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Synthesis, separation and structure determination of atropisomeric ketimines: precursors of new potential chiral ligands and phase-transfer catalysts

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ABSTRACT

Sterically crowded chiral biaryl ketimines have been prepared via nucleophilic addition onto a substituted benzonitrile or 8-cyanoquinoline and subsequent treatment of the resulting methylenimines either with methyl iodide, or with a chiral primary amine. Atropisomerism due to the hindered rotation of the aryl groups about the C–C bond adjacent to C=N has been evidenced in all cases. Physical separation and full characterisation (NMR and X-ray analysis) of atropisomeric imines have been accomplished.

1. Introduction

Asymmetric phase-transfer catalysis (APTC) has become an attractive concept as it allows us to perform organic reactions under mild and safe conditions using inexpensive reagents. A large number of APTC reactions employing chiral catalysts are described in the literature[1] prominently featuring a structurally rigidified cinchona alkaloid system.[2] Such a performance is somewhat intriguing and has triggered the interest of several research groups either to understand the chiral induction mechanism or to design and synthesise sterically and electronically tunable catalysts. Among the non-alkaloid chiral catalysts reported, chiral C_2-symmetric binaphthyl ammonium and C_2-symmetric guanidinium salts have been found to be of great value.[3] In general, enantioselective catalysis requires catalysts possessing multipoint interaction with the substrate in the transition state for good chiral induction. A survey of the literature reveals that this evidence applies to APTC and that, in most cases, the reaction temperature remains a controlling factor for stereoselectivity. Over the course of these interesting contributions, we became interested in a rational design of new chiral phase-transfer agents and ligands.

We have reported earlier the sterically hindered and remarkably stable ketiminium salt **1** (Fig. 1) as being a versatile phase-transfer catalyst.[4] The catalytic properties of **1** were investigated in the C-alkylation of a glycine-derived imine in non-chiral conditions. The alkylation of this substrate was chosen as a model, and it has become a reference, which gives an indication about the performance of newly designed chiral phase-transfer catalysts. Iminium salt **1** displayed comparable catalytic properties with respect to previously described phase-transfer catalysts such as onium salts,[5] crown ethers[6] or metal complexes.[7] The asymmetric version of the catalytic reaction required the design and synthesis of the required hindered chiral iminium salts.[8] In this context, some possibilities for the introduction of chirality have been envisaged depending on (1) the position of the chiral vector on the imine framework (**2** or **3** and **4**, Fig. 1) and (2) the potential chirality due to restricted rotation.[9]

2. Results and discussion

The nucleophilic addition of 1-naphthyllithium onto (*R*)-2-(*sec*-butoxy)-benzonitrile **5** and subsequent quenching of the lithioimine intermediate with methyl iodide (Scheme 1) gave the chiral *N*-methyl imine **6**, a precursor of iminium salt **2**. The quenching conditions have been found to determine the number of observed stereoisomers of imine **6**.

Thus, when *N*-methylation was conducted at low temperature (−50 °C kinetic conditions), ^{13}C NMR of a deuteriochloroform solution of the crude product showed two sets of imino ^{13}C=N signals at δ (168.6, 169.7) and (176.9, 177.1). The chemical shift difference of 10 ppm indicates the presence of a pair of both *syn* and *anti* geometrical configurations.[10] The *N*-methyl group displayed, four different signals in the ^{1}H NMR 300 MHz spectra at δ 3.38, 3.33, 3.07 and 2.79 ppm with a slight doubling of the two upfield signals (7%, 64%, 13% and 16%, respectively) and thus confirmed the presence of

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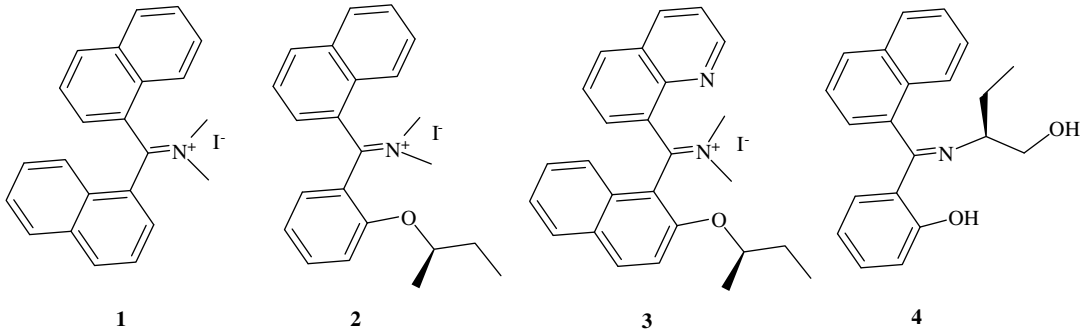
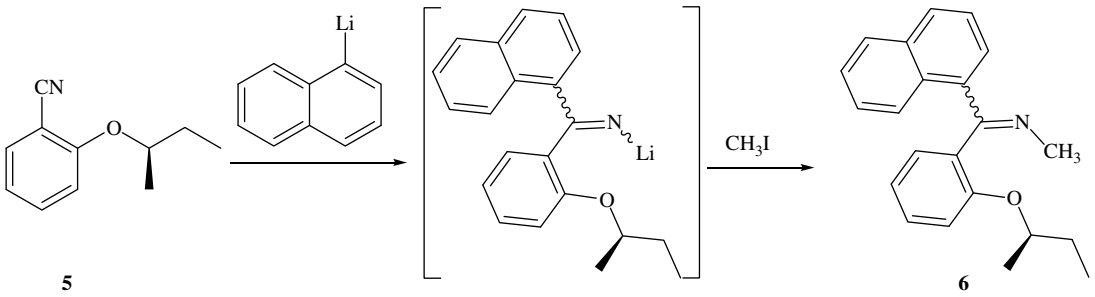


Figure 1.



Scheme 1.

more than two diastereoisomers. Interestingly, when the deuteriochloroform solution was heated to 60 °C for 15 min and allowed to cool to room temperature, the recorded ^{1}H NMR spectrum showed the complete disappearance of the N–CH_3 signal at 3.38 ppm in favour of the most upfield shifted one. On the other hand, the proportions of the other individual signals remain unchanged. This observation indicates, that the steric environment imposed by the aromatic groups in **6** seems to reach the level of the required hindrance that allows the ambient temperature detection of atropisomeric structures for both *syn* and *anti* configurations. However, it is not large enough to inhibit interconversion, at least for one isomer.

The atropisomerism about the C= N bond has previously been reported by Boyd and Jennings in the kinetic and mechanism studies of the isomerisation of chiral and achiral *N*-alkyl imines derived from aryl alkyl ketones.[11] Further conformational investigation by dynamic NMR and molecular mechanic calculations, described by Lunazzi et al.,[12] provided interesting and reliable information with regard to the stereomutation pathway of such enantiomers.

