Synthesis, stereochemical characteristics, and coordination behavior of 2,2'-binaphthyl-1,1'-biisoquinoline as a new axially chiral bidentate ligand

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Dedicated to Prof. Manfred Schlosser in honor of his scientific achievements throughout his career

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Abstract

We describe the synthesis, stereochemical characteristics, and coordination behavior of 2,2'-binaphtyl-1,1'-biisoquinoline (BINIQ), a new axially chiral bidentate ligand. BINIQ was obtained in a racemic form by the diastereoselective Ullmann coupling of 1-(2-iodonaphthalen-1-yl)isoquinoline, which was prepared by the regioselective C-H iodination of 1-(1-naphthyl)isoquinoline. BINIQ has three chiral biaryl axes α and γ at the two naphthyl-isoquinoline and β at the 2,2'-binaphthyl sites and their relative configuration (αR_a^*,βR_a^*, γR_a^*) in solid state was confirmed by X-ray diffraction analysis. The naphthyl-isoquinoline axes α and γ were proven rigid enough in solution to allow for optical resolution by a chiral HPLC method and a solution of the optically pure BINIQ (>98% ee) in chloroform-*d* did not result in racemization while standing at room temperature for 24 h. On the other hand, the 2,2'-binaphthyl axis is stereochemically labile and readily alternates between βR_a and βS_a at room temperature. Accordingly, (αR_a^*,βR_a^*,γR_a^*)- and (αR_a^*,βS_a^*,γR_a^*)-BINIQ are in equilibrium in solution with the former stereoisomer being dominant, though the latter is suitable as a bidentate ligand. Notably, this dynamic stereochemical behavior enabled BINIQ to readily give the relative configuration (αR_a^*,βS_a^*,γR_a^*) upon coordination to a copper(I) ion at room temperature.

Keywords: Chiral bidentate ligand, biisoquinoline, axial chirality, dynamic stereochemistry, copper complex

Introduction

Asymmetric catalysis by chiral metal complexes is currently a formidable synthetic tool for constructing optically active materials. A number of chiral ligands have been so far devised to advance this research area. In particular, those with an axially chiral 1,1'-binaphthyl scaffold represented by BINOL[1], BINAP[2], and BINAM[3] have found many applications in metal-catalyzed asymmetric transformations with great success (Figure 1, **A**).[4-6] Isoquinoline is also a valuable constituent of chiral biaryl ligands and replacing the half aryl group of BINAP with it leads to another practical chiral ligand, QUINAP (Figure 1, **B**).[6,7] On the other hand, although 1,1'-biisoquinoline is a convenient bidentate ligand, it is known to readily racemize at room temperature (Figure 1, **C**).[8] In pursuit of stereochemically stable biisoquinoline-type bidentate ligands with axial chirality, we newly designed 2,2'-binaphthyl-1,1'-biisoquinoline (Figure 2, abbreviated as BINIQ).[9]

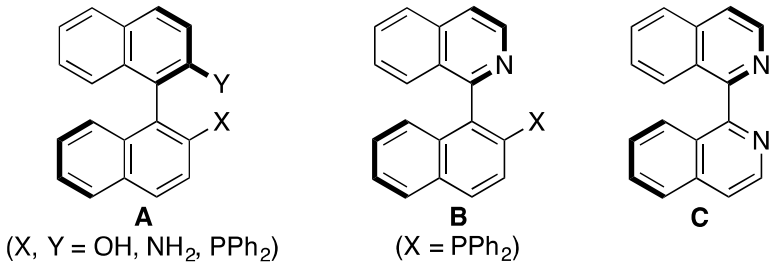


Figure 1. Representative examples of axially chiral biaryl-type chiral bidentate ligands.

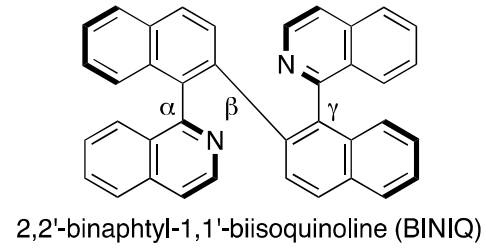


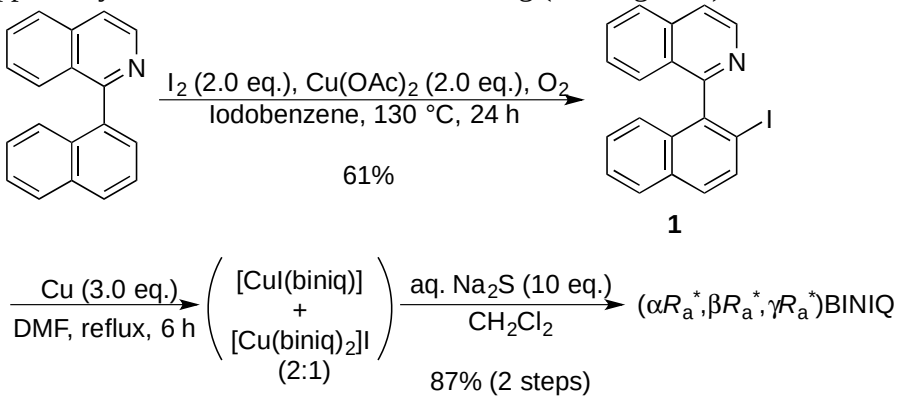
Figure 2. BINIQ designed as a new axially chiral *N*,*N*-bidentate ligand (this work). Its three chiral axes are denoted as α, β, and γ, respectively.

Due to the utility of metal complexes coordinated by 2,2'-bipyridyl and its derivatives as catalysts in organic synthesis, the development of their optically active variants has gained considerable interest.[10,11] Most chiral bipyridyl ligands so far reported possess chiral substituents at both or either of C2 and C6 positions. In contrast, bipyridyl ligands with axial chirality are scarce.[12-16] This is largely attributed to the stereochemical instability of 2,2'-bipyridyl motif as illustrated by 1,1'-biisoquinoline **C**.[6] Thus, there remains much interest in developing axially chiral bipyridine and its related ligands for asymmetric metal catalysis. Herein we wish to report on the synthesis of optically pure BINIQ as a new axially chiral biisoquinoline-type ligand, in which the two isoquinoline groups are linked together by a 2,2'-binaphthyl tether.[17-21] It is also described that BINIQ displays a dynamic stereochemical behavior upon coordination to a copper(I) ion center.

