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Controlling the Helicity of Hydroxyquinoline Metal Complexes Based on a Macrocyclic Peptide Scaffold

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A straightforward synthesis of a C_3-symmetric imidazole-containing macrocyclic peptide with three hydroxyquinoline side arms is presented. Complex formation with various metal ions (Al^{3+}, Ga^{3+}, Fe^{3+}, La^{3+} and Y^{3+}) was investigated by spectrophotometric methods. CD spectroscopy revealed a highly diastereoselective binding of these ions at room temperature. In the case of Al^{3+}, Ga^{3+} and La^{3+} complexes, Job plot analyses gave evidence of pure 1:1 stoichiometry. Ab initio calculations for the Al^{3+} and Ga^{3+} complexes showed that the Λ isomers are considerably stabilized relative to the Δ isomers. Furthermore, the calculated CD spectra for the Al^{3+} complexes confirm the formation of the Λ isomers in solution.

Introduction

The direct stereoselective synthesis of octahedral metal complexes was largely unexplored throughout most of the 20th century.[1] However, over the last 15 years much attention has been paid to control and predetermine the helicity of metal complexes through synthetically tailored ligand systems.[2] In the past, primarily separation methods were employed to obtain the enantiomerically pure Δ and Λ isomers of octahedral metal complexes,[3] but even after being separated, these isomers often racemize and thus ruin the separation. To overcome this problem, recently published methods for synthesizing stereochemically pure metal complexes involve the use of caged ligand structures that possess chiral units.[4] This strategy can also be found in naturally occurring octahedral metal complexes. One example is enterobactin, a well-known triscatecholamide-type siderophore (Figure 1) that consists of a chiral cyclic trilactone scaffold and three achiral catecholate arms.[5] The stereochemistry at the metal centres of the enterobactin metal complexes is of particular interest, as it is known that the configuration of the coordinated iron centre is crucial for the biological activity of the siderophore.[6] In enterobactin, the configuration at the C_3-symmetric metal centre is predetermined by the chiral scaffold, and thus only the Δ diastereomer of ferric enterobactin is found in solution.[7] In contrast to naturally occurring enterobactin, most of the artificial, caged-ligand structures are made up of three chiral binding arms attached to an achiral centre or achiral scaffold.[1,2] For example, Shanzer et al. used this concept to synthesize chiral siderophore analogues.[8] Here the chiral arms contain coordinating sites as well as stereoisomeric information by the linkage of amino acids. The formation of a network of hydrogen bonds and the decrease in steric interactions explain the predetermination of chirality at the metal centre. Von Zelewsky et al. applied the same concept to synthesize stereoselective octahedral complexes of 2,2′-bipyridine by using terpene-based arms.[4a,9]

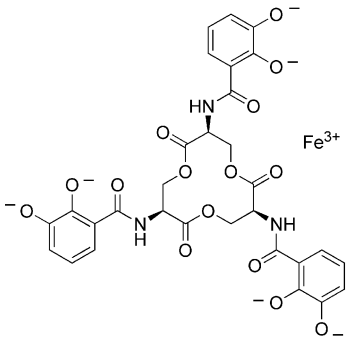

Figure 1. Structural formula of enterobactine.

Our concept for the control of the configuration of metal centres of octahedral complexes is more analogous to the naturally occurring enterobactin. We use azole-containing cyclopeptides as a chiral scaffold to which achiral binding arms can be coupled.[10] Here, the scaffold does not only serve as a spacer, but also preorganizes the conformation of the binding arms, thus leading to chiral discrimination of the metal complexes. By using these azole-containing cyclopeptides we have already succeeded in controlling the configuration in octahedral metal complexes of 2,2′-bipyridine[11] and catecholate[12] and axial and planar chirality.[13,14]

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Herein we demonstrate the wide applicability of our concept by controlling the helicity of 8-quinolate metal complexes. Octahedral hydroxyquinoline metal complexes are of interest in organic research, as their electron-transport and emission properties can be used for small organic light-emitting diodes (OLEDs).[15] The first reported tris(8-quinolate) aluminum(III) (Alq_3) is one of the best-known molecules used as OLEDs for full-colour, flat-panel displays (Figure 2).[16] In the last few years OLEDs with high efficiency,[17] low-drive voltage[18] and long lifetime[19] were developed, and the tuning of an efficient emission colour was achieved by attachment of different substituents.[20–22] Interestingly, until now there have been no reports of a successful synthesis of diastereoselective octahedral hydroxyquinoline complexes. Our intention was to investigate the stereochemistry of the metal complexes of ligand **1**, which consists of a C_3-symmetric imidazole-based scaffold to which three achiral hydroxyquinoline arms were attached (Figure 2).