Fortunately, methylation of the lithioimine intermediate at 20 °C provided in excellent yield the crude imine **6** whose ^{13}C NMR and ^{1}H NMR spectra showed only the first pair of ^{13}C=N signals (168.5, 169.7) and the two N–CH_3 signals at 3.33 and 3.07 ppm (ca. 8:2). It is worth emphasising that TLC (2:8 EtOAc/heptane) of the crude mixture showed imine **6** as two separate spots with a small ΔR_f. Careful chromatographic separation helped us to isolate the most eluted isomer **6a** which crystallised upon solvent removal. On the other hand, isomer **6b** could be recovered as a colourless oil, which does not crystallise upon standing. ^{1}H and ^{13}C NMR unambiguously revealed that both components have the imine **6** skeletal and that isomer **6a** showed N–CH_3 and ^{13}C=N at δ 3.33 and 168.5 ppm, respectively. The pure fractions of **6b** exhibited ^{13}C=N and N–CH_3signals at 169.7 and 3.07 ppm, respectively, but the contribution from isomer **6a** reached ca. 10% after 24 h of standing in solution at ambient temperature (Fig. 2).

Furthermore, heating a deuteriochloroform solution of pure **6a**, which is stable as a solid, resulted in the progressive appearance of isomer **6b** until equilibrium was reached (**6a**:**6b** = 6:4) after 48 h (Fig. 2d). Isomerisation of the same solution at room temperature did not exceed 10% after one week. On the other hand, a *syn*-structure could be found from the X-ray analysis of a crystal of pure **6a** grown in diluted heptane/ether (3:1) (Fig. 3).[13] Also noticeable from this structure is the out of plane position of both aryl moieties, (C10, C11, C13, C18 = −61.5) and (C1, C10, C11, C13 = −48.5), suggesting that their rotation may imply atropisomerism.

Complementary structural information on the stereoisomeric nature of components **6a** and **6b** in solution came from the high-field NMR investigation. Therefore, classical high-field 500 and 600 MHz homo- and hetero- nuclear experiments were undertaken in order to assign all the protons and sp^2 carbons of the individual isomers. Of particular importance was the downfield shift (8.52 ppm) noticed for H8 (numbering according to the corresponding carbon atom of the X-ray spectrum) of the naphthyl group of isomer **6a**. The same proton is shifted 0.7 ppm upfield in isomer **6b** (Fig. 2a and b). In the same way, the *ortho*-protons of the phenoxy group H14 display signals centred at 7.15 ppm for isomer **6a** and 7.86 ppm for isomer **6b**. This cross shift can be related to the orientation of the two rings relative to each other. The absence of a NOESY correlation between the aromatic protons in both cases, is in line with the X-ray results and in accordance with conformations in which the naphthyl and the phenyl groups are twisted out of the imino plane. More importantly, the intense NOESY correlation observed for both isomers **6a** and **6b** between N–CH_3 and the *ortho*-protons of the phenoxy group H14 clearly indicates their spatial proximity and the orientation of the *N*-methyl group *cis* to the chiral aryl moiety, suggesting stereoisomers with a *syn*-configuration for both **6a** and **6b** (Fig. 4). Conversely, only a faint correlation between N–CH_3 and the naphthyl group of **6a** was observed, suggesting that, in chloroform, the alkyl chain is not affected by the naphthyl group proximity.

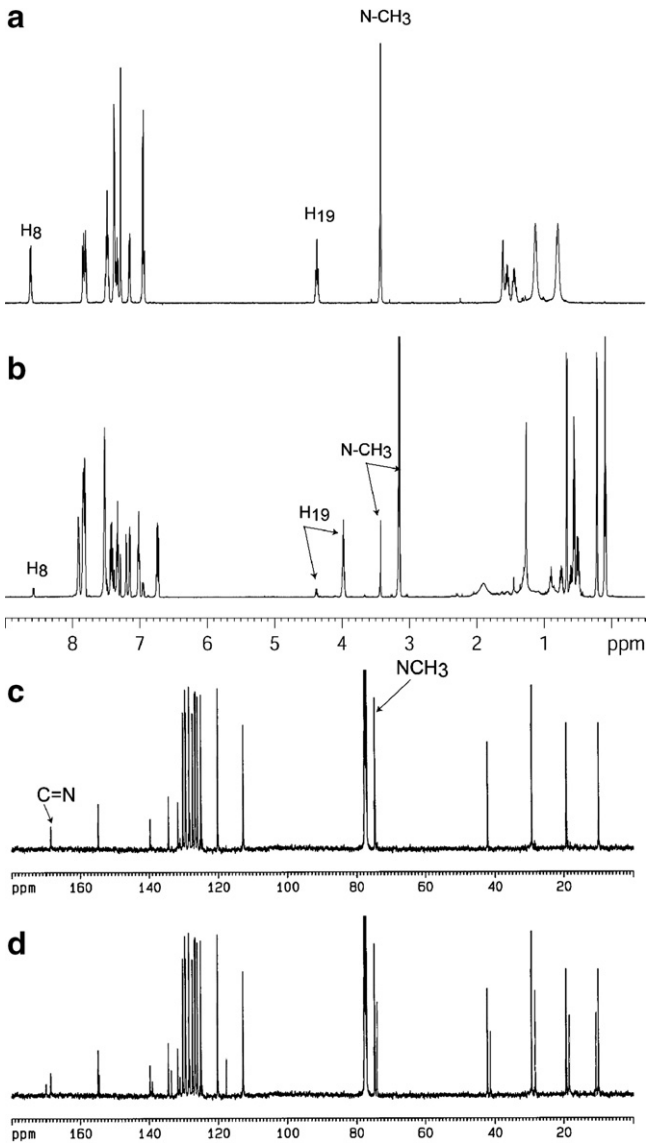


Figure 2. (a) ^{1}H NMR of pure **6a**; (b) ^{1}H NMR of **6b** with progressive contribution of **6a**; (c) ^{13}C NMR of pure **6a**; (d) ^{13}C NMR of pure **6a** after 48 h of heating.

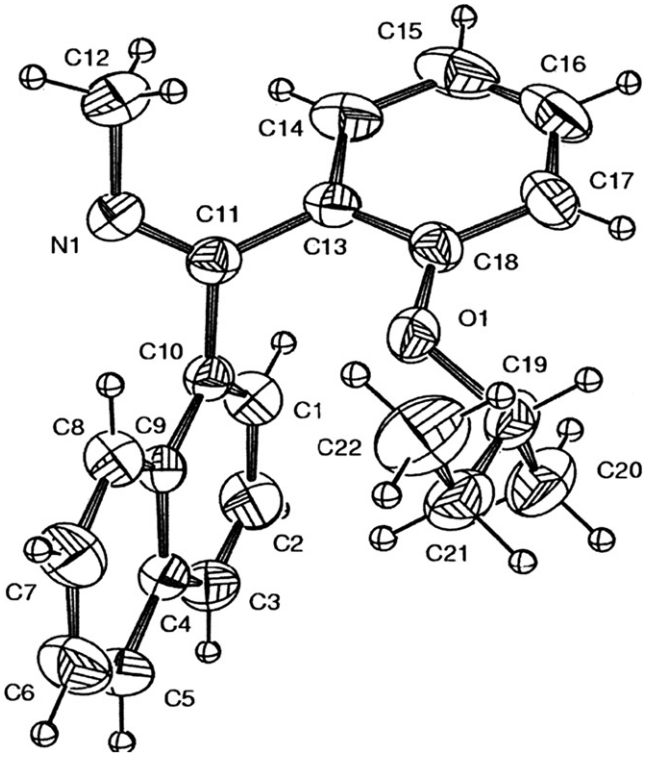


Figure 3. X-ray crystallographic structure of pure **6a**.