Results and Discussion

The synthesis of BINIQ was carried out as shown in Scheme 1. Regioselective C-H iodination of the readily available 1-(naphthalen-1-yl)isoquinoline[22] under the Yu's conditions[23] gave **1** in a reasonable chemical yield. The copper(0)-mediated Ullmann coupling reaction of **1** nicely proceeded to afford two different copper(I) complexes coordinated by BINIQ, one of which is [CuI(biniq)],[24,25] as the primary products. The cuprous ions in these complexes were readily removed by the treatment with aqueous sodium sulfide to give the free ligand in high yield. The molecular structure of BINIQ was determined by X-ray crystallography (Figure 3), which confirmed its relative stereochemistry for the two naphthyl-isoquinoline and the 2,2'-binaphthyl axes to be all R_a^*. Namely, the Ullmann coupling of **1** was completely diastereoselective to give (αR_a^*,βR_a^*,γR_a^*)-BINIQ and did not produce the other stereoisomer (αR_a,βR_a^*,γS_a)-BINIQ.[26,27]

This high stereoselectivity observed in the Ullmann coupling reaction of **1** should be attributed to the chelating ability of the (αR_a^*,βS_a^*,γR_a^*)-BINIQ[28] and may be achieved by either kinetic control or thermodynamic control.[29-33] In contrast, the two isoquinoline in (αR_a,βR_a^*,γS_a)-BINIQ are apparently unable to assemble a chelate ring (see, Figure 4).



Scheme 1. Synthesis of (αR_a^*,βR_a^*,γR_a^*)-BINIQ.[26]

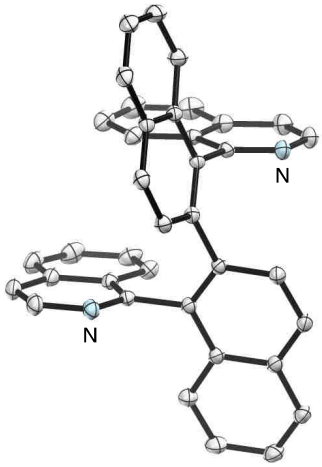
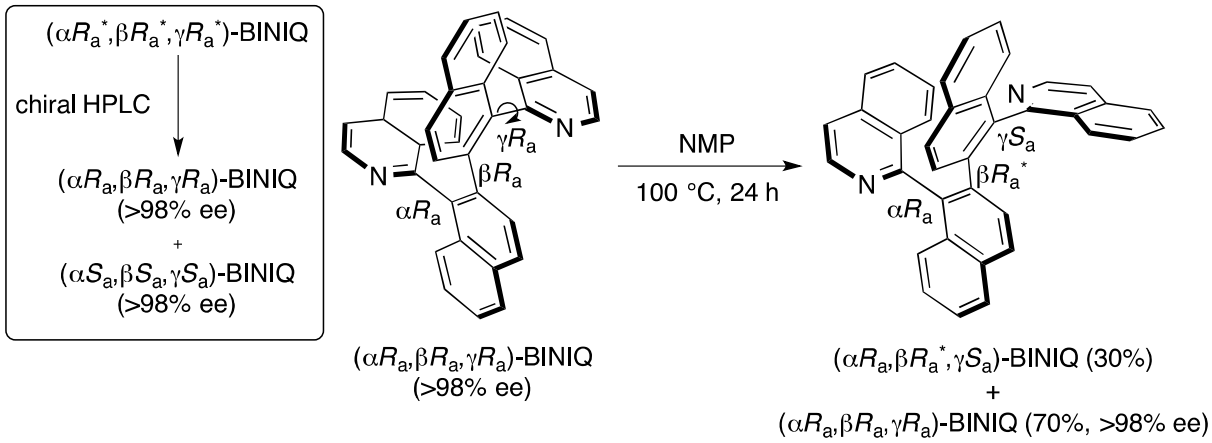


Figure 3. An ORTEP diagram for the molecular structure of ($\alpha R_a^*,\beta R_a^*,\gamma R_a^*$)-BINIQ, where only one enantiomer is shown. Hydrogen atoms and solvate molecules are omitted for clarity.

Optical resolution of BINIQ was achieved by a chiral HPLC method to isolate the both enantiomers of ($\alpha R_a,\beta R_a,\gamma R_a$)-(+)-BINIQ and ($\alpha S_a,\beta S_a,\gamma S_a$)-(–)-BINIQ in an enantiomerically pure form at room temperature (Scheme 2).[26] We assigned the stereochemistry based on the stereospecific Ullman coupling of the enantiomerically pure **1** of which absolute configuration was determined by X-ray diffraction analysis (vide supra). Notably, no racemization occurred even on heating a solution of ($\alpha R_a,\beta R_a,\gamma R_a$)-BINIQ (>98% ee) in *N*-methylpyrrolidone (NMP) at 100 °C for 24 h, although partial epimerization proceeded to form ($\alpha R_a,\beta R_a^*,\gamma S_a$)-BINIQ in 30%, leaving ($\alpha R_a,\beta R_a,\gamma R_a$)-BINIQ (>98% ee) intact in 70% (Scheme 2).[26,27] These results should indicate that ($\alpha R_a,\beta R_a^*,\gamma S_a$)-BINIQ is more stereochemically stable to withstand the turnover of the naphthyl-isoquinoline axis than ($\alpha R_a,\beta R_a,\gamma R_a$)-BINIQ.[34] The ($\alpha R_a,\beta R_a,\gamma S_a$)-BINIQ was isolated by column chromatography on silica gel and its molecular structure was unambiguously determined by X-ray crystallography (Figure 4).



Scheme 2. Optical resolution of BINIQ and partial epimerization of ($\alpha R_a,\beta R_a,\gamma R_a$)-BINIQ[26].