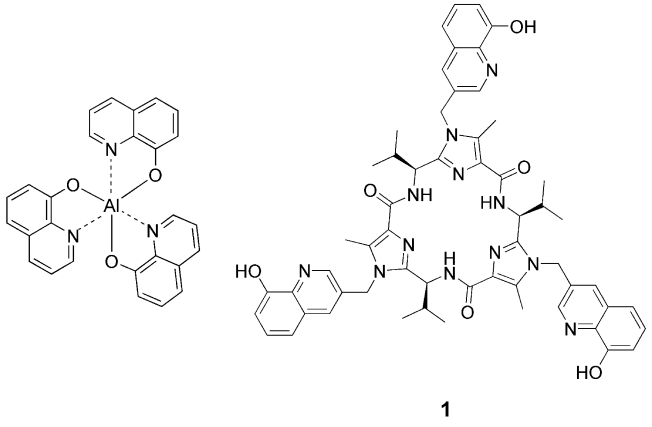
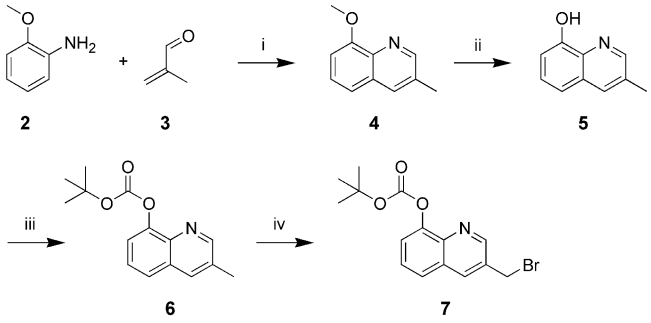


Figure 2. Structural formula of the aluminum(III) complex of 8-hydroxyquinoline and cyclohexapeptide-based tris(hydroxyquinoline) ligand **1**.

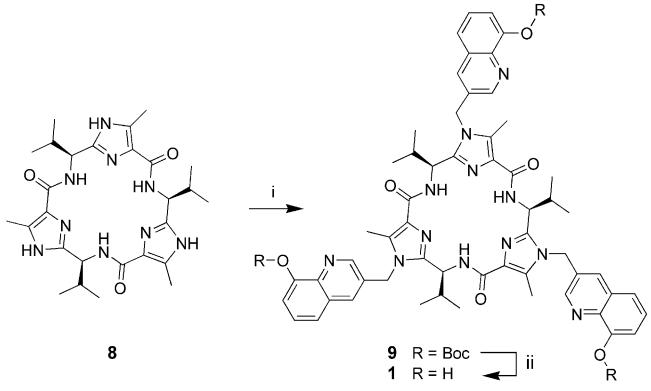
Results and Discussion

Synthesis of Ligand 1

The synthetic pathway for ligand **1** is shown in Schemes 1 and 2. Firstly, methoxyquinoline **4** was synthesized starting from *o*-anisidine (**2**) and methacrolein (**3**) by a Skraup–Döbner–von Miller quinoline synthesis.[23] Deprotection of the methyl ether was achieved by treatment with boron tribromide in dichloromethane to form hydroxyquinoline **5**. After introduction of the Boc group, the methyl group in quinoline **6** was brominated by using *N*-bromosuccinimide (NBS) in CCl_4, which provided desired receptor arm **7** in moderate yields. The exchange of the methyl protecting group by the Boc group was necessary to avoid the formation of byproducts during the bromination: The conversion of quinoline **4** with NBS in CCl_4 at reflux leads also to substitution reactions on the aromatic ring. Treatment of imidazole-containing cyclopeptide **8**[10] with an excess amount of bromide **7** in the presence of K_2CO_3 as a base in CH_3CN provided **9** in a rather good yield. Deprotection of **9** was accomplished by treatment with trifluoroacetic acid (TFA) in dichloromethane to afford ligand **1** as a white solid in almost quantitative yield. The analyses of ligand **1** by MS (ESI) and NMR, IR and UV/Vis spectroscopy are in agreement with its structure. The NMR spectrum in $CDCl_3$ shows an ideal C_3 symmetry. The methylene signals of the benzylic group are separated by 0.04 ppm (δ =5.56 and 5.60 ppm) as doublets of doublets, which indicates that the diastereotopic protons of this group, on a time-averaged scale, have a different chemical environment.



Scheme 1. Synthesis of receptor arm **7**: (i) H_2SO_4, NaI, 110 °C, 50%; (ii) BBr_3, CH_2Cl_2, 0 °C, 66%; (iii) Boc_2O, NEt_3, CH_2Cl_2, room temp., 97%; (iv) NBS, CCl_4, Δ, 31%.



Scheme 2. Synthesis of ligand **1**: (i) K_2CO_3, **7**, CH_3CN, Δ, 56%; (ii) TFA, CH_2Cl_2, 0 °C, 99%.

Investigation of Complex Formation by *UV Absorption and CD Spectroscopy*

To a methanolic solution of ligand **1** was added a methanolic solution of Al^{3+}, Ga^{3+}, Fe^{3+}, La^{3+} and Y^{3+} ions, respectively, in a molar ratio of 1:2 and the UV absorption and the CD spectra of the formed complexes were measured simultaneously as a function of time. For all metal ions the same behaviour was found: the spectra of the complexes are different in comparison to those of pure ligand **1**, but no spectral changes were found in dependence of time; thus complex formation is very fast.

