably too low to render these ligands useful for application in asymmetric catalysis at room temperature or above. Their use at temperatures below ambient, however, might be possible, and that prompted us to study their potential application in the diethylzinc addition to aldehydes.

Since the pioneering work of Oguni in 1984 [26], a myriad of β-amino alcohols [27,28], amines [29,30], and amino thiol-based ligands [31] have been successfully applied in the diethylzinc addition to aldehydes. Such is the extent of the investigation into this asymmetric alkylation process, that it is now regarded as a benchmark reaction for understanding the catalytic potential of a new ligand. However, the efficacy of the reaction is ligand-specific so, despite the large volume of research completed on this transformation, the search for new ligands is still a field of continuous interest.

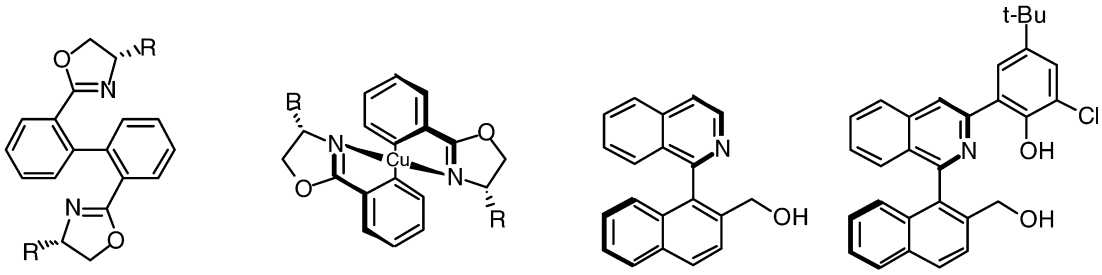
In order to study the effectiveness of resolved ligand **4**, it was employed initially in the diethylzinc addition to benzaldehyde, Scheme 3. A number of factors influencing the effectiveness of both lig-



Scheme 3

ands were of interest, including the catalyst loading and the temperature. However, despite varying a range of reaction conditions, the addition proceeded in only moderate to good yields of 50–60 %, with the product being formed as a racemate.

As we had already determined that the ligand should not racemize significantly at the reaction temperature of –20 °C, we believe that the chelation of zinc plays a role in accelerating the racemization process. A similar observation by Ikeda was exploited as the rapidly interconverting diastereomers **15** gave one diastereomer upon complexation with Cu [32].



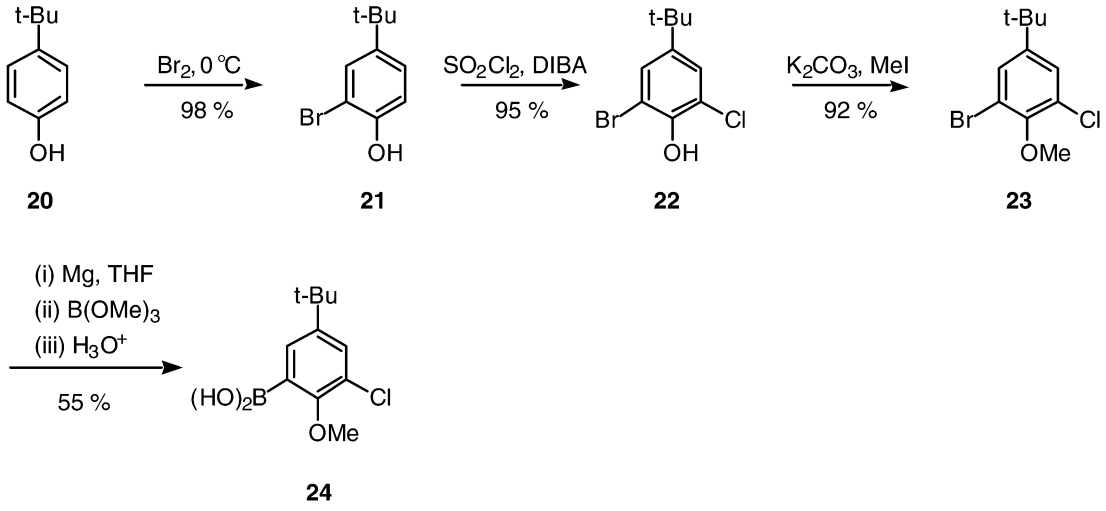
15 R = *i*-Pr, *t*-Bu (a*S*,*S*,*S*)-**15** **16** **17**