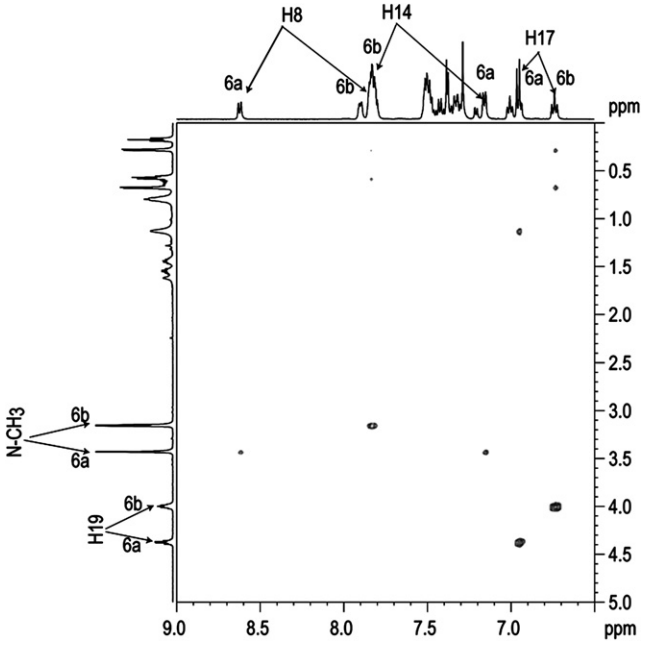


Figure 4. NOESY chart of a mixture of isomers **6a** and **6b** showing correlation between NCH_3–H(14) and H(17)–H(19).

Another point of concern is the strong correlation between H17 and H19 in both **6a** and **6b**. For isomer **6b**, the NOESY experiment allowed us to gain insight into the space orientation of the chiral moiety since two clear sets of correlations are observed with the aromatic protons (Fig. 5). We suggest that the downfield shift observed for H8, as well as the upfield shift of the chiral auxiliary protons, are the results of the rotation of the naphthyl group (variation of the dihedral angle C10, C11, C13, C18), which brings the alkyl chain in a closer proximity to the naphthyl ring current. On the other hand, the slight doubling observed for the N–CH_3 group can be attributed to the existence of two stable rotamers, on the NMR timescale, which are different only as regards the orientation of the alkyl side chain referring to the naphthyl group because of a switching orientation around H19–H17.

The X-ray and NMR studies prompt us to conclude that components **6a** and **6b** are conformers of the same geometric stereoisomer *syn*. Therefore, interconversion noticed in ageing or heating solutions can be attributed to conformational equilibrium related to slow motion of the naphthyl about the chiral axis C10-C11, and not to *syn* → *anti* isomerisation (Fig. 6).

Subtraction of **6a** and **6b** signals from the ^{1}H and ^{13}C NMR spectra of the kinetically formed mixture allowed us to assign the non-separated *anti* stereoisomers. It has to be mentioned that the upfield *N*-methyl signal shows a slight doubling similar to the one observed for the same group of isomer **6b**. This phenomenon can also be attributed to the existence of stable isoenergetique conformations in solution. Therefore, the fast isomerisation upon heating of the kinetically formed crude mixture, together

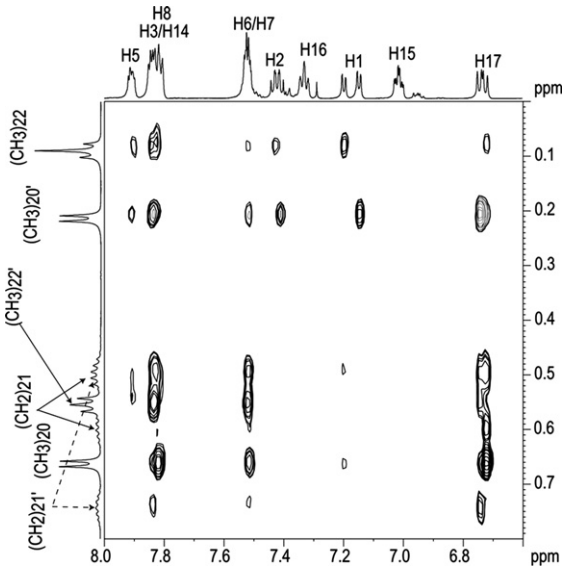


Figure 5. NOESY chart expansion for pure **6b** underlying correlations between the alkyl chain and the naphthyl group protons.

with the unchanged individual proportions of **6a** and **6b**, evidenced both the absence of *syn* → *anti* isomeriztion and the presence of *anti* atropisomers. These observations are in accordance with the earlier reported conformational studies on hindered imines, which concluded that barrier to interconversion of atropisomers is significantly lower than the barrier to *syn* → *anti* isomerisation.[12]

The observed stereoisomer distribution, depending on methyl iodide-quenching conditions, is obviously related to the structure of the intermediate lithioimine species in solution. Thus, under thermodynamic conditions, exclusive formation of the *syn* stereoisomers **6a** and **6b** implies alkylation *cis* to the phenoxy group. This requires the nitrile face differentiation during the nucleophilic addition conducting to the less-hindered lithioketimines. A possible explanation of the resulting stereoselectivity is the rigidification under thermodynamic conditions of the intermediate lithioimine by further intramolecular electronic interaction between oxygen and lithium atoms. The study of molecular models helped to notice that the chiral auxiliary orientation, referring to the naphthalene moiety, controls the pseudocycle formation through favourable interaction with oxygen *pro R* doublet in both cases (Fig. 7). Under kinetic conditions, the formation of anti isomer could be the result of methylation of open species.

This first result confirms that isolation of stable rotamers of ketimines is feasible when a sufficient hindrance is provided. In an attempt to increase the stability, we came to the more hindered ketimine **8**, arguing that the quinoline nitrogen ring could contribute to favourable electronic interactions. The precursor of iminium salt **3** was prepared in the same way by the addition of the chiral 1-naphthyllithium derivative onto 8-cyanoquinoline and subsequent quenching with methyl iodide (Scheme 2).