The thermodynamic parameters of the metal complexes of **1** were determined by titration experiments at room temperature. For this purpose, a methanolic solution containing ligand **1** (10^{-5} M) together with NaOH (10^{-4} M) and a titrant solution containing both **1** and the appropriate metal salt ([**1**] = 10^{-5} M, [M^{3+}] = 2×10^{-4} M in MeOH; [NaOH] = 10^{-4} M) were prepared. The titration was performed by using an automatic titration unit connected to the spectropolarimeter by adding the titrant solution in discrete steps to the solution containing ligand **1** and recording the spectra after a mixing time of 2 min.

The UV spectrum of ligand **1** shows two main absorptions, one located below 210 nm and the other at 246 nm (Figure 3). The imidazole scaffold and the hydroxyquinoline side arms both contribute to the absorption at the short wavelength, whereas the absorption at 246 nm can be assigned only to the hydroxyquinoline side arms. The CD spectrum of ligand **1** exhibits a small positive Cotton effect at 213 nm and a strong one at 274 nm. The latter is caused by the hydroxyquinoline side arms. Furthermore, there are two negative Cotton effects at 244 and 251 nm that are about the same size. If Al^{3+} ions were used as guests, the absorption band at 246 nm showed a strong bathochromic shift to 263 nm, whereas the band below 210 nm underwent a moderate shift (Figure 3). Also in the CD spectra the formation of the complexes can be observed. Upon addition of Al^{3+} ions to ligand **1** the two negative Cotton effects at 244 and 251 nm merge into one strong band at 256 nm and a positive Cotton effect emerges at 270 nm (Figure 3). The same qualitative spectral changes in the UV region could be observed during the titration of **1** with Ga^{3+}, Fe^{3+}, La^{3+} and Y^{3+} ions, and the CD spectra of the complexes after the addition of 2 equivalents of metal ions look like the same (Figure 4). The obtained titration curves for the complexes of **1** with Al^{3+}, Ga^{3+} and La^{3+} ions show that after adding approximately 2.0 equivalents of the guest the curve fades into a plateau and a saturation of the host begins to arise. In contrast to this, for the Y^{3+} ion, saturation was reached before adding 2.0 equivalents of the guest, which indicates a different stoichiometry for this complex than that of the Al^{3+}, Ga^{3+} and La^{3+} complexes. In the case of complexation of **1** with Fe^{3+} ions no saturation could be observed.

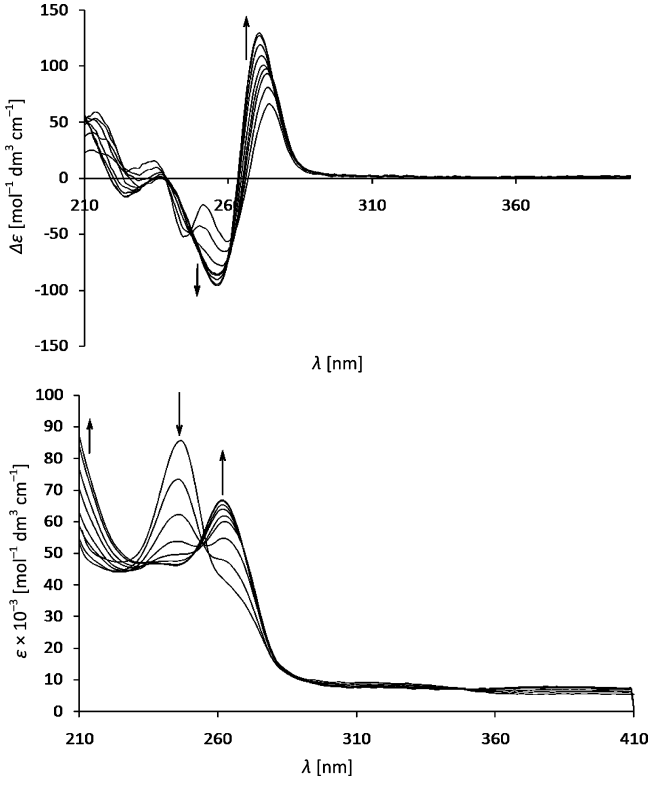


Figure 3. CD and UV absorption titration curves for complexation of **1** with Al^{3+} [**1**] = 10^{-5} M, MeOH; 10^{-4} M NaOH. Top: CD spectra; bottom: UV absorption spectra.

