Sterically non-hindering endocyclic ligands of the bi-isoquinoline family

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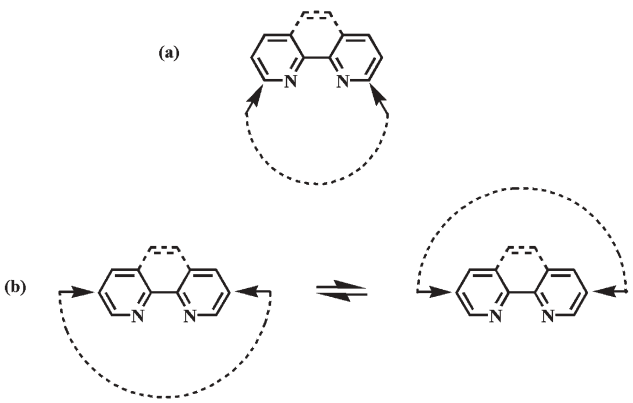
Bi-isoquinoline can be used as a building block to prepare a new family of non-sterically hindering chelates, including a macrocyclic system; the endocyclic nature of the ligands has been confirmed by the X-ray structure of an octahedral tris-chelate iron(II) complex, which shows that the three chelates are easily accommodated in the coordination sphere of the metal in spite of their crescent shape.

The incorporation of a bidentate chelate of the bipy or the phen family (bipy: 2,2′-bipyridine; phen: 1,10-phenanthroline) in a ring in an endocyclic fashion, has been used for decades in macrocyclic chemistry.[1] It requires that the chelate be substituted at the two positions α to the nitrogen atoms so as to ensure an endocyclic coordination mode. If the other positions (meta or para) are used, the coordination mode will not be controlled and exocyclic coordination is very likely to prevail over the endocyclic mode, as indicated in Scheme 1.

The copper(I)-templated synthesis of numerous catenanes and rotaxanes[2] relies on the dpp fragment (dpp: 2,9-diphenylphenanthroline), whose geometry is such that, once incorporated in a ring, endocyclic coordination is strongly favoured over any other mode of complexation. The dpp chelate is sterically strongly hindering, which leads to very stable tetrahedral complexes such as $[Cu(dpp)_2]^+$. Macrocyclic ligands, incorporating non-sterically hindering chelates, may be needed either to build new topologies around octahedral metal centres[3] or, in the field of molecular machines,[4] to make the metal more accessible to entering ligands and thus facilitate ligand substitution.[5]



Scheme 1 Situation (a) is ideally suited to endocyclic coordination whereas (b) may lead to both endo- or exocyclic coordination.

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We would like to report a new family of diimine ligands which correspond to the following prerequisites:

(i) no substituents α to the N atoms

(ii) crescent shaped allowing the inscribing of the ligand in a ring, with endocyclic coordination.

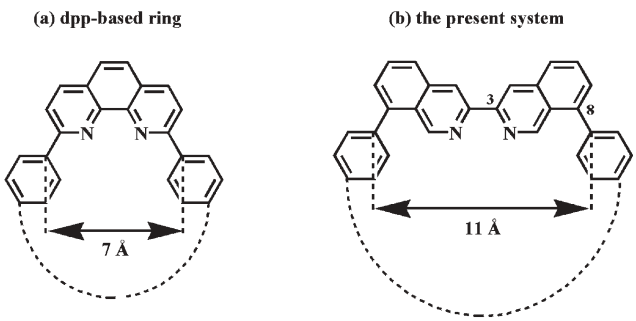
The principle is indicated in Scheme 2.

The bi-isoquinoline-containing system is such that endocyclic coordination will be certain and, equally important, the complexed metal centre will be remote from any organic group of the ligand organic backbone. In dpp (Scheme 2 (b)), the shortest C–C distance between the phenyl rings borne by the phen nucleus at its 2 and 9 positions is around 7 Å whereas it is around 11 Å for the two corresponding phenyl rings of the system represented in (b) of Scheme 2 (attached at the 8 and 8′ positions of the bi-isoquinoline ligand).

The synthetic routes leading to the desired bi-isoquinoline derivatives are represented in Figs. 1 and 2.