Due to the relatively low barrier to racemization of ligands **3** and **4** and the poor results obtained in diethylzinc additions, a new design of ligand was required. In an effort to increase the barrier to rotation [33] and to change to a metal axial-chelate of seven, optimal in other ligand systems such as the Carreira ligand **5** and Baker's ligand **16** [6,34] 4-*tert*-butyl-2-chloro-6-[1-(2-hydroxymethyl-naphthalen-1-yl)-isoquinolin-3-yl]-phenol **17** was identified as a suitable candidate.

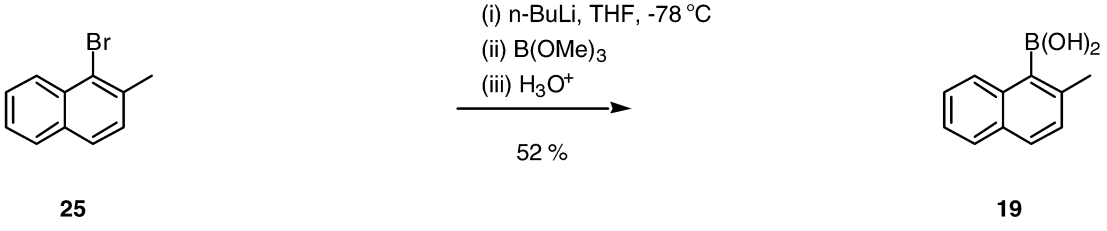
The strategy employed to prepare ligand **17** was similar to the synthetic route which provided access to ligands **3** and **4**, although in this case we wished to use 1,3-dibromoisoquinoline due to the higher reactivity at the 3-position after the first proposed Suzuki coupling and the presence of the chloro-substituent on the aryl ring. The remaining two key intermediates were 5-*tert*-butyl-1-chloro-2-methoxy-phen-3-ylboronic acid **18** and 2-methylnaphth1-ylboronic acid **19**.

The synthesis of **18** began with the near quantitative mono-bromination of 4-*tert*-butyl-phenol **20**, followed by the chlorination of 2-bromo-4-*tert*-butyl-phenol **21** in 95 % yield using the procedure of Sheldon which had been developed for the regioselective *ortho*-chlorination of phenol (Scheme 4) [35]. Methylation of 2-bromo-4-*tert*-butyl-6-chlorophenol **22** using anhydrous potassium carbonate and methyl iodide gave 1-bromo-5-*tert*-butyl-3-chloro-2-methoxybenzene **23** in 92 % yield [36]. The synthesis of the desired boronic acid **24** in 55 % yield was then completed by chemoselective formation of the Grignard reagent, and subsequent quenching with trimethylborate and hydrolysis.

The preparation of 2-methylnaphth-1-ylboronic acid **19** in 52 % yield was accomplished by direct lithiation of 1-bromo-2-methylnaphthalene **25** in THF using *n*-butyllithium at –78 °C, Scheme 5, and subsequent reaction of the resulting anion with trimethylborate, followed by hydrolysis.