Interestingly, in this case, the quenching conditions have not been found to control the nature and number of observed stereoisomers. After the reaction was complete, TLC (1:9, EtOAc/Heptane) of the crude mixture showed two well-separated spots. ^{1}H NMR of each isolated isomer showed the N–CH_3 signals at δ = 3.99 ppm for the most eluted **8a** and δ 3.86 ppm for the less eluted isomer **8b**. Alternatively, proton H8 of the naphthyl group of **8a** is shifted 1 ppm upfield compared to the same proton of **8b** (7.09 vs 8.12 ppm). Again, careful NMR investigation revealed that the methyl group faces the naphthyl group in both cases, and by analogy with the preceding results, we postulate the presence of two rotamers of one single geometric isomer with a *syn* configuration. Additionally, no trace of isomerisation between **8a** and **8b** conformers was observed. However, while **8b** is stable upon heating, the ^{1}H NMR of an ageing solution of **8a** showed the complete transformation of the N–CH_3 signal, which split into three sets of multiplets between 3.06 and 3.97 ppm.

Chiral ketimine **4**, featuring the N-linked chiral moiety, was prepared following an adapted transimination protocol[15] between 2-(*S*)-aminobutanol and 1-naphthyl-1-(2-hydroxyphenyl)-methylidenamine **9** (Scheme 3).

Imine **4** has been isolated as a crystallised mixture of two inseparable isomers (7:3). While stable in the crystallised form, isomerisation in $CDCl_3$ to a 1/1 mixture has $t_{1/2}$ = 1 h at 27 °C. Highfield NMR spectroscopy (^{1}H, ^{13}C, HMQC, COSY and NOESY) helped to differentiate two sets of naphthyl protons and outlined an intense NOESY effect between the naphthyl group and the hydroxyalkyl chain protons (Fig. 8), which clearly evidenced the geometric *anti*-configuration. The correlations observed for both isomers

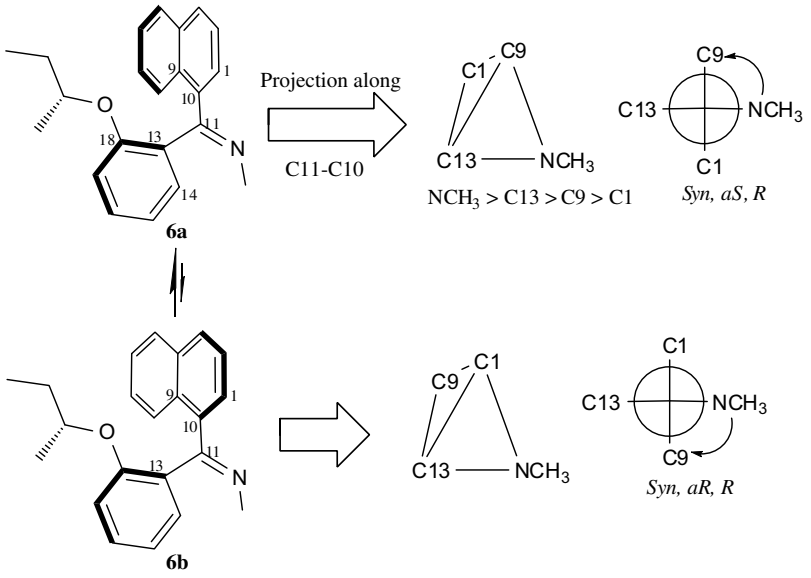


Figure 6. Interconversion **6a**–**6b** by rotation of the naphthyl group and configuration assignment.[14]

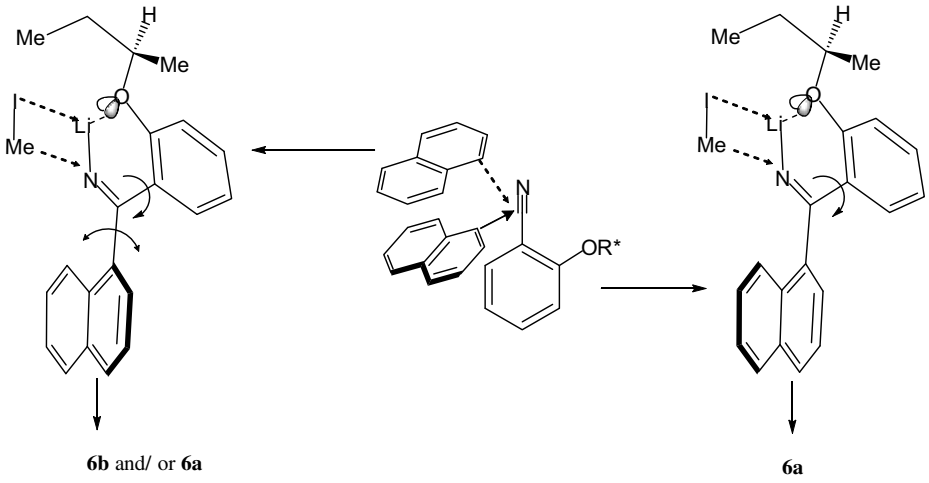
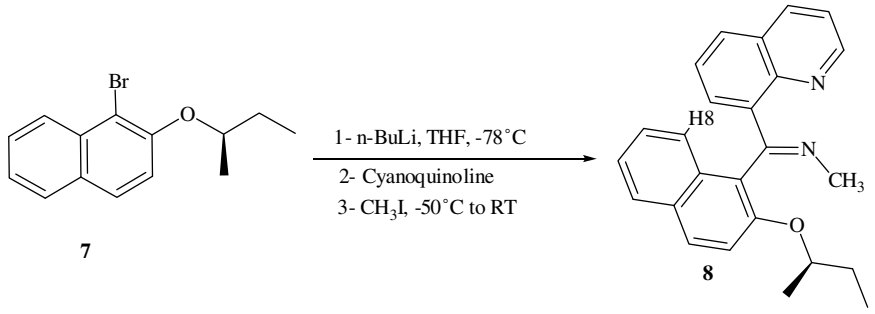
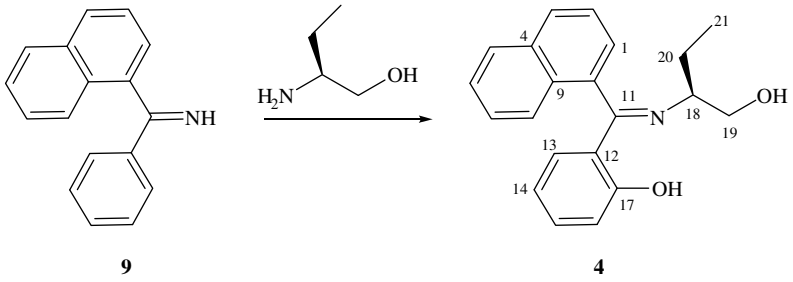


Figure 7. Possible lithioimine intermediate species in THF solution under thermodynamic conditions.



Scheme 2.



Scheme 3.

between H16 of the phenol moiety and the hydroxymethyl, and the minor one between H13 and H18, are probably due to the spatial proximity of the two hydroxy groups.

