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Synthesis, resolution and racemisation studies of new tridentate ligands for asymmetric catalysis

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Abstract—A method for the high-yielding preparation of two tridentate, isoquinoline-derived ligands, involving successive Suzuki cross-coupling reactions, is described. The first ligand could be resolved via molecular complexation with *N*-benzylcinchonidinium chloride, while the second was resolved by chromatographic separation of its epimeric camphorsulfonates. The barrier to rotation about the central biaryl axis was evaluated via racemisation studies, and the absolute configuration assigned by X-ray crystallography.

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**, 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. Ligands **2** and **3** (Fig. 1) were identified as potential candidates for a wide range of asymmetric transformations, including Ti(IV)-catalysed asymmetric aldol reactions and diethylzinc addition to aldehydes.

The synthesis of ligands **2** and **3** began with Suzuki cross-coupling of 1,3-dichloroisoquinoline **4** and 2-methoxynaphth-1-ylboronic acid **5** to yield biaryl **6**. Compound **4** has previously been shown to react selectively at the 1-position under the standard Suzuki conditions employing $Pd(PPh_3)_4$.[10] Reacting **6** with the required boronic acid under analogous conditions, produced **7** and **8** in poor to moderate yields and only when it was performed under forcing conditions (110 °C in DMF). Recently, Buchwald and co-workers[1] XPhos **9** has emerged as an excellent ligand for the Suzuki cross-coupling of aryl chlorides and tosylates.[11] By heating biaryl **6** 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 **7** and **8** were isolated in excellent yields (85% and 95%, respectively). Double demethylation with 48% HBr provided the desired tridentate ligands **2** and **3** in good overall yield (Scheme 1).

A number of examples for the resolution of racemic compounds via derivatisation to their diastereomers, which may then be separated by either crystallisation or chromatography, have been reported.[12,13] Recently Ding et al. reported the optical resolution of Kocovsky's NOBIN, a binaphthyl aminoalcohol, by molecular complexation with *N*-benzylcinchonidinium chloride **10**.[14,15]

We envisaged that our structurally related compounds might be suitable candidates for resolution by this method. To our delight, ligand **2** could be resolved by employing a modified procedure. Stirring racemic ligand **2** with 0.5 equiv of *N*-benzylcinchonidinium chloride **10** in acetone for 18 h produced a white precipitate, (*R*)-(+)-**2**·**10** (Scheme 2). This precipitate was filtered off, washed with acetone and then stirred in a HCl (3 M)/EtOAc biphasic mixture until all the precipitate had dissolved. The organic layer was then separated, washed

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† Single-crystal X-ray analysis.

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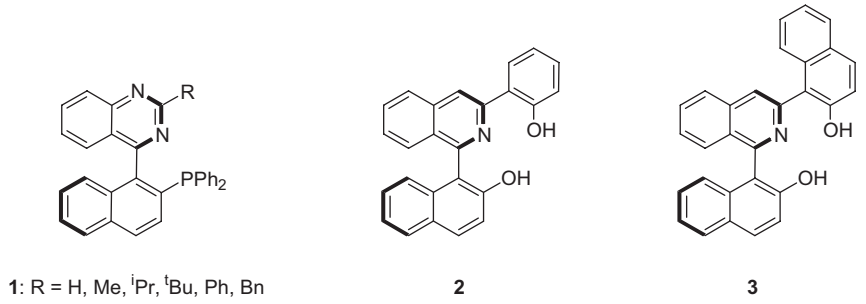
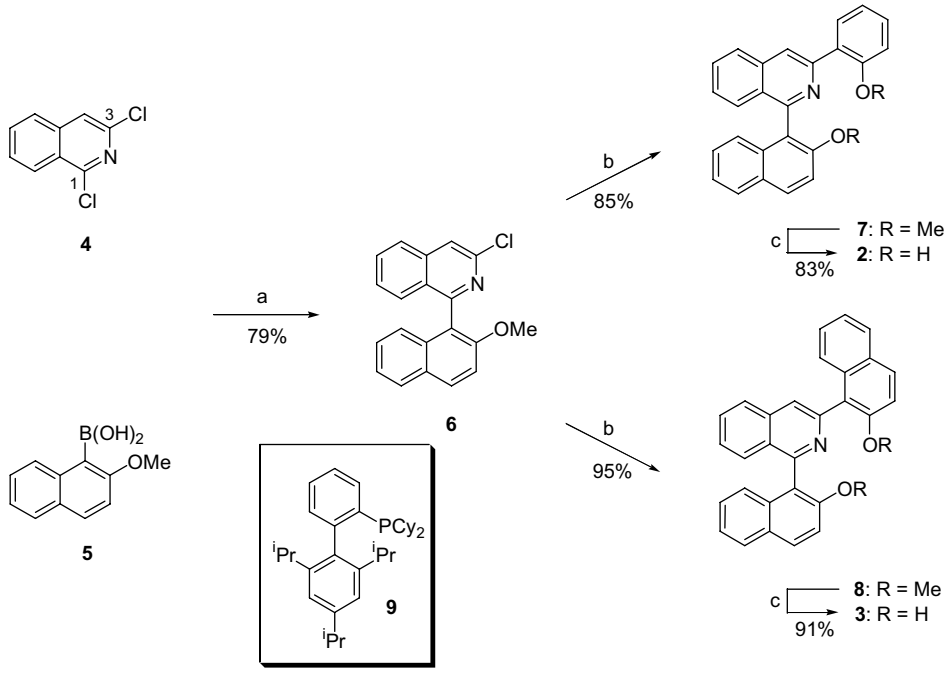