Isoquinoline **4**, functionalized on its 3 and 8 positions, is synthesized following an existing methodology:[6] sodium diethoxy acetate **1** is first activated with thionyl chloride and subsequently condensed with 2-bromobenzylamine **2** in 60% yield. The resulting amide **3** cyclizes in concentrated sulfuric acid to form 8-bromo-isoquinolin-3-ol **4** in a so-called Pomeranz–Fritsch reaction (50 ± 10% yield).

Activation of its alcohol function using triflic anhydride results in the formation of triflate compound **5** in nearly quantitative yield (95%). The latter is coupled to commercially available 4-methoxy-phenylboronic acid in a highly selective and efficient (90% yield) Suzuki coupling reaction[7] that leads to 8-anisyl-3-triflylisoquinoline **6**. Ligand **7** is obtained in 70% yield by palladium catalyzed homocoupling reaction[8] between two triflate molecules **6**. The overall yield of the three-step synthesis of **7** from precursor **4** is 60%.



Scheme 2 (a) The use of a dpp fragment as chelate leads to pronounced steric hindrance once a metal centre is coordinated; (b) by using a 3,3′-bi-isoquinoline chelate substituted at the 8,8′-positions, a sterically non-hindering macrocycle should be obtained.

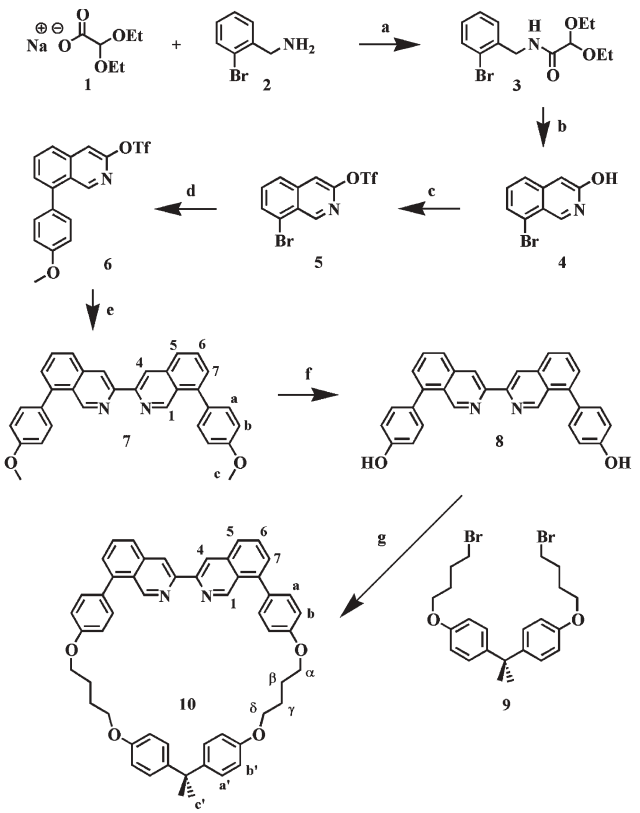


Fig. 1 Synthesis of a macrocycle based on a bi-isoquinoline. *Reagents* a: $SOCl_2$, Et_2O, reflux, then pyridine, toluene, reflux, 60%. b: H_2SO_4, r.t., 16 h, 50%. c: Tf_2O, pyridine, r.t., 16 h, 95%. d: anisyl boronic acid, Pd_2dba_3, P^tBu_3, KF, THF, r.t., 2 h, 90%. e: Zn, $PdCl_2dppf$, KI, DMF, 90 °C, 2 h, 70%. f: pyridinium chloride, reflux, 100%. g: high dilution, Cs_2CO_3, DMF, 65 °C, 40%.