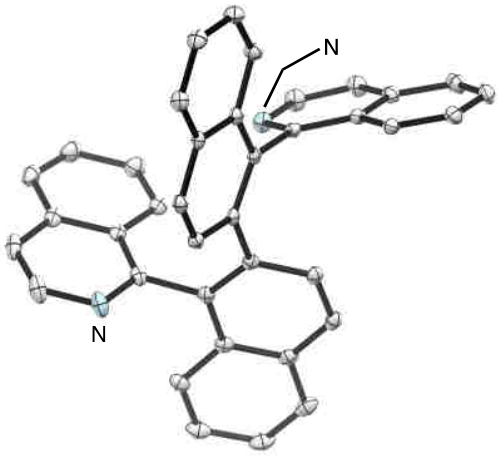
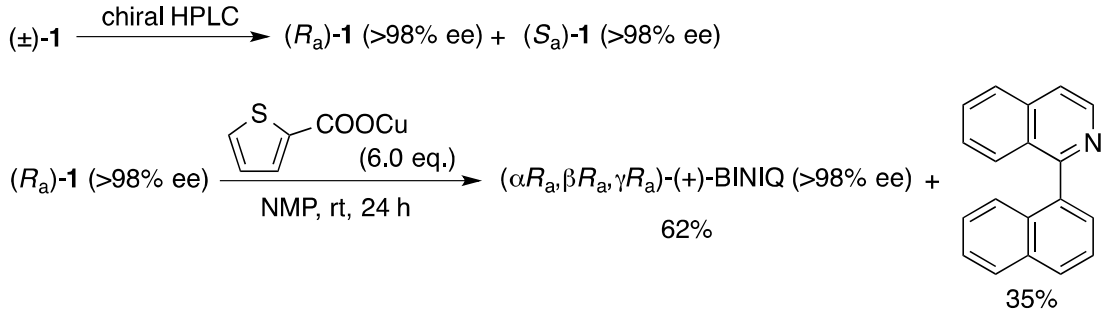


Figure 4. An ORTEP diagram for the molecular structure of (αR_a,βR_a^*,γS_a)-BINIQ, where only one enantiomer is shown. Hydrogen atoms are omitted for clarity.

It should be also noted that the coupling precursor **1** was capable of optical resolution into each enantiomer, (R_a)-**1** and (S_a)-**1**, by a chiral HPLC method and turned out to be stereochemically stable at room temperature (Scheme 3). Recrystallization of (S_a)-**1** from dichloromethane and hexane gave single crystals suitable for X-ray diffraction analysis to determine its molecular structure and absolute configuration (Figure 5).[35] More interestingly, (R_a)-**1** (>98% ee) underwent the Ullman coupling with copper(I) thiophene-2-caroboxylate at room temperature to provide (+)-BINIQ in >98% ee together with a significant amount of the dehalogenated byproduct (Scheme 3). Since it should be reasonable to assume that this reaction proceeds with retention of the stereochemistry based on the coupling mechanism,[36] we assigned the absolute configuration at the naphthyl-isoquinoline axes α and γ in (+)-BINIQ to be (αR_a,γR_a).



Scheme 3. Optical resolution of **1** and the Ullman coupling of the enantiopure (R_a)-**1** to (αR_a,βR_a,γR_a)-BINIQ[26] with retention of stereochemistry.

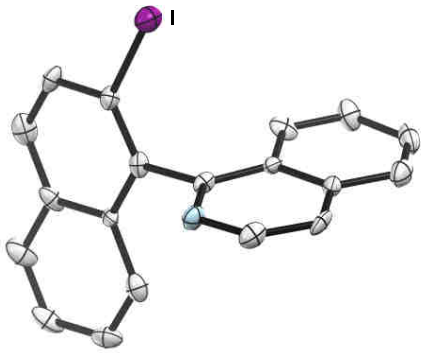
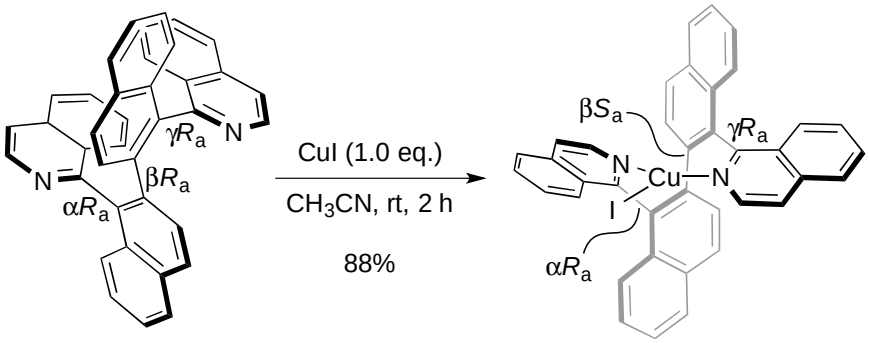


Figure 5. An ORTEP diagram for the molecular structure of (S_a)-**1**. Hydrogen atoms are omitted for clarity.

In contrast to the naphthyl-isoquinoline axis, the 2,2'-binaphthyl linking the two isoquinoline rings exhibits a dynamic stereochemical behavior upon coordination to a transition metal.[37-39] Thus, (αR_a^*,βR_a^*,γR_a^*)-BINIQ was allowed for complexation quantitatively with an equimolar amount of CuI in acetonitrile at room temperature. Recrystallization of the resulting copper complex from dichloromethane gave single crystals suitable for X-ray diffraction analysis to disclose its molecular structure (Scheme 4 and Figure 6). Comparison of the X-ray structures in Figure 3 and Figure 6 clearly shows the large contrast in the relative stereochemistry of BINIQ: (αR_a^*,βR_a^*,γR_a^*) in free ligand and (αR_a^*,βS_a^*,γR_a^*) in [CuI(biniq)] (Scheme 4). This change in stereochemistry is caused by the turnover of the axial chirality at the 2,2'-binaphthyl group from βR_a^* to βS_a^* upon coordination.



Scheme 4. Drastic conformational change of BINIQ upon complexation with a Cu(I) ion.

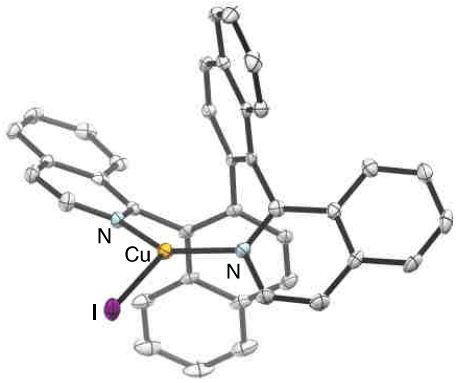


Figure 6. An ORTEP diagram for the molecular structure of [CuI((αR_a^*,βS_a^*,γR_a^*)-biniq)], where only one enantiomer is shown. Hydrogen atoms and solvate molecules are omitted for clarity.