These NMR observations are consistent with the results of semi-empirical AM1 calculation.[16] First, the energy barrier computed for the *syn*/*anti* interconversion via trigonal *N*-inversion has been determined to be 20.7 kcal/mol. The sp^2 N-inversion is the unique pathway considered since tautomerisation and acid-catalysed mechanisms do not apply for imine **4**. Secondly, the energetic profile associated with the naphthyl and phenol rotation about the respective adjacent C–C bonds (variation of the dihedral angles α = [C1, C10, C11, C12] and α' = [C13, C12, C11, C10], respectively) for both *syn*- and *anti*-stereoisomers, showed the lowest minima for the *anti*-imine owing to naphthyl rotation (−12.86 and −14.79 kcal/mol) (Fig. 9). The interconversion process between the two stable conformers requires a free energy of activation of 13 kcal/mol. Moreover, rotation of the phenol group for the same geometric isomer showed a less stable conformer (−14.52 kcal/mol) for which the hydroxy group is located close to the nitrogen. Again, these studies allowed us to conclude that atropisomerism is due to the naphthyl-group slow motion.

Finally, independent methylation of the separated isolated-conformers (**6a**, **6b**) and (**8a**, **8b**) in acetonitrile led to iminium salts **2** and **3**, respectively. It has to be noticed that each pair led to two iminium salts with a different specific rotation. On the other hand, ^{1}H NMR spectra were identical except for the methyl groups which displayed two pairs of slightly doubled singlets attributable to a partial conformational interconversion during the quaternisation process. The difference of specific rotations for the salts of each pair indicates that this interconversion is slow. Atropisomeric stability therefore requires design of more sterically hindered chiral iminium salts.

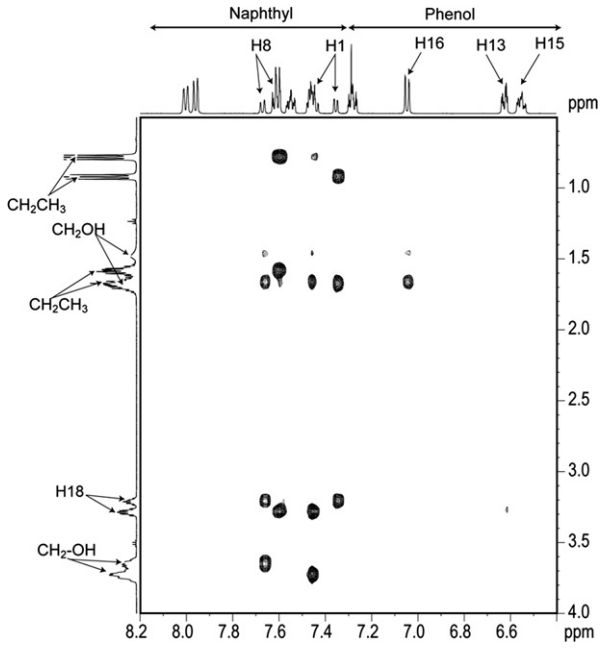


Figure 8. NOESY chart of isomers of imine **4** evidencing the *anti*-geometric configuration and the presence of two rotamers.

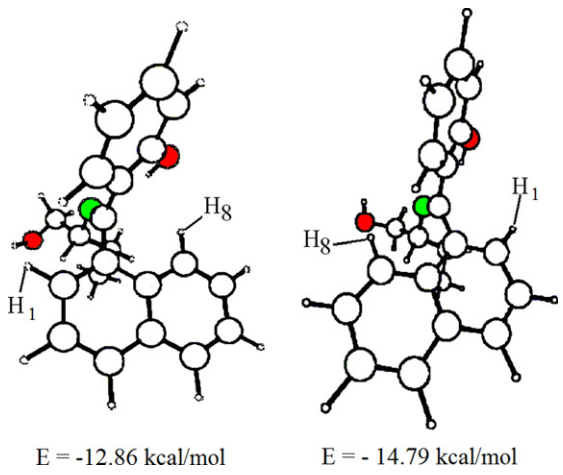


Figure 9. Computer generated structure of the stable rotamers of *anti* imine **4**.

The catalytic properties of the four isolated chiral iminium salts and ligand **4** were thereafter investigated in the asymmetric allylation of benzophenone imine **10** under L/L and S/L phase-transfer conditions, respectively (Scheme 4).

3. Conclusion

While only a 5% ee was observed with iminium salts, the in situ generated chiral metal complex derivative of **4** revealed enantioselection in the α-allylation with ees reaching 17%. Optimisation of enantiomeric excess necessitated the incorporation of crowded biaryls for hindered rotation and chiral auxiliaries, which differentiate the iminium salts faces for better ion-pairing. This will certainly be beneficial for both atropisomeric homogeneity and the steric environment around the metal coordination sphere or the charged nitrogen atom.

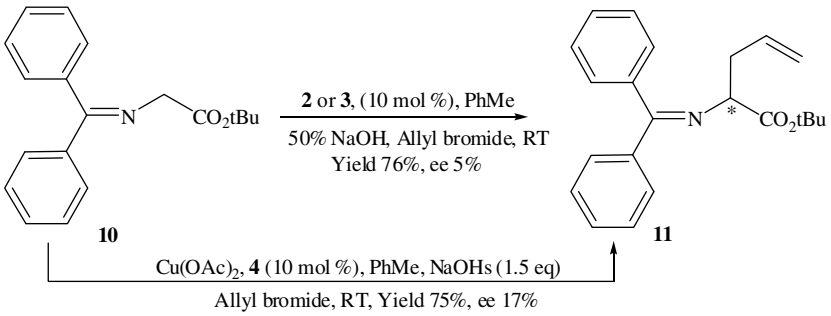
4. Experimental

4.1. General

Uncorrected melting points were determined on a Büchi 510 instrument. Optical rotations were determined at 25 °C on Perkin–Elmer 341 polarimeter using the sodium D line and concentrations are given in g/100 ml. IR spectra were recorded on Perkin–Elmer 16 PC FT instrument (in cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on Bruker AC 300 spectrometer at 300 and 75 MHz, respectively.1D and 2D NMR experiments were performed at 500 or 600 MHz on Bruker Avance DMX 500 or Bruker Avance DMX 600. Chemical shifts are in ppm referenced to TMS in $CDCl_3$. Mass spectra were determined on ATI Unicom automass spectrometer and ThermoFinnigan SSQ 7000 GC/MS. Elemental analyses were performed on Thermo Finnigan Elementary Analyser Flash EA 1112. Analytical thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} glass plates (0.25 mm) and compounds were visualised by UV light (254 nm) or phosphomolybdic acid–ethanol (22.1 g–180 ml) spray. Column chromatography was carried out on Merck Kieselgel. Chiral HPLC was performed on Kontron 420 and JASCO 875 equipped with Whelk-01 column, eluent: hexane/*i*PrOH = 90:10, 1 ml/min, retention times: **11** (*S*): 5.37 min; **11**®: 7.46 min.[5b] Chemicals were purchased from either Sigma–Aldrich or Fluka and used as received. Solvents were distilled according to known procedures.

