

Ligand designed with pending phenol group

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Abstract—The synthesis of a salicylaldehyde derivative facing an encumbered phenol group on a naphthalene block as a molecular shaft is reported. This molecular unit has been designed to elaborate coordinating ligands holding non-coordinating phenol group for the generation of phenoxyl radical in the close proximity of a metal complex.

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1. Introduction

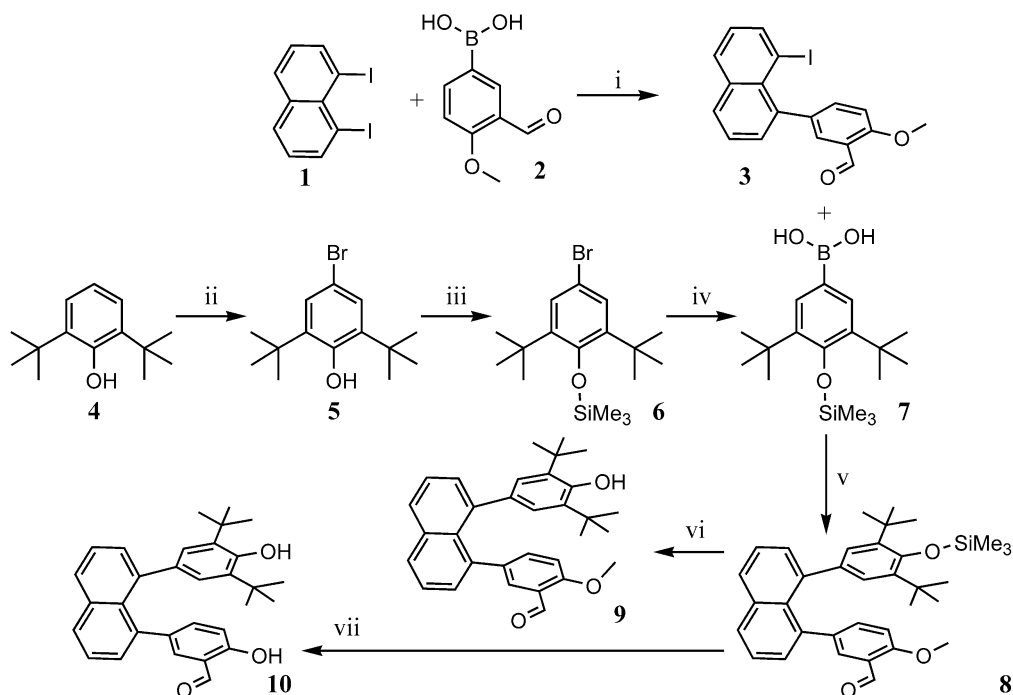
Tyrosyl radicals are known to play an essential role in the functioning of different metalloenzymes. In photosystem II (PSII), the tyrosyl radicals named Y_z^* and $Y_D^{1,2}$ are crucial for the photooxidation of water. Y_z stands between the manganese cluster of the oxygen evolving complex and the pigment P_{680} and plays the role as an electron relay in the photoaccumulation of oxidising power at the OEC. In the Ribonucleotide Reductase R2 protein, responsible for the transformation of ribonucleotides to deoxyribonucleotides, the tyrosyl radical, Tyr₁₂₂, is oriented towards the dimetallic core where the closest distance between the phenolic oxygen atom and the iron atom is 5.3 Å.^{3–5} Other selected examples can be found in a seminal review by Stubbe et al.⁶ A striking feature in the two above-mentioned examples is that the tyrosyl radical cofactor is not directly coordinated to the metal core. Across the years, bioinorganic chemists have designed well elaborated ligands to generate as closely as possible the first coordination sphere of the metal ions as found in the natural systems. However, although a high degree of sophistication has been introduced in the ligand design for the biomimetic modelisation of enzymes, still a great synthetic effort must be done to take into account other cofactors, which are not in the first coordination sphere of the metal catalytic centre.