The coordination geometry of [CuI((αR_a^*,βS_a^*,γR_a^*)-biniq)] should be also noted. Its crystal structure revealed that the two isoquinoline nitrogen atoms of (αR_a^*,βS_a^*,γR_a^*)-BINIQ and the iodide anion were located in the equatorial plane in a trigonal planar geometry around the Cu(I) center (Figure 6). A relatively large bite angle of BINIQ (∠NCuN = 138.1°) is remarkable, being contrasted with those much smaller values reported for 2,2'-bipyridine derivatives.[40] This geometrically unique feature of BINIQ as a ligand would be of a great benefit in constructing effective chiral coordination spheres around various metal centers for useful asymmetric catalyst systems.[41,42]

Interestingly, the ^{1}H NMR spectrum of (αR_a^*,βR_a^*,γR_a^*)-BINIQ in $CDCl_3$ also changes distinctly upon coordination to a cuprous ion (Figure 7). Of particular note is that (αR_a^*,βR_a^*,γR_a^*)-BINIQ exhibits the characteristic proton signals in a significantly high magnetic field (Figure 7a), whereas this peak pattern is deformed after complexation with a Cu(I) ion (Figure 7b). We tentatively assign these peculiar signals to the protons at C6~C8 positions in the isoquinoline ring. Namely, these protons in free ligand may be located in a shielding area created by the π-π stacking interaction between the two isoquinoline rings as indicated by the close contact of the relevant aromatic groups in the X-ray structure of (αR_a^*,βR_a^*,γR_a^*)-BINIQ (Figure 3).[43,44] On the other hand, as shown in Figure 7b, these diagnostically important signals are not observed in the ^{1}H NMR spectrum of the [CuI((αR_a^*,βS_a^*,γR_a^*)-biniq)], which should be correlated to its X-ray structure with no such π-π stacking interaction as described above (Figure 6). Thus, ^{1}H NMR analysis provides an effective measure to monitor the stereochemical transformation from βR_a^* in free BINIQ to βS_a^* in its metal complexes.

To be further noted, the ^{1}H NMR spectrum of (αR_a^*,βR_a^*,γR_a^*)-BINIQ in $CDCl_3$ exhibits the peak broadening as shown in Figure 7a. This should imply that although (αR_a^*,βR_a^*,γR_a^*)-BINIQ is more stable and dominant in solution than (αR_a^*,βS_a^*,γR_a^*)-BINIQ,[45] these two stereoisomers are in equilibrium along with relatively slow rotation around the 2,2'-binaphthyl axis in the absence of a Cu(I) ion.[46] In line with this dynamic stereochemical behavior of the 2,2'-

binaphthyl moiety in BINIQ, demetallation of the [CuI((αR_a^*,βS_a^*,γR_a^*)-biniq)] with sodium sulfide at room temperature lead to the formation of (αR_a^*,βR_a^*,γR_a^*)-BINIQ, which showed the same ^{1}H NMR spectrum as before complexation (Figure 7a).

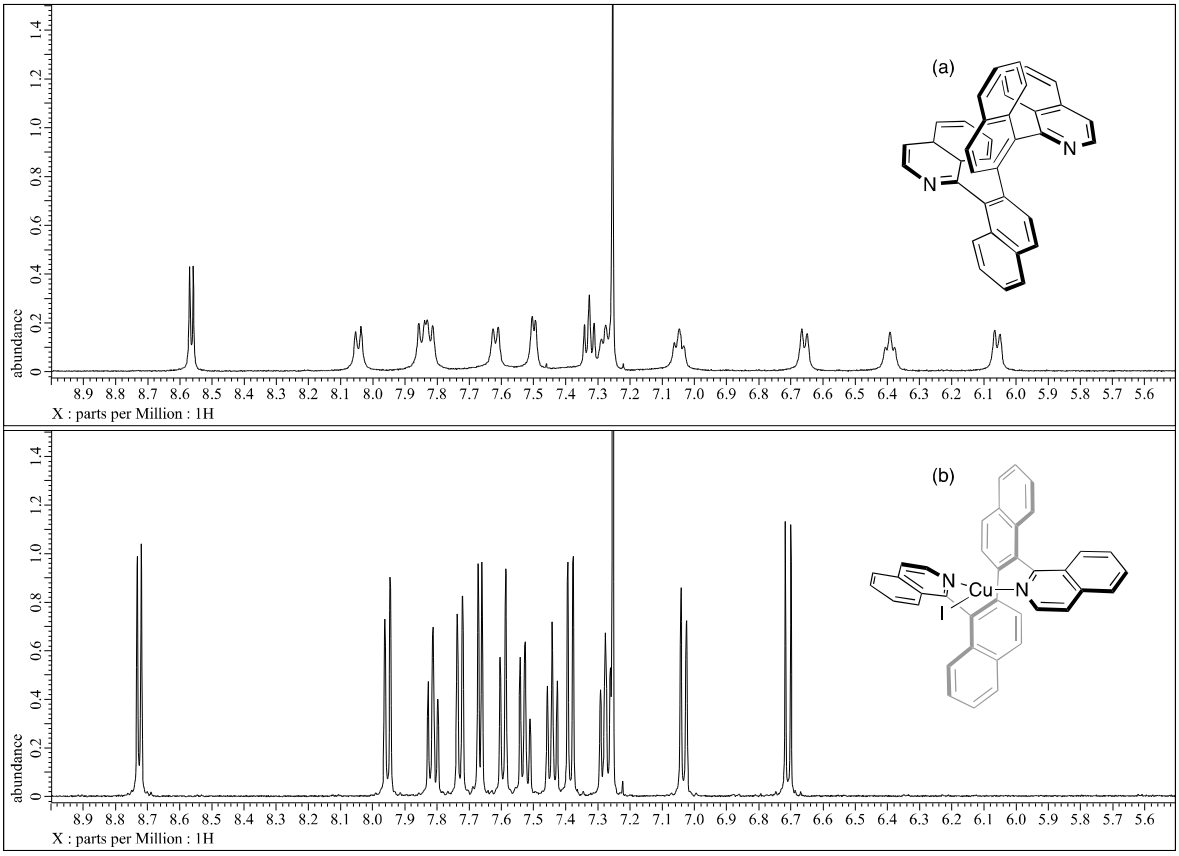


Figure 7. Characteristic change in chemical shift in the ^{1}H NMR spectra of BINIQ upon coordination to a copper(I) ion: ^{1}H NMR spectra of (a) (αR_a^*,βR_a^*,γR_a^*)-BINIQ and (b) [CuI((αR_a^*,βS_a^*,γR_a^*)-biniq)].