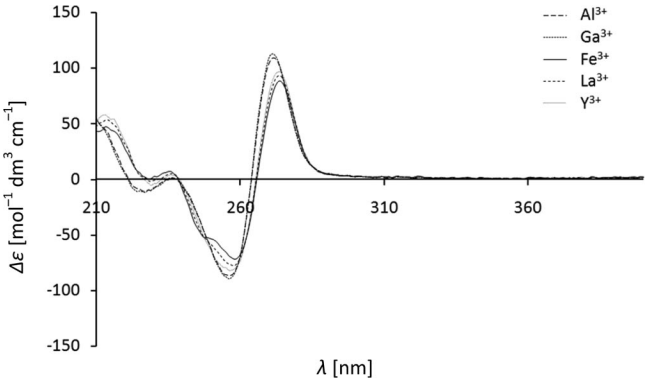


Figure 4. CD spectra for complexation of **1** with Al^{3+}, Ga^{3+}, Fe^{3+}, La^{3+} and Y^{3+} ions ([**1**] = 10^{-5} M, [M^{3+}] = 2×10^{-5} M, MeOH; 10^{-4} M NaOH).

Job plot analyses of the two-component system of **1** and the metal ions reflect the above-observed behaviour of the individual ions.[24] In the case of Al^{3+}, Ga^{3+} and La^{3+} ions, a pure 1:1 stoichiometry was found (Figure 5). In contrast thereto, ligand **1** forms a complex with Y^{3+} in a 2:1 stoichiometry. For the complexation of **1** with Fe^{3+} ions no defined stoichiometry was detected.

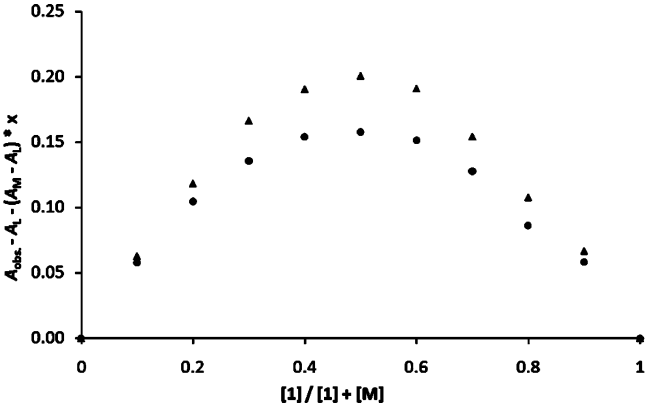


Figure 5. UV absorption Job plots for complexation of **1** with Al^{3+} (circles) and Ga^{3+} (triangles) ions at 246 nm ([**1**] + [M^{3+}] = 10^{-5} M, MeOH; 10^{-4} M NaOH buffer), $\{y = A_{obs.} - A_L - (A_M - A_L)x$ vs. $x = [\mathbf{1}]/([\mathbf{1}] + [M^{3+}])\}$.

The affinities of ligand **1** for the metals under the conditions employed were evaluated as virtual binding constants according to Equation (1), which represents a simplified association constant involving all protonation/deprotonation and metal ion coordination steps. Although this constant is only applicable for the pH value applied for the measurement, it can provide information about the selectivity toward different cationic guests.

$$K_{virt}^{LM} = \frac{[LM]}{([L]_{tot} - [LM])([M]_{tot} - [LM])} \quad (1)$$

The virtual association constants of the complexation systems were calculated by nonlinear least-square fitting according to the modified Benesi–Hildebrand equation from the UV absorption data set. Best reproducible results and lowest error could be obtained if absorption values at 246 and 263 nm were used for evaluation. Nonlinear curve fit for a simple 1:1 binding model was carried out with the SigmaPlot program. The highest stability constant was determined for La^{3+} (2.29×10^6 dm^3 mol^{-1}), followed by Al^{3+} (7.67×10^5 dm^3 mol^{-1}) and Ga^{3+} (1.13×10^5 dm^3 mol^{-1}). A simple explanation for this relative order could not be found.

Investigation of the Configuration of the Metal Complexes by Using Ab Initio Methods

The extent of diastereoselective complex formation caused by the chiral macrocyclic scaffold of ligand **1** was investigated by ab initio calculations.[25] Full geometry optimizations were performed for the Δ and Λ complexes of **1** with Al^{3+} and Ga^{3+} ions by applying the DFT method at the B3LYP/6-31G* level of theory. The energy differences between the diastereomers of **1** vary between 88.3 kJ mol^{-1} for the aluminum complex and 89.0 kJ mol^{-1} for the gallium complex, both in favour of the Λ stereoisomers. On the basis of these energy differences between the two diastereomers, the ratio of the Boltzmann population between the Λ and Δ complexes of **1** with Al^{3+} and Ga^{3+} ions should be approximately 10^{15}:1 at 298 K, which accounts for complete diastereoselectivity at room temperature according to Boltzmann–Gibbs distribution. With the assumption that the enthalpy of interaction between the complexes and the solvent does not differ significantly for the two possible helical isomers, this stereoselectivity must persist in solution, too.