4.2. (*R*)-2-*sec*-Butoxybenzonitrile 5

To a solution of 2-cyanophenol (1.54 g, 13 mmol), triphenylphosphine (3.7 g, 14.14 mmol) and 2-(*S*)-*sec*-butanol (1 ml, 14.1 mmol) in anhydrous ether (60 ml) was slowly added with stirring a solution of diisopropylazodicarboxylate (DIAD) (2.84 g, 14.1 mmol) in anhydrous ether (15 ml). The resulting suspension was stirred at room temperature for 3 h, after which the white precipitate was filtered off and the solvent was removed in vacuo. The residue was distilled under low pressure to give compound **5** as colourless oil (2.35 g, 80%) Eb. 160–163 °C/10 mmHg; [α] = −54 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.87 (t, *J* = 6.5 Hz,



Scheme 4. Allylation of Schiff base 10 under phase-transfer conditions.

3H), 1.23 (d, J = 6.0 Hz, 3H), 1.55 (m, 2H), 4.3 (m, 1H), 6.69–7.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 9.1, 18.6, 28.6, 76.2, 102.3, 113.3, 116.3, 120.0, 133.3, 133.9, 159.7; IR (neat): 1263, 1462, 1270, 1590.3, 2226.9, 2935.9, 2974.4; EIMS 175(M^+), 146, 120, 91, 57.

4.3. 1-Bromo-2-((*R*)-*sec*-butoxy)naphthalene 7

Following the above procedure using 1-bromo-2-naphthol instead of 2-cyanophenol, compound **7** was isolated as a colourless oil (94%); Eb. 140 °C/0.8 mmHg; $[\alpha] = -2.1$ (c 0.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.95 (t, J = 8.7 Hz, 3H), 1.26 (d, J = 9.6 Hz, 3H), 1.60 (m, 2H) 4.32 (m, 1H), 7.11–8.39 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 10.2, 20.0, 29.6, 78.6, 117.7, 124.8, 126.8, 127.0, 128.3, 129.0, 134.0, 134.3, 156.5; IR (neat): 945, 1242, 1266, 1462, 1593, 1624, 2932, 2971, 3065; EIMS 279(M^+), 255, 199, 172, 157, 145, 115, 57.

4.4. *N*-Methyl-1-(2-(*R*)-*sec*-butoxyphenyl)-1-(1-naphthyl) methylenimine 6

To a solution of 1-bromonaphthalene (935 mg, 4.54 mmol) in anhydrous ether (5 ml) was added n-BuLi (1.2 equiv) at −78 °C under an N_2 atmosphere. The temperature was allowed to rise to −50 °C for a complete halogen–metal exchange before a solution of **5** (1.02 g, 5.4 mmol) in anhydrous ether (1 ml) was added. The reaction mixture was then left to warm up to ambient temperature under stirring.

4.4.1. N-Methylation at 20 °C

Methyl iodide (920 mg, 1.2 equiv) was added to the lithioimine and the resulting mixture was left to react for 15 min, after which TLC (2:8 EtOAc/iPrOH) showed imine **6** as two spots (R_f = 0.55 and 0.6), the most eluted atropisomer **6a** being the major component. The solvent was removed under reduced pressure, after which ether (5 ml) was added, the suspension was filtered off and the filtrate was concentrated to dryness. The pure-collected column chromatography (2:8 EtOAc/Heptane) fractions afforded a first crop of **6a** as a white powder (930 mg). A second crop of isomer **6a** (78 mg) crystallised out upon cooling overnight. Heptane washing and subsequent drying provided pure **6a** (1.05 g, 73%); mp 135–137 °C; $[\alpha]_D = -59$ (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.74 (m, 3H, H22), 1.13 (m, 3H, H20), 1.52 (m, 1H, H21), 1.54 (m, 1H, H21), 3.41 (s, 3H, N–CH_3), 4.38 (m, 1H, H19), 6.96 (m, 2H, H15,17), 7.15 (d, J = 6.5 Hz, 1H, H14), 7.34 (d, J = 6.4 Hz, 1H, H16), 7.38 (m, 2H, H1,2), 7.5 (m, 2H, H7,6), 7.81 (d, J = 6.5 Hz, 1H, H3,), 7.84 (d, J = 6.5 Hz, 1H, H5), 8.61 (d, J = 6.5 Hz, 1H, H8); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 10.1(C22), 19.3 (C20), 29.4 (C21), 42.2 (C12), 74.7 (C19), 112.8 (C17), 120.2 (C15), 125.0 (C1), 126.0 (C6), 126,6 (C7), 126.8 (C8), 127.4 (C2), 128.2 (C4), 128.4 (C5), 129.4 (C3), 129.6 (C14), 130.2 (C16), 131.7 (C9), 134.3 (C10), 139.6 (C13), 154.8 (C18), 168.6 (C11); IR (KBr): 1263, 1462. Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.48; H, 7.32; N, 4.38.

The washing filtrate and the impure fractions were combined, after which the solvent was removed under vacuo, and a second column chromatography provided pure fractions of isomer **6b** as a colourless oil (330 mg, 23%); $[\alpha]_D = -32$ (c 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 0.1 (t, J = 7.7 Hz, 1.5H, H22), 0.21 (d, J = 5.8 Hz, 1.5H, H20′), 0.5 (m, 0.5H, H21′ + 0.5H, H21), 0.55 (t, J = 7.7 Hz, 1.5H, H22′), 0.59 (m, 0.5H, H21), 0.66 (d, J = 5.8 Hz, 1.5H, H20), 0.74 (m, 0.5H, H21′), 3.14 and 3.15 (2s, 3H, N–CH_3), 3.9–4.05 (m, 1H, H19), 6.72 and 6.73 (2d, J = 8.4 Hz, 1H, H17), 6.9–7.02 (m, 1H, H15), 7.14–7.2 (2d, J = 7.0 Hz, 1H, H1), 7.3–7.35 (dd, J = 7 and 8.4 Hz, 1H, H16), 7.37–7.45 (m, 1H, H2), 7.5–7.55 (m, 2H, H6,7), 7.8–7.84 (m, 3H, H3,8,14), 7.85–7.87 (m, 1H, H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 11.0 (C22), 18.5 (C20), 28.0 (C21), 41.9 (C12), 74.0 and 73.9 (C19), 112.5 and 113.0 (C17), 120.2 (C15), 124.5 (C1), 125.5 (C2), 126.6 (C6), 127.0 (C7), 127.8 (C8), 128.6 (C3), 128.7 (C5), 131.1 (C14), 132.0 (C13), 133.5 and 133.3 (C16), 137.7 and 137.9 (C10), 139.0 (C9), 156.5 and 156.5 (C18), 169.94 and 169.98 (C11); IR (neat): 1628; EIMS 317 (M^+), 246, 217, 154, 127.