Conclusions

We synthesized the binaphthyl-linked biisoquinoline (BINIQ) as a new axially chiral bidentate ligand, which formed a Cu(I) complex with a remarkably large bite angle. Moreover, BINIQ was demonstrated stereochemically stable for the naphthyl-isoquinoline axis to permit optical resolution by a chiral HPLC method. On the other hand, BINIQ was found to change the configuration at the 2,2'-binaphthyl axis, which links the two isoquinoline rings, dynamically at room temperature upon coordination to a copper(I) ion center. Development of catalytic

asymmetric reactions with Cu(I) as well as other metal complexes of BINIQ are currently underway in our laboratory.

Experimental Section

General. Melting points were measured on a Yanaco Micro Melting Point Apparatus MP-J3. ^{1}H NMR spectra were recorded at 500 MHz on a JEOL 500-ECX instrument or 600 MHz on a JEOL 600-ECA instrument, and ^{13}C NMR spectra were recorded at 125 MHz on a JEOL 500-ECX instrument. IR spectra were obtained with SHIMADZU FTIR-8400 instrument. High-resolution mass (HR-FABMS) spectra were recorded on a JEOL JMS-HX-110 mass spectrometer with 3-nitrobenzyl alcohol as matrix. Column chromatography was conducted on silica gel 60N (spherical, neutral), 63-210 μm, available from Kanto Chemical Co. (Japan) and thin-layer chromatography was performed on Merck silica gel plate (60 F-254).

(±)-1-(2-iodonaphthalen-1-yl)isoquinoline ((±)-1). A mixture of 1-(naphthalen-1-yl)isoquinoline (10.2 g, 40.0 mmol)[22], $Cu(OAc)_2$ (13.0 g, 72.0 mmol), and I_2 (18.3 g, 72.0 mmol) in iodobenzene (80 mL) was stirred at 150 °C for 24 h. After cooling to room temperature, the mixture was filtered through a pad of Celite. To the filtrate were successively added aq. sat. $NaHSO_3$ (5 mL) and aq. sat. Na_2S (5 mL). The organic phase with a small amount of black insoluble materials was separated out of the mixture and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with gradient eluent of toluene and ether (from 10:1 to pure ether) to give (±)-**1** (9.2 g, 61%) as a colorless solid. Mp 150-151 °C. IR (KBr, cm^{-1}): 1620, 1583, 1556, 1500, 1404, 1371, 1317, 1299, 1257, 1137, 1016, 964, 875, 866, 823, 798, 754. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (d, *J* 8.6 Hz, 1H), 7.24-7.29 (m, 1H), 7.39-7.50 (m, 3H), 7.69-7.73 (m, 2H), 7.82 (d, *J* 5.7 Hz, 1H), 7.90 (d, *J* 8.0 Hz, 1H), 7.97 (d, *J* 8.6 Hz, 1H), 8.02 (d, *J* 9.2 Hz, 1H), 8.75 (d, *J* 5.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 97.2, 120.7, 126.3, 126.4, 126.9, 127.0, 127.1, 127.5, 127.6, 128.1, 129.9, 130.5, 132.8, 133.6, 136.5, 141.2, 142.6, 162.0. HRMS (FAB), found: *m/z* 382.0095 $[M]^+$. $C_{19}H_{12}IN$. Calcd: M 382.0093

Optical resolution of (±)- 1-(2-iodonaphthalen-1-yl)isoquinoline. Separation of the (±)-**1** to each enantiomer was performed by preparative HPLC (hexane:2-propanol = 2:1, 4.0 mL/min) using a chiral column (DAICEL CHIRALCEL OJ-H, column size 20 mm X 250 mm).

(*R*$_a$)-1-(2-iodonaphthalen-1-yl)isoquinoline. Mp 124-125 °C. $[\alpha]_D^{25}$ = -73.4 (*c* 1.00, $CHCl_3$). Retention time in chiral HPLC 36.1 min (hexane:2-propanol = 2:1, flow rate 0.5 mL/min, DAICEL CHIRALCEL OJ-H, column size 4.6 mm X 250 mm).

(*S*$_a$)-1-(2-iodonaphthalen-1-yl)isoquinoline. Mp 124-125 °C. $[\alpha]_D^{25}$ = +72.6 (*c* 1.00, $CHCl_3$). Retention time in chiral HPLC 13.8 min (hexane:2-propanol = 2:1, flow rate 0.5 mL/min, DAICEL CHIRALCEL OJ-H, column size 4.6 mm X 250 mm).
A single crystal suitable for X-ray analysis was obtained by recrystallization from CH_2Cl_2 and hexane. The crystallographic data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1030825. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