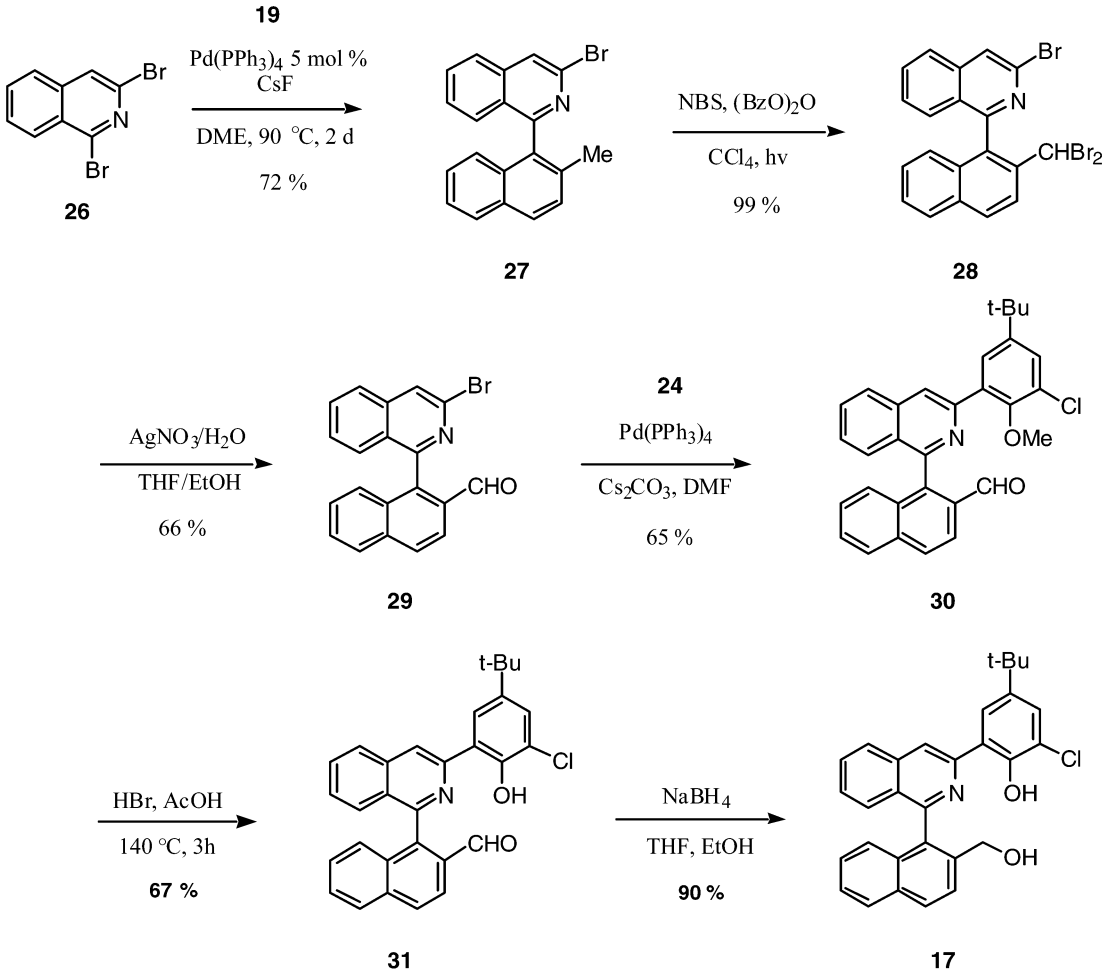
Scheme 4



Scheme 5

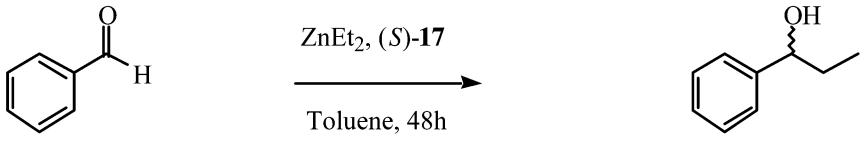
The coupling of 2-methylnaphth-1-ylboronic acid **19** and 1,3-dibromoisoquinoline **26** was completed using 3 mol % tetrakis(triphenylphosphine)palladium in refluxing DME to afford 3-chloro-1-(2-methyl-naphthalen-1-yl)-isoquinoline **27** in 72 % yield, Scheme 6. The next step was the bromination of **27** using *N*-bromosuccinimide and dibenzoyl peroxide under irradiation in carbon tetrachloride to give 3-(5-*tert*-butyl-3-bromo-2-methoxy-phenyl)-1-(2-dibromomethyl-naphthalen-1-yl)-isoquinoline **28** in 99 % yield. Thereafter, **28** was converted to aldehyde **29** in 66 % yield using silver nitrate in a modification of the protocol of Walsh [37,38]. The cross-coupling of 5-*tert*-butyl-1-chloro-2-methoxy-phen-3-ylboronic acid **24** with **29** was catalyzed by tetrakis(triphenylphosphine)palladium to afford 1-[3-(5-*tert*-butyl-3-chloro-2-methoxy-phenyl)isoquinolin-1-yl]-naphthalene-2-carbaldehyde **30** in 65 % yield. As in the preparation of ligands **3** and **4**, the harsh reaction conditions of HBr in acetic acid at 140 °C were required for demethylation to form 1-[3-(5-*tert*-butyl-3-chloro-2-hydroxy-phenyl)-isoquinolin1-yl]-naphthalene-2-carbaldehyde **31** in 67 % yield. Finally, racemic ligand **17** was formed by the reduction of the aldehydic functionality with sodium borohydride in 92 % yield.