4.4.2. N-Methylation at −50 °C

The lithioimine was cooled to −50 °C and methyl iodide (1.2 equiv) was added at once. After 2 h of stirring between −50 °C and −30 °C TLC (2:8, EtOAc/heptane) showed two heavy and less resolved spots both having roughly equal intensities. Following the above work-up, crude mixture of diastereoisomers of imine **6** was isolated as brownish oil (95%). Data for the non-separated *anti* stereoisomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.1 (br s, 3H), 1.3 (br s, 3H), 1.72 (m, 2H), 2.79 and 3.38 (2s, 3H), 3.9 (m, 1H), 6.59–7.95 (m, 9H), 8.01–8.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.6, 22.0, 30.3, 43.0, 71.5, 113.9, 115.7, 122.0, 125.2, 126.2, 126.4, 126.5, 127.1, 128.6, 129.4, 131.7, 132.5, 133.9, 134.1, 135.6, 155.1, 176.9, 177.1.

4.5. *N*-Methyl-1-(8-quinolinyl)-1-(2-(*R*)-*sec*-butoxynaphtyl)-methylenimime 8

Following the above halogen–metal exchange procedure and N-methylation at −50 °C, compounds **7** (1.13 g, 4.05 mmol) and 8-cyanoquinoline (620 mg, 4.04 mmol) gave imines **8a** (535 mg, 36%) and **8b** (370 mg, 25%).

Data for **8a**: yellow powder; mp 120–122 °C; R_f = 0.18 (1:9 EtOAc/cyclohexane); $[\alpha]_D = -18.6$ (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):1.03–01.25 (t, J = 7.9, 3H), 1.26–1.33 (d, J = 8.1, 3H), 1.55–1.72 (m, 1H), 1.74–1.86 (m, 1H), 3.99 (s, 3H), 4.40–4.49 (m, 1H), 7.14–7.17 (m, 2H), 7.22–7.29 (m, 1H), 7.3–7.35 (m, 1H), 7.37–7.55 (m, 2H), 7.67–7.85 (m, 4H), 8.12 (m, 1H), 10.5 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 9.1, 19.3, 29.2, 31.9, 61.0, 117.5, 117.7, 119.2, 121.3, 123.3, 123.9, 124.1, 125.6, 125.7, 125.8, 125.9, 126.0, 127.5, 127.6, 127.6, 128.6, 128.7, 134.3, 153.7, 167.5; IR (KBr) 1211, 1424, 1558, 3682; EIMS 368 (M^+), 354, 298, 268, 211, 169,155, 83, 58. Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60. Found: C, 81.52; H, 6.55; N, 7.63.

Data for **8b**: a colourless oil R_f = 0.14; $[\alpha]_D = -10.5$ (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.39–0.5 (m, 3H), 0.80–1.02 (m, 5H), 3.86 (s, 3H), 4.0–4.20 (m, 1H), 7.05–7.15 (m, 3H), 7.25–7.35 (m, 3H), 7.4–7.55 (m, 2H), 7.75–7.9 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 9.2, 19.4, 29.3, 31.9, 61.1, 117.7, 119.3, 123.4, 124.0, 124.1, 125.0, 125.6, 125.7, 125.8, 125.9, 126.0, 127.0, 127.6, 128.6, 128.7, 129.1, 134.4, 153.6, 167.5; IR (neat): 1211, 1424, 1514, 3682; EIMS 368 (M^+), 354, 298, 268, 211, 169,155, 83, 58.

4.6. 1-(1-Naphthyl)-1-(2-(1-hydroxyphenyl))methylenimine 9

After a complete halogen–metal exchange using 1-bromonaphthalene (1.1 g, 5.378 mmol), 2-cyanophenol (230 mg, 0.5 equiv) was added at −50 °C and the reaction mixture was allowed to warm up to room temperature (2 h) before adding methanol (1 ml). Stirring was continued for 30 min, water (1 ml) was added and the resulting solution was concentrated to dryness under vacuo. Column chromatography (3:7 EtOAc/heptane) purification afforded methylenimine **9** as a yellow oil (964 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.53 (m, 1H), 6.8 (m, 1H), 6.83 (m, 1H) 6,99–7.84 (m, 8H), 9.44 (s, 1H), 14.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 118.3, 118.6, 119.8, 125.2, 125.5, 125.7, 126.9, 127.4, 128.8, 130.0, 130.4, 132.6, 133.8, 134.00, 137.0, 163.6, 181.7; IR (neat): 1624, 3548; EIMS 246 (M^+), 230, 217, 128, 91, 69.

4.7. *N*-(2(*S*)-1-Hydroxybut-2-yl)-1-naphtyl-1-(2′-hydroxyphenyl)methylenimine 4

A solution of **9** (500 mg, 1.56 mmol) and 2-(*S*)-aminobutanol (139 mg, 1.56 mmol) in 1,2-dichloroethane (5 ml) was stirred at reflux overnight. Column chromatography (3:7 EtOAc/heptane) purification of the residual oil obtained after solvent removal afforded imine **4** (mixture of two stereoisomers, 7:3) as yellow powder (400 mg, 80%); mp 138–140 °C; $[\alpha]_D$ = +76.3 (*c* 0.535, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.63–0.68 (major) and 0.77–0.82 (minor) (2t, 5.9 Hz, 3H, H21), 1.43–1.57 (m, 3H, H20 and OH), 3.0–3.25 (m, 1H, H18,), 3.52–3.61 (m, 2H, H19), 6.57 (m, 1H, H14), 6.63 (d, *J* = 7.5 Hz, 1H, H13), 7.05 (d, *J* = 8.7 Hz, 1H, H16), 7.28 (m, 1H, H15), 7.37 (d, *J* = 5.8 Hz, 0.4H, H1), 7.45 (dd, *J* = 3.1 and 6.2 Hz, 1H, H7), 7.48 (d, *J* = 6.0 Hz, 0.6H, H1), 7.57 (dd, *J* = 6.9 and 7.8 Hz, 1H, H6), 7.61–7.64 (m, 1H, H2,8), 7.69 (d, *J* = 8.7 Hz, 1H, H8), 7.96 (d, *J* = 8.7 Hz, 1H, H5), 8.04 (d, *J* = 8.2 Hz, 1H, H3), 15.73 (minor) and 15.75 (major) (2s, 1H, Ph–*OH*); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): both stereoisomers: 10.92 and 10.99 (C21), 25.8 and 26.2 (C20), 64.3 and 64.5 (C18), 66.0 and 66.4 (C19), 117.9 (C14), 118.6 (C16), 120.3 (C12), 125.4 and 125.5 (C2), 126.0 and 126.06 (C5), 126.07 and 126.91 (C1), 126.98 and 127.1 (C7), 127.2 and 127.5 (C6), 128.9 (C8), 129.7 and 129.8 (C3), 130.8 and 130.9 (C9), 132.02 and 132.06 (C13), 131.86 and 132.24 (C2), 133.09 (C9), 133.1 (C15), 133.71 and 133.74 (C4), 163.9 (C17), 174.9 and 175.1 (C11); EIMS 320 (M+1), 288, 260, 246, 231, 169, 141, 127, 101, 77. Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.99; H, 6.58; N, 4.38; Found: C, 79.05; H, 6.42; N, 4.35.