(α*R*$_a^*$,β*R*$_a^*$,γ*R*$_a^*$)-2,2'-Binaphthyl-1,1'-biisoquinolione ((α*R*$_a^*$,β*R*$_a^*$,γ*R*$_a^*$)-BINIQ). A mixture of (±)-**1** (1.14 g, 3.00 mmol) and copper bronze (0.571 g, 9.00 mmol) in DMF (6 mL) was stirred at 150 °C for 2 h under argon atmosphere. After cooling to room temperature, the mixture was filtered through a pad of Celite. An aliquot of the filtrate was taken for ^{1}H NMR analysis in $CDCl_3$ to prove a 2:1 mixture of [CuI(biniq)] and [Cu(biniq)$_2$]I as the primary products. The whole filtrate was diluted with CH_2Cl_2 (20 mL) and washed with conc. aq. NH_3 (20 mL) followed by extraction of the washing with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel with as a mixture of $CHCl_3$ and methanol (50:1) as eluent to give (α*R*$_a^*$,β*R*$_a^*$,γ*R*$_a^*$)-BINIQ (664 mg, 87%) as a colorless solid. Mp 256-257 °C. IR (KBr, cm^{-1}): 1622, 1579, 1556, 1501, 1447, 1404, 1375, 1337 1319, 1258, 1240, 1105, 1068, 1043, 949, 878, 864, 829, 818, 756, 745, 692, 665. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.06 (br. d, *J* 8.5 Hz, 2H), 6.40 (br. dd, *J* 8.0, 7.5 Hz, 2H), 6.66 (br. d, *J* 8.5 Hz, 2H), 7.05 (br. dd, *J* 7.5, 7.5 Hz, 2H), 7.28 (br. dd, *J* 7.0, 7.0 Hz, 2H), 7.34 (br. dd, J 7.0, 7.0 Hz, 2H), 7.51 (br. d, *J* 5.5 Hz, 2H), 7.62 (br. d, *J* 8.0 Hz, 2H), 7.83 (br. d, *J* 8.0 Hz, 2H), 7.86 (br. d, *J* 8.5 Hz, 2H), 8.05 (br. d, *J* 8.5 Hz, 2H), 8.57 (d, *J* 5.5 Hz, 2H). The equilibration between (α*R*$_a^*$,β*R*$_a^*$,γ*R*$_a^*$)- and (α*R*$_a^*$,β*S*$_a^*$,γ*R*$_a^*$)-BINIQs should contribute the peak broadening observed.[46] ^{13}C NMR (125 MHz, $CDCl_3$): 119.8, 125.5, 125.9, 126.1, 126.3, 126.5, 126.6, 127.2, 127.7, 128.3, 129.6, 131.7, 132.3, 134.3, 135.5, 138.8, 141.8, 159.1. HRMS (FAB), found: *m/z* 509.2019 $[M]^+$. $C_{38}H_{24}N_2$. Calcd: M 509.2018
A single crystal suitable for X-ray analysis was obtained by recrystallization from CH_2Cl_2 and hexane. The crystallographic data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1030826. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

Optical resolution of (α*R*$_a^*$,β*R*$_a^*$,γ*R*$_a^*$)-BINIQ. (α*R*$_a^*$,β*R*$_a^*$,γ*R*$_a^*$)-BINIQ was resolved into each enantiomer by preparative chiral HPLC using a chiral column (hexane:2-propanol = 1:1, flow rate 4.0 mL/min, DAICEL CHIRALCEL OD-H, column size 20 mm X 250 mm).

(α*R*$_a$,β*R*$_a$,γ*R*$_a$)-BINIQ. Mp 137-138 °C. $[\alpha]_D^{25}$ = +175.3 (*c* 1.00, $CHCl_3$). Retention time in chiral HPLC 9.5 min (hexane:2-propanol = 2:1, flow rate 0.5 mL/min, DAICEL CHIRALCEL OD-H, column size 4.6 mm X 250 mm).

(α*S*$_a$,β*S*$_a$,γ*S*$_a$)-BINIQ. Mp 137-138 °C. $[\alpha]_D^{25}$ = -176.8 (*c* 1.00, $CHCl_3$). Retention time in chiral HPLC 8.9 min (hexane:2-propanol = 2:1, flow rate 0.5 mL/min, DAICEL CHIRALCEL OD-H, column size 4.6 mm X 250 mm).

Ullmann coupling of (*R*$_a$)-1. A mixture of (*R*$_a$)-**1** (81.5 mg, 0.256 mmol) and copper(I) thiophene-2-carboxylate (293 mg, 1.54 mmol) in NMP (1.0 mL) was stirred at room temperature for 24 h under argon atmosphere. The mixture was filtered through a pad of Celite. The filtrate was diluted with CH_2Cl_2 (10 mL) and washed with conc. aq. NH_3 (10 mL) followed by extraction of the washing with CH_2Cl_2 (3 X 10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and methanol (50:1) as eluent to give (α*R*$_a$,β*R*$_a$,γ*R*$_a$)-BINIQ (40.3 mg, 62%) as a colorless solid and 1-(naphthalen-1-yl)isoquinoline (22.9 mg, 35%) as a colorless solid.

Thermal stereochemical isomerization of (α*R*$_a$,β*R*$_a$,γ*R*$_a$)-BINIQ. A solution of (α*R*$_a$,β*R*$_a$,γ*R*$_a$)-BINIQ (10.2 mg, 20 μmol) in NMP (1.2 mL) was allowed to stand at 100 °C for 24 h under argon atmosphere. After cooling to room temperature, an aliquot of the reaction mixture was taken and purified by thin-layer chromatography (SiO_2, CH_2Cl_2:MeOH = 10:1) for HPLC analysis (hexane:2-propanol = 2:1, flow rate 0.5 mL/min, DAICEL CHIRALCEL AD-H, column size 4.6 mm X 250 mm) to prove the formation of a 70:30 mixture of (α*R*$_a$,β*R*$_a$*,γ*S*$_a$)-BINIQ (retention time 12.6 min) and (α*R*$_a$,β*R*$_a$,γ*R*$_a$)-BINIQ (retention time 18.1 min). Under the conditions described above, (α*S*$_a$,β*S*$_a$,γ*S*$_a$)-BINIQ (retention time 28.4 min) was not detected.

(α*R*$_a$,β*R*$_a$*,γ*S*$_a$)-BINIQ. Mp 220-221 °C. IR (KBr, cm^{-1}): 2187, 1705, 1620, 1583, 1558, 1499, 1454, 1400, 1369, 1317, 1259, 1204, 1138, 1096, 1015, 953, 907, 866, 818, 781, 729, 691, 679, 633. ^{1}H NMR (600 MHz, $CDCl_3$, -40 °C): δ 6.85 (d, 9.0 Hz, 1H), 6.88 (d, 8.4 Hz, 1H), 6.92 (d, 8.4 Hz, 1H), 7.08 (dd, 7.8, 7.5 Hz, 1H), 7.19 (d, 7.2 Hz, 1H), 7.30 (d, 8.4 Hz, 2H), 7.34 (dd, 7.5, 7.2 Hz, 1H), 7.39 (dd, 7.5, 7.2 Hz, 1H), 7.47 (dd, 7.5, 7.2 Hz, 1H), 7.51 (dd, 7.5, 7.2 Hz, 1H), 7.59 (dd, 8.1, 6.6 Hz, 2H), 7.65-7.67 (m, 3H), 7.70-7.73 (m, 3H), 7.91 (d, 8.4 Hz, 1H), 8.08 (d, 9.1 Hz, 1H), 8.38 (d, 6.0 Hz, 1H), 8.69 (d, 5.4 Hz, 1H) ^{13}C NMR (125 MHz, $CDCl_3$): δ 119.7, 120.1, 125.5, 125.9, 126.1, 126.4, 126.8, 127.1, 127.6, 129.9, 130.2, 132.2, 135.6, 138.4, 141.4, 142.5, 159.6, 159.9. HRMS (FAB), found: *m/z* 509.2016 $[M]^+$. $C_{38}H_{24}N_2$. Calcd: M 509.2018
A single crystal suitable for X-ray analysis was obtained by recrystallization from CH_2Cl_2 and hexane. The crystallographic data have been deposited with Cambridge Crystallographic Data