Examination of the calculated structures of the isomers of complex **1**·Al should help to explain the high energetic discrimination between the isomers (Figure 6). In the case of the Λ isomer, the three arms are perfectly arranged in a helix-like orientation and the metal ion can be octahedrally bonded to the three hydroxyquinoline units. In the case of the Δ isomer, the quinoline arms must point into the other direction and a strong repulsive interaction between the arms and the methyl groups on the imidazole rings occurs. To avoid this interaction, the arms of the Δ complex are not as strongly bent as in the case of the Λ complex. A consequence of this bending is the different distances between the metal ions and the scaffold of the cyclopeptide. For the Δ isomer, the distance between the aluminum ion and the hydrogen atom of the amide bond was calculated to be 7.91 Å. In the case of the Λ isomer where the arms relative to the scaffold are more strongly bent, a value of 7.19 Å was found. This distortion from ideal octahedral geometry in the Δ complex leads to a high energetic discrimination between the isomers. The calculated energetic difference being caused by steric interaction explains why this is independent from the used trivalent metal ions (Al^{3+} and Ga^{3+} ions). This is in accordance with the fact that the CD spectra of the complexes of **1** with the used trivalent metal ions look the same (Figure 4).

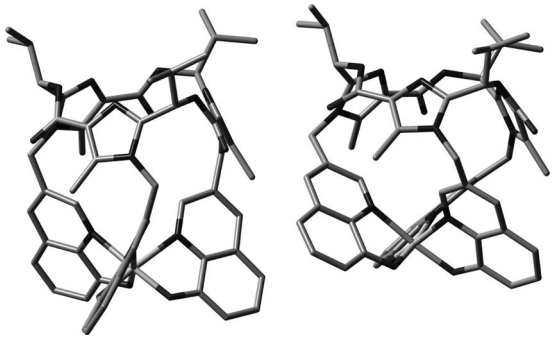


Figure 6. Molecular structures of the Δ (left) and Λ isomers (right) of complex **1**·Al calculated by using B3LYP/6-31G*; all hydrogen atoms were omitted for clarity.

For further evidence that only Λ stereoisomers are formed in solution, the UV and CD spectra of both stereoisomers of the aluminum(III) complex of **1** were simulated on the basis of time-dependent density functional theory (TD-DFT) with the B3LYP functional and by employing the 6-31G* basis set. For each metal complex, TD-DFT calculations were performed at the optimized ground-state geometry, calculating the energy, oscillator strength and rotatory strength for each of the 250 lowest singlet excitations. The calculated maxima of the UV spectra show a hypsochromic shift of 13 nm relative to the measured UV spectrum. To correct this deviation all calculated spectra were shifted bathochromically by this value. The CD spec-

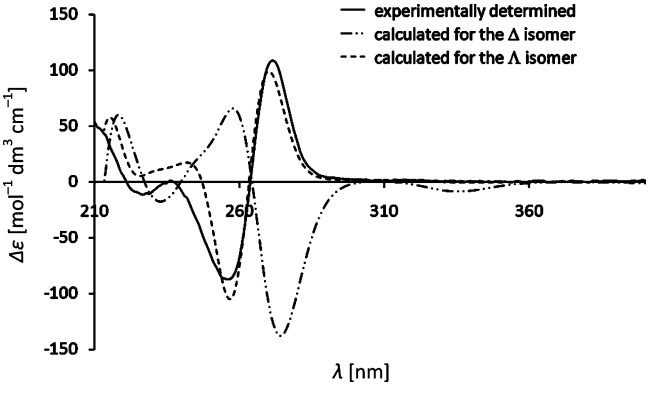


Figure 7. CD spectra of complex **1**·Al experimentally determined and calculated at the TD-DFT-B3LYP/6-31G* level.

tra were simulated by overlapping Gaussian functions for each transition where the width of the band at 1/*e* height was fixed at 0.3 eV and the resulting intensities of the combined spectra were scaled to the experimental values. As usual, the calculated band intensities were larger than their experimental counterparts. The measured and the calculated spectra of complex **1**·Al are depicted in Figure 7. The almost perfect congruence between the measured CD spectrum and the calculated one for the Λ isomer shows that indeed this stereoisomer is present in solution.

Conclusions

In summary, we presented a straightforward synthesis for a C_3-symmetric imidazole-containing macrocyclic peptide with three hydroxyquinoline side arms. We could show that this ligand binds various trivalent metal ions (Al^{3+}, Ga^{3+}, Fe^{3+}, La^{3+} and Y^{3+}), but only in the case of the Al^{3+}, Ga^{3+} and La^{3+} complexes was a pure 1:1 stoichiometry observed. The stability constants for these complexes range from 1.13×10^5 $dm^3 mol^{-1}$ for Ga^{3+} to 2.29×10^6 $dm^3 mol^{-1}$ for La^{3+}. All metal complexes exhibit the Λ configuration at the octahedrally bonded metal ions, which was proved by their CD spectra and by ab initio methods. Thus, the imidazole-containing macrocyclic scaffold is an excellent system for controlling the helicity at a coordinated metal centre.

Experimental Section

General Remarks: All chemicals were reagent grade and used as purchased. Reactions were monitored by TLC analysis by using silica gel 60 F_{254} thin-layer plates. Flash chromatography was carried out on silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were measured with Bruker Avance DMX 300 and Avance DRX 500 spectrometers. All chemical shifts (δ) are given in ppm relative to TMS. The spectra were referenced to deuterated solvents indicated in brackets in the analytical data. HRMS spectra were recorded with a Bruker BioTOF III Instrument. IR spectra were measured with a Varian 3100 FTIR Excalibur Series spectrometer. UV/Vis absorption spectra were obtained with a Varian Cary 300 Bio; CD-absorption spectra were taken with a Jasco J-815 spectrophotometer equipped with a Jasco ATS-443 automatic titration unit.