Various attempts at resolving ligand **17** via complexation with *N*-benzylcinchonidinium chloride **13** failed. Initial attempts at synthesizing the bis[(1*S*)-camphor-10-sulfonate] derivatives of **17** were also unsuccessful. Fortunately, ligand **17** was successfully resolved via semipreparative HPLC using a Chiralpak AD Column.



Scheme 6

With enantiopure ligand at hand, it was of interest to determine its efficacy in the diethylzinc addition to benzaldehyde, Scheme 7. Gratifyingly, (*S*)-**17** afforded (*S*)-1-phenyl-1-propanol in excellent enantioselectivities with even low catalyst loadings of 1 mol %, giving >99 % ee as most systems operate at a minimum of 5 mol %, Table 2. Even at 0.1 mol % the ligand is still catalytic, producing the desired alcohol in nearly quantitative yield although the enantiomeric excess was reduced to 91 %. The loss of enantiomeric excess in the case of the 0.1 mol % reaction may be due to competition between a noncatalytic pathway and the catalytic pathway.

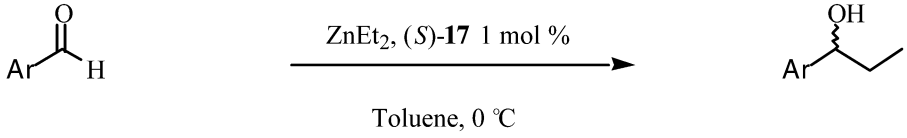


Scheme 7

Table 2

Ligand mol %	Temp. (°C)	Yield (%)	ee (%)	Config.
10	–20	85	95	(*S*)
5	–20	99	>99	(*S*)
1	–20	99	>99	(*S*)
5	0	98	98	(*S*)
0.1	25	99	91	(*S*)

In view of the excellent results obtained with benzaldehyde as substrate, we wished to determine the effectiveness of **17** with a range of aromatic aldehydes, Scheme 8, and the results of our investigation are given in Table 3. We were pleased to find that excellent enantioselectivities (95–98 %) were obtained for the isomeric naphthaldehydes and 4-chlorobenzaldehyde at 1 mol % ligand loading. For the more electron-rich substrates, 4-anisaldehyde, and ferrocenealdehyde the enantioselectivities dropped to 70 and 82 % ee, respectively.



Scheme 8

Table 3

Aldehyde	Time (h)	Yield (%)	ee (%)	Config.
1-Naphthaldehyde	36	74	95	(*S*)
2-Naphthaldehyde	36	95	98	(*S*)
4-Chlorobenzaldehyde	40	65	95	(*S*)
4-Anisaldehyde	40	82	70	(*S*)
Ferrocenealdehyde	40	65	82	(*S*)

CONCLUSIONS

We have prepared a series of tridentate, axially chiral ligands employing a series of Suzuki reactions to form the two aryl–aryl bonds. We successfully managed to resolve two of the first class of ligand, ligands **3a** and **4**, the former by a co-crystallization technique and the latter by separation of epimeric bis[(1*S*)-camphor-10-sulfonate] derivative. We determined that **3a** and **4** would lose 1 % of its optical purity after 33.6 and 37 h at room temperature, respectively. Applying ligand **4** in the addition of diethylzinc to benzaldehyde gave racemic products in moderate to good yield. A new tridentate ligand, 4-*tert*-butyl-2-chloro-6-[1-(2-hydroxymethyl-naphthalen-1-yl)-isoquinolin-3-yl]-phenol **17**, was prepared in good yield and resolved by semipreparative HPLC. Its application in the addition of diethylzinc to a range of aromatic aldehydes proceeded in near perfect enantioselectivities even at low ligand loadings of 1 mol %. Work is currently in progress investigating the catalytic behavior of complexes of the ligands **17** in a range of asymmetric transformations. These and other applications, in addition to the preparation of analogous tridentate ligands, will form the subject of future publications from these laboratories.

ACKNOWLEDGMENTS

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