Lippard et al. described the first example of a biomimetic model of the R2 active site where they incorporated two main features, a (μ-oxo)(μ-carboxylato)-diiron(III) core and a stable phenoxyl radical held close but not coordinated to the metallic core.⁷ However, the phenoxyl radical was not oriented towards the metallic core contrary to what is observed in the ‘real thing’. If the topology of dinuclear metal complexes for biomimicry has been widely developed, there is still a paucity on the design of ligands capable to hold at the same time the metal ions and other features like potential centre for generation of radicals in close proximity but not directly coordinated to the metal ions. Recently, Nocera et al. has devised a series of ‘Hangman ligands’ containing porphyrin or salophen as redox molecular platforms with a well positioned acid–base function acting as proton shuttle.^{8,9} These molecular systems have been used to illustrate the proton coupled electron transfer events.

Following the goal of bioinorganic chemists of understanding the basic principles of the structure–function relationship of metalloprotein in our laboratory, we have developed a series of ligands and studied the reactivities of the metal complexes.^{10–12} In an effort to translate the microenvironment of the metal ions at the active sites of metalloproteins especially those where a tyrosine residue plays a redox role, we describe hereby the synthetic tactics to reach a novel family of ligands bearing a salen-type coordinating cavity surmounted by a pending phenol group. Our idea is to elaborate a superstructure where a phenoxyl radical could be generated in the right topology towards the metal ions in order to gain insights into the physical properties of such metalloradical species.

Keywords: Suzuki coupling; Duff reaction; Salen-type ligand; Pending phenol.

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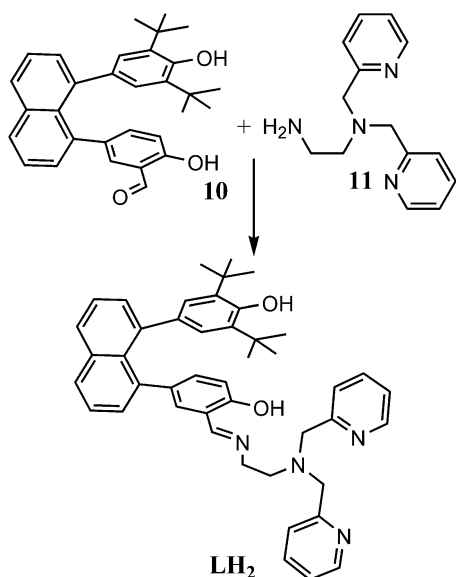
Scheme 1. Reagents and conditions: (i) Na_2CO_3 , $\text{Pd}(\text{PPh}_3)_4$ (5 mol %) in toluene/EtOH/ H_2O (2/2/1) reflux 12 h; (ii) Br_2 in CHCl_3 0 °C; (iii) *n*-BuLi/ ClSiMe_3 in THF –78 °C; (iv) *n*-BuLi/ $\text{B}(\text{OMe})_3$ in THF; (v) Na_2CO_3 , $\text{Pd}(\text{PPh}_3)_4$ (5 mol %) in toluene/EtOH/ H_2O (2/2/1) reflux 12 h; (vi) HCl 1 M; (vii) BBr_3 in CH_2Cl_2 0 °C.

The synthetic scheme leading to our target ligand is shown in Scheme 1. The 1,8-diodonaphthalene derivative **1** was chosen as the molecular shaft¹³ and the first deck was fixed following a Suzuki cross coupling reaction¹⁴ using 1 equiv of 3-formyl-4-methoxyphenylboronic acid **2** and 1 equiv of **1** in typical literature procedure in a mixture of toluene/ethanol/water (2/2/1) using Na_2CO_3 as base and $\text{Pd}(\text{PPh}_3)_4$ (5 mol %) as catalyst. After conventional workup, compound **3** was purified from a silica gel column chromatography using CH_2Cl_2 as eluent with a yield of 35%. The other compounds were characterised as the dicoupled compound and the unreacted material. The upper module for our synthesis, 3,5-di-*tert*-butyl-4-trimethylsilyloxyphenyl boronic acid **7** was prepared following literature procedures starting from the commercially available compound 2,6-di-*tert*-butylphenol **4**. Bromination in the *para* position of the OH group was carried out at low temperature and under inert atmosphere with bromine to give compound **5**.¹⁵ The OH group was protected upon treatment with *n*-BuLi followed by addition of chlorotrimethylsilane **6**.¹⁶ The boronic acid derivative **7** was synthesised by treatment of **6** with *n*-BuLi at low temperature followed by the addition of trimethylborate.¹⁷ The presence of the *tert*-butyl groups on the phenol ring is to enhance the solubility on one side and to protect the *ortho* positions of the oxygen atom from performing radical chemistry as it is known that the spin density on a phenoxy radical is strongly delocalised in the *ortho* and *para* positions. Moreover, the bulky *tert*-butyl groups should also prevent any direct coordination with the metal centre in the coordinating cavity on the lower deck. The coupling reaction was realised under the same conditions as mentioned