Centre as supplementary publication no. CCDC-1030827. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

Synthesis and characterization of [CuI((αR_a^*,βS_a^*,γR_a^*)-biniq)]. A mixture of (αR_a^*,βR_a^*,γR_a^*)-BINIQ (50.9 mg, 0.10 mmol) and CuI(I) (19.1 mg, 0.10 mmol) in CH_3CN (1 mL) was stirred at room temperature for 2 h under argon atmosphere. After evaporation of the solvent, the residue was recrystallized from CH_2Cl_2 to give the desired copper(I) complex as single crystals (61.5 mg, 88%). IR (KBr, cm^{-1}) 1622, 1589, 1558, 1501, 1321, 955, 866, 824, 745, 698, 673, 631. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 6.77 (d, 8.5 Hz, 2H), 7.05 (d, 9.0 Hz, 2H) 7.30 (ddd, 7.5, 7.5, 1.0 Hz, 2H), 7.43 (d, 8.5 Hz, 2H) 7.47 (ddd, 8.5, 7.5, 1.0 Hz, 2H), 7.54-7.61 (m, 4H), 7.73 (d, 6.5 Hz, 2H), 7.79 (d, 9.0 Hz, 2H), 7.85 (ddd, 7.5, 7.5, 1.0 Hz, 2H), 8.00 (d, 8.5 Hz, 2H), 8.66 (d, 6.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 121.3, 126.2, 126.4, 126.5, 127.3, 127.4, 128.0, 128.4, 128.6, 128.9, 130.2, 131.4, 132.0, 132.2, 134.0, 135.7, 137.5, 144.6, 158.1. HRMS (FAB), found: *m/z* 571.1229 $[M-I]^+$. $C_{38}H_{24}N_2Cu$. Calcd: M 571.1235
A single crystal suitable for X-ray analysis was obtained by recrystallization from CH_2Cl_2. The crystallographic data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1030828. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

Epimerization of (αR_a,βR_a^*,γS_a)-BINIQ. A solution of an equimolar mixture of (αR_a,βR_a^*,γS_a)-BINIQ and CuI in DMF was heated at 150 °C for 3 h. An aliquot of the mixture was taken for ^{1}H NMR analysis in chloroform-*d*, which indicated the quantitative formation of [CuI((αR_a^*,βS_a^*,γR_a^*)-biniq)].

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References and Notes

1. R. Noyori; I. Tomino; Y. Tanimoto, *J. Am. Chem. Soc.* **1979**, *101*, 3129. http://dx.doi.org/10.1021/ja00505a056
2. A. Miyashita; A. Yasuda; H. Takaya; K. Toriumi; T. Ito; T. Souchi; R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932.

http://dx.doi.org/10.1021/ja00547a020
3. S. Miyano; M. Nawa; H. Hashimoto, *Chem. Lett.* **1980**, *9*, 729. http://dx.doi.org/10.1246/cl.1980.729
4. P. Kočovský; Š. Vyskočil; M. Smrčina, *Chem. Rev.* **2003**, *103*, 3213. http://dx.doi.org/10.1021/cr9900230
5. S. G. Telfer; R. Kuroda, *Coord. Chem. Rev.* **2003**, *242*, 33. http://dx.doi.org/10.1016/S0010- 8545(03)00026-2
6. Y. Canac; R Chauvin, *Eur. J. Inorg. Chem.* **2010**, 2325. http://dx.doi.org/10.1002/ejic.201000190
7. N. W. Alcock; J. M. Brown; D. I. Hulmes, *Tetrahedron: Asymm.* **1993**, *4*, 743. http://dx.doi.org/10.1016/S0957-4166(00)80183-4
8. M. Crawford; I. F. B. Smyth, *J. Chem. Soc.* **1954**, 3464. http://dx.doi.org/10.1039/jr9540003464
9. BINIQ has three chiral biaryl axes at the two naphthyl-isoquinoline and the 2,2'-binaphthyl sites. In this paper we use small capital letters α, β, and γ to denote each chiral axis as shown in Figure 2.
10. N. C. Fletcher, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831. http://dx.doi.org/10.1039/b204272j
11. G. Chelucci; R. P. Thummel, *Chem. Rev.* **2002**, *102*, 3129. http://dx.doi.org/10.1021/cr0101914
12. Optically active 2,2'-bipyridyls with an induced axial chirality by the additional stereogenic centers or chiral axes have been reported, albeit with partial success in asymmetric synthesis. See references 13-16.
13. H. L. Wong; Y. Tian; K. S. Chan, *Tetrahedron Lett.* **2000**, *41*, 7723. http://dx.doi.org/10.1016/S0040-4039(00)01306-X
14. R. Annunziata; M. Benaglia; M. Cinquini; F. Cozzi; C. R. Woods; J. S. Siegel, *Eur. J. Org. Chem.* **2001**, 173. http://dx.doi.org/10.1002/1099-0690(200101)2001:1<173::AID- EJOC173>3.0.CO;2-#
15. X.-L. Bai; C.-Q. Kang; X.-D. Liu; L.-X. Gao, *Tetrahedron: Asymm.* **2005**, *16*, 727. http://dx.doi.org/10.1016/j.tetasy.2004.12.015
16. G. Chelucci; C. Sanfilippo, *Tetrahedron: Asymm.* **2010**, *21*, 1825. http://dx.doi.org/10.1016/j.tetasy.2010.06.021
17. For the related chiral 1,1'-binaphthyl-2,2'-bipyridine derivatives used as *N*,*N*-bidentate ligands, see references 18-21.
18. J. P. H. Charmant; I. A. Fallis; N. J. Hunt; G. C. Lloyd-Jones; M. Murray; T. Nowak, *J. Chem. Soc. Dalton Trans.* **2000**, 1723. http://dx.doi.org/10.1039/b000651n
19. J. P. H. Charmant; N. J. Hunt; G. C. Lloyd-Jones; T. Nowak, *Collect. Czech. Chem. Commun.* **2003**, *68*, 865. http://dx.doi.org/10.1135/cccc20030865