Figure 1.



Scheme 1. Reagents and conditions: (a) $Pd(PPh_3)_4$ (5 mol%), CsF, DME, 90 °C, 18 h; (b) 2-methoxyphenyl or 2-methoxynaphth-1-ylboronic acid, $Pd(OAc)_2$, XPhos, K_3PO_4, THF, 80 °C, 18 h; (c) 48% HBr, AcOH, 140 °C, 18 h.

with brine, dried over Na_2SO_4, filtered and evaporated in vacuo to yield (*R*)-**2** in 36% yield with 90% ee. The mother liquor was worked up in a similar manner to give the opposite enantiomer in 56% yield and 88% ee. This resolution process could be repeated with the enantioenriched (*R*)-**2** and (*S*)-**2** to yield each enantiomer in 99% and 98% ee, respectively. A single crystal of the molecular complex (*R*)-(+)-**2**·**10** was grown by slow diffusion of pentane into an Et_2O solution at room temperature. X-ray crystal analysis revealed formation of an intramolecular hydrogen bond between the phenol hydrogen and the isoquinoline nitrogen of (*R*)-**2** and an intermolecular bond between the naphthol hydrogen and the chloride anion (Fig. 2). Crystallographic data for (*R*)-(+)-**2**·**10** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 266371.

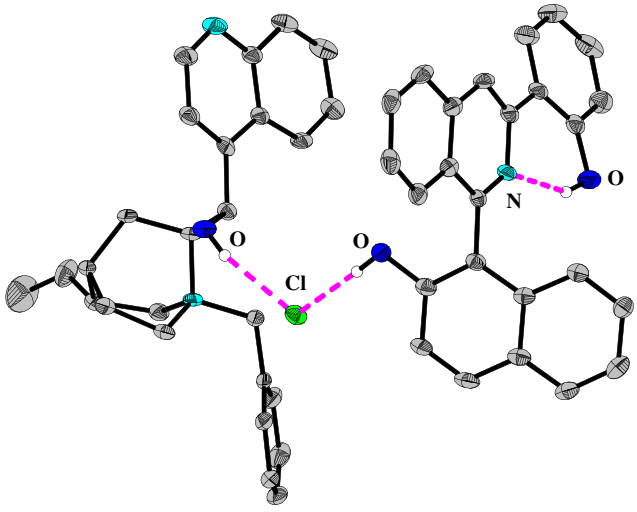
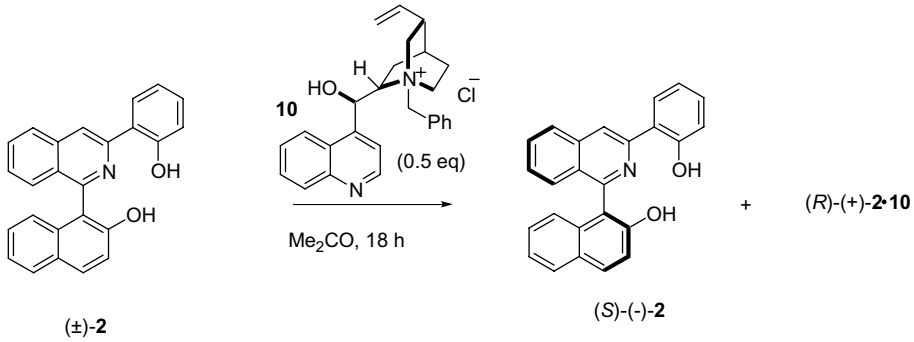
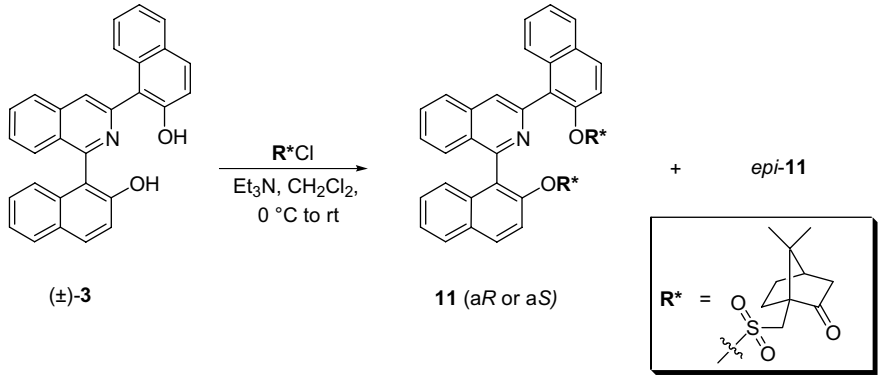