8-Methoxy-3-methylquinoline (4): *O*-Anisidine (34.0 mmol, 5.0 mL) and sodium iodide (0.5 mmol, 70 mg) were dissolved in 70% H_2SO_4 (16.0 mL) at 0 °C. The solution was then heated at 110 °C. Methacrolein (54.1 mmol, 10.0 mL) was added dropwise over 3 h. The reaction mixture was stirred for 3 h at 110 °C, cooled to room temperature and stirred for a further 16 h at that temperature. Methylene chloride was added, and the mixture was neutralised with 1 M sodium hydrogen carbonate solution. The layers were separated, and the aqueous layer was washed with dichloromethane. The combined organic layers were dried with anhydrous magnesium sulfate. The solution was concentrated to dryness. The crude product was purified by column chromatography (silica gel; ethyl acetate/*n*-hexane, 1:6) to yield **4** (2.96 g, 50%) as a brown solid. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.63 (s, 1 H, H_{ar}), 7.66 (s, 1 H, H_{ar}), 7.24 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, H_{ar}), 7.12 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, H_{ar}), 6.79 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, H_{ar}), 3.90 (s, 3 H, Ar-CH_3), 2.30 (s, 3 H, O-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.1 (q, C_{ar}), 150.8 (t, C_{ar}), 138.1 (q, C_{ar}), 134.3 (t, C_{ar}), 130.8 (q, C_{ar}), 129.0 (q, C_{ar}), 126.5 (t, C_{ar}), 118.7 (t, C_{ar}), 106.4 (t, C_{ar}), 55.9 (p, O-CH_3), 18.4 (p, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3428, 3061, 2960, 1497, 1377, 1268, 1107, 765 cm^{-1}. UV/Vis (DCM, $c = 1.88 \times 10^{-3}$ mmol mL^{-1}): λ (log ε) = 303 (3.77) nm. HRMS (ESI): calcd. for $C_{11}H_9NO$ $[M + H]^+$ 174.0913; found 174.0927. HRMS (ESI): calcd. for $C_{11}H_9NO$ $[M + Na]^+$ 196.0733; found 196.0749. $C_{11}H_9NO$ (171.20): calcd. C 76.28, H 6.40, N 8.09; found C 76.00, H 6.67, N 7.67.

8-Hydroxy-3-methylquinoline (5): Quinoline **4** (3.46 mmol, 600 mg) was dissolved in dichloromethane (10.0 mL) and cooled to 0 °C. At that temperature, a solution of BBr_3 in dichloromethane (1 M; 6.93 mmol, 6.9 mL) was added dropwise. The solution was stirred at room temperature for 16 h. Methylene chloride and water were added. The organic layer was separated and dried with anhydrous magnesium sulfate. The solution was concentrated to dryness. The product (364 mg, 66%) was obtained as a brown solid. ^1H NMR (300 MHz, MeOD): δ = 8.89 (s, 1 H, H_{ar}), 8.83 (s, 1 H, H_{ar}), 7.72 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, H_{ar}), 7.62 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H, H_{ar}), 7.36 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, H_{ar}), 2.51 (s, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, MeOD): δ = 150.0 (q, C_{ar}), 146.4 (t, C_{ar}), 145.9 (t, C_{ar}), 134.5 (q, C_{ar}), 132.0 (t, C_{ar}), 131.7 (q, C_{ar}), 129.9 (q, C_{ar}), 119.5 (t, C_{ar}), 116.0 (t, C_{ar}), 18.6 (p, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3442, 2961, 2881, 2781, 1679, 1632, 1558 cm^{-1}. UV/Vis (DCM, $c = 1.73 \times 10^{-3}$ mmol mL^{-1}): λ (log ε) = 312 (3.57), 322 (3.56), 368 (3.43) nm. HRMS (ESI): calcd. for $C_{10}H_9NO$ $[M + H]^+$ 160.0757; found 160.0762. HRMS (ESI): calcd. for $C_{10}H_9NO$ $[M + Na]^+$ 182.0576; found 182.0589.