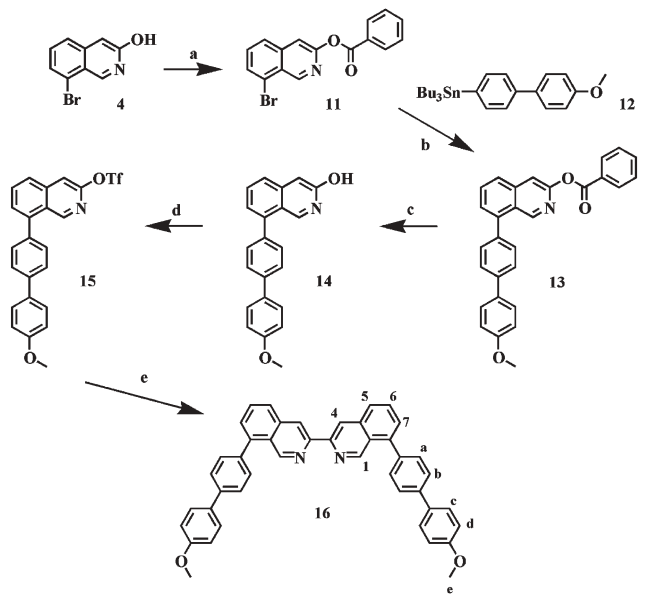


Fig. 2 Synthesis of a long-legged bi-isoquinoline. *Reagents* a: benzoyl chloride, pyridine, 0 °C. b: $Pd(PPh_3)_2Cl_2$, toluene/THF (1 : 1), LiCl, reflux, 2 days, 65%. c: THF/2M KOH in H_2O (1 : 1), reflux, 2 h. d: Tf_2O, pyridine, r.t., 16 h, 95%. e: Zn, $PdCl_2dppf$, KI, DMF, 90 °C, 8 h, 70%.

Deprotection of the anisyls, using pyridinium chloride at high temperature, quantitatively affords diphenol **8**. A double Williamson high-dilution reaction between diphenol **8** and dibromo-linker **9** (easily obtained in a one-step reaction from commercially available 4,4′-isopropylidenediphenol, and 1,4-dibromobutane) affords macrocycle **10** in 40% yield.

For the synthesis of ligand **16** we have used the same precursor (**4**) as for chelate **7**, but followed an entirely different synthetic strategy: the alcohol function is first protected using benzoyl chloride, and the resulting 8-bromo-isoquinoline-3-benzoyl ester (**11**) is coupled to stannane **12**[9] in 65% yield following existing synthetic methodologies.[10] Deprotection of benzoyl ester **13** in basic solution affords **14** which is subsequently reacted with triflic anhydride. Thereby triflate **15** is formed in nearly quantitative yield (95%). The final step is a palladium-catalyzed coupling of two triflate molecules **15** to one another. Under identical reaction conditions as for chelate **7** (*vide infra*), we obtained ligand **16** in 70% yield. The overall yield for the five-step synthesis of **16** from **4** is 39%.[11]

To demonstrate that these ligands are also not sterically hindering, we decided to make a homoleptic complex of an octahedral transition metal with ligand **7**. To our knowledge, such homoleptic octahedral complexes, with three endocyclic ligands, are very uncommon.

By mixing bis(tetrafluoroborate) iron(II) and ligand **7** during two hours at room temperature in dichloromethane, and after an anion exchange with potassium hexafluorophosphate, we easily obtained bis(hexafluorophosphate) tris(bi-isoquinoline) iron(II) **17**. This complex affords big red crystals that allow X-ray analysis, the corresponding crystallographic structure is shown in Fig. 3.

Interestingly, the coordination sphere of the Fe(II) centre is perfectly octahedral in spite of the 6 anisyl groups present in the complex, although stacking interactions are clearly observed. This again confirms the non sterically-hindering nature of the chelate **7**. On the other hand, the two anisyl groups of each ligand are pointing in ideal directions if one wants to construct rings.

In conclusion, the new disubstituted bi-isoquinoline ligands described in the present communication are ideally suited to the synthesis of octahedral transition metal complexes, their endocyclic nature being obvious from their geometry, as shown by the X-ray structure of complex **17**.†

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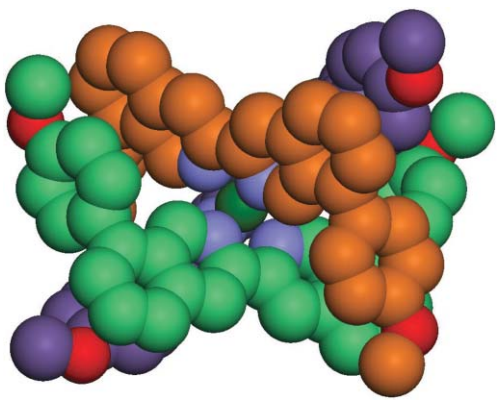

Fig. 3 Crystallographic structure of complex **17**.

Science Foundation. We also thank Dr A. De Cian for the resolution of the X-ray structure (**17**).