4.8. *N*,*N*-Dimethyl-1-naphthyl-1-(2-(*R*)-*sec*-butoxyphenyl) methyleniminium iodide 2

A mixture of imine **6a** or **6b** (50 mg, 0.13 mol) and methyl iodide (55 mg, 3 equiv) in acetonitrile (2 ml) was stirred for 1 h at room temperature. Acetonitrile was evaporated under reduced pressure, ether (3 ml) was then added and the solid was collected by filtration and washed with ether to yield iminium salt **2** as a white powder in both cases (69 mg, 73%).

Quaternisation of **6a**: mp 195–197 °C; $[\alpha]_D$ = −19 (*c* 0.31, CH_2Cl_2).

Quaternisation of **6b**: mp 195–197 °C; $[\alpha]_D$ = −12 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.73 (m, 3H), 1.98 (m, 3H), 2.25 (m, 2H), 3.28 and 3.30 (2s, 3H), 3.52 and 3.58 (2s, 3H), 3.9 (m, 1H), 6.59–7.95 (m, 9H), 8.01–8.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.6, 13.4, 21.1, 22.2, 30.2, 30.5, 71.5, 72.1, 117.7, 117.9, 119.0, 128.6, 129.4, 131.7, 132.5, 133.8, 134.4, 135.6, 138.9, 155.1, 156.3, 196.8, 198.3; IR (KBr): 1628; IMS 332 (M^+-I), 318, 302, 246, 217, 154, 127. Anal. Calcd for $C_{23}H_{26}NOI$: C, 60.13; H, 5.66; N, 3.05. Found: C, 60.10; H, 5.42; N, 3.08.

4.9. *N*,*N*-Dimethyl-1-(8-quinolinyl)-1-(2-(*R*)-*sec*-butoxynaphtyl)-methyleniminium iodide 3

Quaternisation of **8a** or **8b** (50 mg, 0.135 mmol) following the above procedure gave iminium salt **3** as a white solid in both cases (58 mg, 85%).

Quaternisation of **8a**: mp 186–187 °C; $[\alpha]_D$ = −17 (*c* 1, $CHCl_3$).

Quaternisation of **8b**: mp 186–187 °C; $[\alpha]_D$ = −11.5 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.13 (t, *J* = 7.3 Hz, 3H), 1.21 (m, 3H), 1.28 (m, 2H), 3.01 and 3.32 (2s, 3H), 4.02 (m, 1H), 7.27–7.89 (m, 9H), 8.01–8.28 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.2, 14.2, 22.1, 26.2, 33.5, 70.3, 73.1, 117.1, 118.0, 119.7, 127.6, 127.8, 128.6, 128.7, 129.4, 132.0, 132.6, 134.0, 134.3, 136.4, 138.9, 153.7, 155.1, 157.3, 179.3, 195.8, 199.8; IR (KBr): 1190, 1260, 1270, 1300, 1520, 1620, 3245; EIMS 383,21 (M^+-I), 383, 368, 298, 129. Anal. Calcd for $C_{26}H_{27}IN_2O$: C, 61.18; H, 5.33; N, 5.49. Found: C, 61.27; H, 5.01; N, 5.45.

4.10. Allylation of imine 10

4.10.1. Liquid/liquid system

To a solution of **10** (100 mg, 0.34 mmol), a solution of **2** or **3** (10 mol %) and allyl bromide (105 mg, 0.87 mmol) in toluene (3 ml) was added at room temperature, and under stirring, 50% aqueous KOH (1.2 ml) was added. The mixture was then vigorously stirred at room temperature until the reaction was complete (TLC, 10:90 EtOAc/hexane). Ether (3 ml) was added and the organic layer was washed with water and dried over $MgSO_4$. Evaporation of solvents and purification of the residual oil by column chromatography (EtOAc/hexane = 1:9) gave α-allylglycine schiff base **11** as a colourless oil (80 mg, 70%).

4.10.2. Solid/liquid system

A solution of imine **4** (10 mg, 0.034 mmol) and $Cu(OAc)_2$ (8.16 mg, .068 mmol) in methanol (2 ml) was refluxed for 2 h. The metal complex which crystallised out was collected by filtration, washed with the minimum of water and methanol, dried and added to a suspension of imine **10** (100 mg, 0.34 mmol), allyl bromide (105 mg, 0.87 mmol) and solid KOH (57 mg, 1.02 mmol) in toluene (3 ml). After 6 h of stirring at room temperature, ether (5 ml) was added, the solid was removed by filtration and the filtrate was washed with water and dried over $MgSO_4$. Evaporation of solvents and purification of the residual oil by column chromatography (EtOAc/hexane = 1:9) gave product **11** as a colourless oil (86 mg, 76%). Chiral HPLC showed 2-(*S*)-allylglycine iminoester as the major enantiomer with 17% ee.

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ıtZ = 2, D_x = 1.297 Mg m^{-3}, λ(MoKα) = 0.71073 Å, μ = 0.69 cm^{-1}, F(000) = 340, T = 293 K. The sample (0.38 ∗ 0.25 ∗ 0.18 mm) was studied on a NONIUS Kappa CCD with graphite monochromatised MoKα radiation. The cell parameters were obtained with Denzo and Scalepack (Otwinowski & Minor, 1997) with 10 frames (psi rotation: 1° per frame). The data collection (Nonius, 1999) ($2\theta_{max}$ = 60°, 183 frames via 2.0° omega rotation and 14 s per frame, range *HKL*: *H* 0, 9 *K* 0, 20 *L* −10, 10) gives 11,180 reflections. The data reduction with Denzo and Scalepack (Otwinowski and Minor, 1997) led to 2197 independent reflections from which 1842 with $I > 2.0\sigma(I)$. The structure was solved with SIR-97 (Altomare et al., 1998) which reveals the non-hydrogen atoms. After anisotropic refinement, many hydrogen atoms may be found with a Fourier Difference. The whole structure was refined with SHELXL97 (Sheldrick, 1997) by the full-matrix least-square techniques (use of F square magnitude; x, y, z, β_{ij} for O, C and N atoms, x, y, z in riding mode for H atoms; 218 variables and 1842 observations with $I > 2.0\sigma(I)$; calcd $w = 1/[\sigma^2(F_o^2) + (0.096P)^2 + 0.028P]$, where $P = (F_o^2 + 2F_c^2)/3$ with the resulting R = 0.046, R_w = 0.130 and S_w = 1.055 (residual around solvent molecules) $\Delta\rho < 0.20$ e Å^{-3}).Atomic scattering factors from International Tables for X-ray crystallography (1992). Ortep views realised with PLATON98 (Spek, 1998). All the calculations were performed on a Pentium NT Server computer. CCDC 676002.

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