20. T. Hoshi; M. Katano; E. Nozawa; T. Suzuki; H. Hagiwara, *Tetrahedron Lett.* **2004**, *45*, 3489. http://dx.doi.org/10.1016/j.tetlet.2004.02.155
21. K.-C. Sham; C.-S. Lee; K.-Y. Chan; S.-M. Yiu; W.-T. Wong; H.-L. Kwong, *Polyhedron* **2011**, *30*, 1149. http://dx.doi.org/10.1016/j.poly.2011.01.017
22. C.-H. Yang; C.-C. Tai; Y.-T. Huang; I-W. Sun, *Tetrahedron* **2005**, *61*, 4857. http://dx.doi.org/10.1016/j.tet.2005.02.088
23. X. Chen; X.-S. Hao; C. E. Goodhue; J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790. http://dx.doi.org/10.1021/ja061715q
24. The relative stereochemistry of the ligand coordinated to a copper(I) metal center was assigned as (αR_a^*,βS_a^*,γR_a^*).
25. The other copper complex is also diamagnetic and tentatively assigned as [Cu((αR_a^*,βS_a^*,γR_a^*)-biniq)$_2$]I by ^{1}H and ^{13}C NMR analyses.
26. Facile rotation along the axis β renders (αR_a,βR_a,γR_a)- and (αR_a,βS_a,γR_a)-BINIQs as well as (αS_a,βS_a,γS_a)- and (αS_a,βR_a,γS_a)-BINIQs to be in equilibrium in solution at room temperature (or higher). In analogy, (αR_a,βR_a,γS_a)- and (αR_a,βS_a,γS_a)-BINIQs are also rapidly interconverted.
27. Due to a molecular symmetry, the BINIQ with a (αR_a,γS_a) relative stereochemistry does not change the configuration at the chiral axes α and γ by the reflective-symmetry operation just like meso compounds. However, (αR_a,βR_a^*,γS_a)-BINIQ is a chiral molecule and can be R_a or S_a for the configuration at the axis β, which is indicated by an asterisk according to the IUPAC nomenclature.
28. (αR_a^*,βS_a^*,γR_a^*)-BINIQ is an interconvertible isomer with (αR_a^*,βR_a^*,γR_a^*)-BINIQ in equilibrium as described in reference 26.
29. Under kinetic control, the transition state would be possibly stabilized by chelation of BINIQ to a copper species. See reference 30-32.
30. T. D. Nelson; A. I. Meyers, *Tetrahedron Lett.* **1993**, *34*, 3061. http://dx.doi.org/10.1016/S0040-4039(00)93379-3
31. T. D. Nelson; A. I. Meyers, *J. Org. Chem.* **1994**, *59*, 2655. http://dx.doi.org/10.1021/jo00088a066
32. T. D. Nelson; A. I. Meyers, *Tetrahedron Lett.* **1994**, *35*, 3259. http://dx.doi.org/10.1016/S0040-4039(00)76879-1
33. Consistent with thermodynamic control, heating a equimolar mixture of (αR_a,βR_a^*,γS_a)-BINIQ and CuI in DMF led to the quantitative formation of [CuI((αR_a^*,βS_a^*,γR_a^*)-biniq)]. See the experimental section.
34. For racemization, (αR_a,βR_a,γR_a)-BINIQ must undergo stereochemical inversion at both the naphthyl-isoquinoline axes (α and γ), involving the stereochemical isomerization step at the relevant axis of the intermediary epimer (αR_a,βR_a^*,γS_a)-BINIQ.
35. The absolute configuration of (S_a)-**1** was determined by refinement of the flack parameter to 0.016 with a standard uncertainty of 0.008.

36. S. Zhang; D. Zhang; L. S. Liebeskind, *J. Org. Chem.* **1997**, *62*, 2312. http://dx.doi.org/10.1021/jo9700078
37. 2,2'-Binaphthyl was reported to be stereochemically labile with a rotation barrier of 1.4 kcal/mol around the biaryl axis. See reference 38.
38. A. Almenningen; O. Bastiansen; L. Fernholt; B. N. Cyvin; S. J. Cyvin; S. Samdal, *J. Mol. Struct.* **1985**, *128*, 59. http://dx.doi.org/10.1016/0022-2860(85)85041-9
39. The biaryl axis β in BINIQ is likely to require a higher energy for the rotation than 2,2'-binaphthyl due to the steric hindrance caused by the C1(1')-isoquinoline groups. We are currently investigating this dynamic stereochemical issue in more detail.
40. M. Munakata; S. Kitagawa; A. Asahara; H. Masuda, *Bull. Chem. Soc. Jpn*. **1987**, *60*, 1927. http://dx.doi.org/10.1246/bcsj.60.1927
41. B. M. Trost; D. J. Murphy, *Organometallics* **1985**, *4*, 1143. http://dx.doi.org/10.1021/om00125a039
42. BINIQ was also found to form complexes with a Ag(I) and a Zn(II) ion.
43. For characteristic change of chemical shifts in ^{1}H NMR spectra diagnostic for π-π stacking interaction, see reference 44.
44. M. Majumder; N. Sathyamurthy, *Theor. Chem. Acc.* **2012**, *131*, 1092, and references cited therein. http://dx.doi.org/10.1007/s00214-012-1092-3
45. This speculation relies on the X-ray structure (Figure 3) and the comparative analysis of the ^{1}H NMR spectra of (αR_a^*,βR_a^*,γR_a^*)-BINIQ and [CuI((αR_a^*,βS_a^*,γR_a^*)-biniq)] (Figure 7). However, we can not completely rule out that (αR_a^*,βS_a^*,γR_a^*)-BINIQ is more stable than (αR_a^*,βR_a^*,γR_a^*)-BINIQ in solution.
46. It might be also possible that other conformers are involved in equilibrium to cause the peak broadening in the ^{1}H NMR spectrum. The conformational analysis is currently being investigated in more detail.