Notes and references

† Crystal structure analysis of **17**: $C_{96}H_{72}F_{12}FeN_6O_6P_2$, M = 1751.39, monoclinic, a = 15.4180(3), b = 34.4150(6), c = 17.0120(4) Å, β = 116.3621(8)°, V = 8088.0(3) Å^3, T = 173(2) K, space group $P2_1/n$, Z = 4, μ(Mo Kα) = 0.316 mm^{-1}, 45635 collected reflections, 23640 independent reflections [R(int) = 0.048], final R indices R_1 = 0.052, wR_2 = 0.1261. CCDC 283554. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b513222c.

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9 Stannane **12** is obtained in two steps: commercially available 4-bromo-[1,1′-biphenyl]-4-ol is reacted with methyl iodide to afford 4-bromo-4′-methoxybiphenyl. The latter is converted to the stannane using n-butyllithium and tributyltin chloride.

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11 Characterisations of the new compounds. **7**: ^{1}H-NMR (CD_2Cl_2, 300 MHz): δ = 9.42 (s, 2H; H^1), 8.94 (s, 2H; H^4), 7.96 (d, ^3J = 8.2 Hz, 2H; H^5), 7.74 (t, ^3J = 8.2 Hz, 2H; H^6), 7.53 (d, ^3J = 8.2 Hz, 2H; H^7), 7.52 (d, ^3J = 8.8 Hz, 4H; H^a), 7.09 (d, ^3J = 8.8 Hz, 4H; H^b), 3.91 (s, 6H; H^c) ppm. ES-MS: m/z = 469.1907 [**7** + H]$^+$ (calculated 469.1911 for $C_{32}H_{25}N_2O_2$). **10**: ^{1}H-NMR (CD_2Cl_2, 400 MHz, COSY-ROESY): δ = 9.38 (s, 2H; H^1), 8.37 (s, 2H; H^4), 7.94 (d, ^3J = 8.4 Hz, 2H; H^5), 7.76 (t, ^3J = 8.2 Hz, 2H; H^6), 7.58 (d, ^3J = 8.3 Hz, 2H; H^7), 7.46 (d, ^3J = 8.8 Hz, 4H; H^a), 7.16 (d, ^3J = 8.9 Hz, 4H; H$^{a'}$), 7.08 (d, ^3J = 8.8 Hz, 4H; H^b), 6.81 (d, ^3J = 9.0 Hz, 4H; H$^{b'}$), 4.26 (t, ^3J = 6.3 Hz, 4H; H$^\alpha$), 3.99 (t, ^3J = 6.2 Hz, 4H; H^6), 1.99 (m, 8H; H$^{\beta,\gamma}$), 1.59 (s, 6H; H$^{c'}$) ppm. ES-MS: m/z = 777.3761 [**10** + H]$^+$ (calculated 777.3687 for $C_{53}H_{49}N_2O_4$). **16**: ^{1}H-NMR ($CDCl_3$/CF_3COOD 5%, 300 MHz): δ = 9.72 (s, 2H; H^1), 9.07 (s, 2H; H^4), 8.35 (d, ^3J = 5.1 Hz, 4H; H^{5,7}), 8.12 (t, ^3J = 5.1 Hz, 2H; H^6), 7.83 (d, ^3J = 8.4 Hz, 4H; H^a), 7.67 (d, ^3J = 8.7 Hz, 4H; H^c), 7.60 (d, ^3J = 8.4 Hz, 4H; H^b), 7.07 (d, ^3J = 8.7 Hz, 4H; H^d), 3.93 (s, 6H; H^e) ppm. ES-MS: m/z = 621.2529 [**16** + H]$^+$ (calculated 621.2537 for $C_{44}H_{33}N_2O_2$). **17**: ^{1}H-NMR (CD_2Cl_2, 300 MHz): δ = 8.89 (s, 6H; H^1), 8.10 (d, ^3J = 8.4 Hz, 6H; H^5), 7.87 (s, 6H; H^4), 7.84 (t, ^3J = 8.4 Hz, 6H; H^6), 7.45 (d, ^3J = 7.3 Hz, 6H; H^7), 6.62 (d, ^3J = 8.8 Hz, 12H; H^a), 6.31 (d, ^3J = 8.8 Hz, 12H; H^b), 3.58 (s, 18H; H^c) ppm. ES-MS: m/z = 730.2431 [**17**]$^{2+}$ (calculated 730.2428 for $C_{96}H_{72}FeN_6O_6$).