***tert*-Butyl 3-Methylquinolin-8-yl Carbonate (6):** Quinoline **5** (0.56 mmol, 89 mg) was dissolved in dichloromethane (10.0 mL) under an argon atmosphere. Di-*tert*-butylcarbonate (0.64 mmol, 140 mg), triethylamine (2.73 mmol, 0.2 mL) and DMAP (10 mg) were added at room temperature. The solution was stirred at room temperature for 14 h. Then, dichloromethane and water were added, and the organic layer was separated, washed with brine and dried with anhydrous magnesium sulfate. The solution was concentrated to dryness. The crude product was purified by column chromatography (silica gel; ethyl acetate/*n*-hexane, 1:1) to yield **6** (140 mg, 97%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.78 (s, 2 H, H_{ar}), 7.92 (s, 2 H, H_{ar}), 7.61–7.63 (m, 1 H, H_{ar}), 7.43–7.49 (m, 2 H, H_{ar}), 2.51 (s, 3 H, CH_3), 1.60 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.4 (t, C_{ar}), 152.1 (q, C=O), 147.4 (q, C_{ar}), 139.5 (q, C_{ar}), 134.4 (t, C_{ar}), 131.3 (q, C_{ar}), 129.4 (q, C_{ar}), 126.2 (t, C_{ar}), 125.0 (t, C_{ar}), 119.9 (t, C_{ar}), 83.5 [q, $C(CH_3)_3$], 27.7 [p, $C(CH_3)_3$], 18.7 (p, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3493, 3055, 2934, 1756, 1372, 1276, 1235, 1148 cm^{-1}. UV/Vis (DCM, $c = 1.18 \times 10^{-3}$ mmol mL^{-1}): λ (log ε) = 237 (4.49), 302 (4.38) nm. HRMS (ESI): calcd. for $C_{15}H_{17}NO_3$ $[M + H]^+$ 260.1281; found 260.1293. HRMS (ESI): calcd. for $C_{15}H_{17}NO_3$ $[M + Na]^+$ 282.1101; found 282.1116. $C_{15}H_{17}NO_3$ (259.30): calcd. C 69.48, H 6.61, N 5.40; found C 69.18, H 6.57, N 5.41.

3-(Bromomethyl)quinolin-8-yl *tert*-Butyl Carbonate (7): Quinoline **6** (2.51 mmol, 650 mg), NBS (2.51 mmol, 450 mg) and AIBN (10 mg) were dissolved in tetrachloromethane (50 mL). The solution was heated to 100 °C and irradiated for 6 h with visible light. After cooling to room temperature, the reaction mixture was filtered. The solution was concentrated to dryness. The crude product was purified by column chromatography (silica gel; ethyl acetate/*n*-hexane, 1:9) to yield **7** (269 mg, 31%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.95 (s, 1 H, H_{ar}), 8.15 (s, 2 H, H_{ar}), 7.69–7.71 (m, 1 H, H_{ar}), 7.53–7.55 (m, 2 H, H_{ar}), 4.64 (s, 2 H, CH_2), 1.60 [s, 9 H,

$C(CH_3)_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.1 (q, C=O), 151.3 (t, C_{ar}), 147.6 (q, C_{ar}), 140.8 (q, C_{ar}), 135.6 (t, C_{ar}), 131.6 (q, C_{ar}), 128.9 (q, C_{ar}), 127.1 (t, C_{ar}), 125.8 (t, C_{ar}), 121.7 (t, C_{ar}), 84.0 [q, $C(CH_3)_3$], 29.8 (s, CH_2-Br), 27.9 [p, $C(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3438, 3062, 3036, 2987, 2978, 2932, 1758, 1281, 1241, 1149 cm^{-1}. UV/Vis (DCM, $c = 2.97 \times 10^{-4}$ mmol mL^{-1}): λ (log ε) = 306 (3.90) nm. HRMS (ESI): calcd. for $C_{15}H_{16}BrNO_3$ [M(^{81}Br) + H]$^+$ 340.0367; found 340.0362. HRMS (ESI): calcd. for $C_{15}H_{16}BrNO_3$ [M(^{79}Br) + H]$^+$ 338.0386; found 338.0381. HRMS (ESI): calcd. for $C_{15}H_{16}BrNO_3$ [M(^{81}Br) + Na]$^+$ 362.0187; found 362.0182. HRMS (ESI): calcd. for $C_{15}H_{16}BrNO_3$ [M(^{79}Br) + Na]$^+$ 360.0206; found 360.0202. $C_{15}H_{16}BrNO_3$ (338.20): calcd. C 53.27, H 4.77, N 4.14, Br 23.63; found C 53.48, H 5.07, N 4.01, Br 23.41.