Figure 2.

Unfortunately, ligand **3** could not be resolved using this method as no precipitate formed when it was stirred in acetone in the presence of *N*-benzylcinchonidinium chloride. Racemic **3** was therefore converted to its bis((1*S*)-camphor-10-sulfonate) (Scheme 3) using the procedure of Chow et al.[16] The epimers formed were separated by column chromatography over silica using pentane–



Scheme 2.



Scheme 3.

EtOAc (3:1) to yield four fractions, the yields and diastereomeric excesses for which are shown in Table 1. The epimers were then converted to enantiomerically enriched **3** by stirring in 50% w/v NaOH at 0 °C, followed by acidic work-up and extraction into CH_2Cl_2.

Following the protocol of Cagle and Eyring, the rotational energy barrier about the biaryl axis of **3** was determined.[17] The racemisation of an individual enantiomer was studied in benzene at a range of temperatures, and the rotational energy barrier was calculated to be ~88 kJ/mol obtained from Arrhenius and Eyring plots (Fig. 3).

Extrapolation of both Arrhenius and Eyring plots indicated that an enantiomerically pure sample of biaryl **3** would lose 1% of its optical purity after 37 h at room temperature (20 °C), implying a racemisation half-life of over 105 days. Due to the structural analogy between **2** and **3**, it may be assumed that **2** displays a similar racemisation rate.

In conclusion, a simple route to two new tridentate isoquinoline-containing ligands has been developed. Both ligands were resolved and the absolute configuration

Table 1.

	Yield (%)	De (%)
1	17	98 (**11**)
2	24	79 (**11**)
3	14	84 (*epi*-**11**)
4	21	95 (*epi*-**11**)

T/K	10^7 k_{racem}/s^{-1}	Eyring functions	
313	7.5 (0.4)	$\Delta H^{\#}$/kJ mol^{-1}	86 (10)
328	41 (4)	$\Delta S^{\#}$/ J mol^{-1}K^{-1}	-88 (29)
348	230 (3)	$\Delta G^{\#}$/ kJ mol^{-1}	112 (9)
363	860 (12)		
		Arrhenius parameters	
		E_a/kJ mol^{-1}	89 (10)
		ln(A/s^{-1})	20 (4)

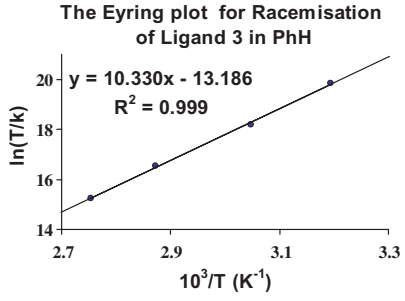


Figure 3. Figures in parentheses are errors calculated for 95% confidence level.

of **2** was assigned by X-ray crystallography. Racemisation studies were carried out to determine the barrier to rotation about the central biaryl axis of **3**. Both ligands are currently being investigated to assess their suitability as ligands for asymmetric catalysis.

Acknowledgements

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