Cyclopeptide 9: To quinoline **7** (46 μmol, 25 mg) in acetonitrile (16 mL) was added anhydrous potassium carbonate (714 μmol, 100 mg) and scaffold **1** (296 μmol, 100 mg). The solution was heated at reflux for 6 h. After cooling to room temperature the solution was stirred for 5 d. Afterwards, the solution was concentrated to dryness. The residue was dissolved in dichloromethane, washed with water and brine and dried with anhydrous magnesium sulfate. The solution was concentrated to dryness. The crude product was purified by column chromatography (silica gel; ethyl acetate/*n*-hexane, 1:9) to yield **9** (27 mg, 56%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.81 (d, $^4J_{H,H}$ = 2.3 Hz, 1 H, H_{ar}), 8.45 (d, $^3J_{H,H}$ = 9.4 Hz, 1 H, NH), 7.67 (s, 1 H, H_{ar}), 7.53–7.55 (m, 1 H, H_{ar}), 7.48–7.49 (m, 1 H, H_{ar}), 7.41–7.43 (m, 1 H, H_{ar}), 5.38 (dd, ^2J = 17.3 Hz, 1 H, CH_2-Ar), 5.30 (dd, ^2J = 17.3 Hz, 1 H, CH_2-Ar), 5.22–5.25 [m, 1 H, NH-CH-CH$(CH_3)_2$], 2.44 (s, 3 H, Imid-CH_3), 2.04–2.06 [m, 1 H, C$H(CH_3)_2$], 1.58 [s, 9 H, C$(CH_3)_3$], 1.05 [d, ^3J = 6.7 Hz, 3 H, CH$(CH_3)_2$], 0.96 [d, ^3J = 6.8 Hz, 3 H, CH$(CH_3)_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1 (q, C=O), 151.8 (q, C=O), 148.6 (t, C_{iso}), 147.5 (q, C_{iso}), 147.3 (q, C_{imi}), 140.8 (q, C_{iso}), 133.1 (t, C_{iso}), 132.0 (q, C_{iso}), 130.5 (q, C_{imi}), 128.9 (q, C_{iso}), 128.8 (q, C_{imi}), 127.0 (t, C_{iso}), 125.6 (t, C_{iso}), 121.5 (t, C_{iso}), 84.0 [q, $C(CH_3)_3$], 60.0 [t, NH-CH-CH$(CH_3)_2$], 45.0 (s, CH_2), 34.7 [t, $C(CH_3)_2$], 27.7 [p, $C(CH_3)_3$], 19.9 [p, $C(CH_3)_2$], 17.6 [p, $C(CH_3)_2$], 9.9 (p, imidazole-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3385, 3066, 2932, 1757, 1655, 1496, 1273, 1234, 1143 cm^{-1}. UV/Vis (MeOH, $c = 1.66 \times 10^{-5}$ mmol mL^{-1}): λ (log ε) = 272 (4.34) nm. HRMS (ESI): calcd. for $C_{72}H_{84}N_{12}O_{12}$ [M + H]$^+$ 1309.6404; found 1309.6511. HRMS (ESI): calcd. for $C_{72}H_{84}N_{12}O_{12}$ [M + Na]$^+$ 1331.6224; found 1331.6327.

Ligand 1: Cyclopeptide **9** (21 μmol, 27 mg) was dissolved in anhydrous dichloromethane (8.0 mL) under an argon atmosphere and cooled to 0 °C. TFA (13.132 mmol, 1.0 mL) was added dropwise. The solution was stirred at 0 °C for 30 min. The reaction mixture was warmed up to room temperature and stirred for 3 h. The solution was concentrated to dryness. The residue was stripped several times to remove the excess amount of TFA to provide **1** (21 mg, 99%). ^1H NMR (500 MHz, MeOD): δ = 8.84 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, H_{ar}), 8.45 (d, $^3J_{H,H}$ = 9.8 Hz, 1 H, H_{ar}), 7.37–7.41 (m, 2 H, H_{ar}), 7.21–7.24 (m, 1 H, H_{ar}), 7.17 (m, 1 H, H_{ar}), 5.70 (dd, ^2J = 17.8 Hz, 1 H, CH_2-Ar), 5.56 (dd, ^2J = 17.8 Hz, 1 H, CH_2-Ar), 5.03 [m, 1 H, NH-CH-CH$(CH_3)_2$], 2.33 (s, 3 H, Imid-CH_3), 2.01–2.14 [m, 1 H, C$H(CH_3)_2$], 1.03 [d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH$(CH_3)_2$], 0.67 [d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH$(CH_3)_2$] ppm. ^{13}C NMR (125 MHz, MeOD): δ = 164.6 (q, C=O), 151.8 (q, C_{imi}), 149.4 (q, C_{iso}), 145.4 (t, C_{iso}), 140.0 (t, C_{iso}), 134.3 (q, C_{iso}), 132.1 (q, C_{imi}), 131.1 (q, C_{iso}), 131.01 (q, C_{iso}), 130.98 (q, C_{imi}), 130.91 (t, C_{iso}), 119.6 (t, C_{iso}), 115.1 (t, C_{iso}), 51.5 [t, NH-CH-CH$(CH_3)_2$], 45.2 (s, CH_2), 36.0 [t, $C(CH_3)_2$], 19.8 [p, $C(CH_3)_2$], 18.3 [p, $C(CH_3)_2$], 9.9 (p, imidazole-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3439, 3076, 2965, 2927, 1681, 1645, 1202, 1136 cm^{-1}. UV/Vis (MeOH, $c = 1.00 \times 10^{-5}$ mmol mL^{-1}): λ (log ε) = 246 (4.84), 335 (3.85) nm. HRMS (ESI): calcd. for $C_{57}H_{60}N_{12}O_6$ [M + H]$^+$ 1009.4832; found 1009.4782. HRMS (ESI): calcd. for $C_{57}H_{60}N_{12}O_6$ [M + Na]$^+$ 1031.4651; found 1031.4616.

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