above and after heating at 100 °C for 12 h. Compound **8** was isolated after purification on column chromatography (silica gel and CH_2Cl_2 as eluent) in a 75% yield. The trimethylsilyloxy group was cleaved by treatment with a one molar solution of HCl to give compound **9**, and both phenol groups could be freed upon treatment with BBr_3 to give compound **10**, which was recovered as a yellow solid (70% yield).^{18,19} The ¹H NMR spectrum of **10** translates the dissymmetry of the protons on the naphthalene skeleton.

The condensation of 1 equiv of the primary amine derivative **11** on the aldehyde derivative **10** leads to the ligand LH_2 , which was isolated as an off yellow solid (Scheme 2).

As an introductory chapter of the coordination chemistry of this family of ligand LH_2 , we have realised the metallation of the pentadentate coordinating cavity with zinc(II) ion. The choice of zinc(II) was guided for its electrochemical inactivity and diamagnetic nature. The metallation was performed upon treatment of 1 equiv of the ligand with 1 equiv of $\text{Zn}(\text{ClO}_4)_2 \cdot 4\text{H}_2\text{O}$ and 1 equiv of 2,6-dimethyl-pyridine as a base, in absolute ethanol. A white solid was isolated. Up to now we have not been able to obtain crystals of sufficient quality for an X-ray diffraction analysis. However, the electrospray mass spectrum of the isolated solid indicates a molecular peak at 739.3 corresponding to $[\text{LHZn}]^+$ motif and the isotopic pattern is well reproduced by the simulation (Fig. S1). Preliminary electrochemical studies have been performed on compound **9** (where only the pending phenol is subjected to oxidation) and the zinc complex for comparison of the redox potential of the pending



Scheme 2. Condensation of primary amine **11** in MeOH.

encumbered di-*tert*-butyl phenol group. Both cyclic voltammetry traces recorded in acetonitrile show an irreversible anodic process associated with the oxidation of the di-*tert*-butyl phenol function at 1.11 V versus SCE and 0.85 V versus SCE, respectively. This shift can be tentatively assigned to a more pronounced polarisation of the O–H group in the presence of the Zn(II) ion.²⁰ Note that a test cyclic voltammogram on the Zn(II) complex within the N₄O only cavity indicates that the oxidation of the coordinated phenol group is observed at 1.18 V versus SCE within the same experimental conditions. More electrochemical studies are currently undertaken to elucidate this issue.

2. Summary and conclusions

This type of ligand opens up a new coordination chemistry where bioinorganic chemists will be able to analyse the properties and reactivities of metalloradical species where the radical stands close to the metal centre but not directly coordinated to the metal ion. Along this line, manganese, iron and copper complexes with LH₂ are currently underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.034.

References and notes

- Rutherford, A. W.; Boussac, A.; Faller, P. *Biochim. Biophys. Acta* **2004**, *1655*, 222–230.
- Rutherford, A. W.; Boussac, A. *Science* **2004**, *303*, 1782–1784.
- Stubbe, J. In *Advances in Enzymology and Related Areas in Molecular Biology*; Meister, A., Ed.; John Wiley and Sons: New York, 1990; Vol. 63, pp 349–420.
- Fontecave, M.; Nordlund, P.; Eklund, H.; Reichard, P. In *Advances in Enzymology and Related Areas in Molecular Biology*; Meister, A., Ed.; John Wiley and Sons: New York, 1992; Vol. 65, pp 147–183.
- Stubbe, J. *Curr. Opin. Chem. Biol.* **2003**, *7*, 183–187.
- Stubbe, J.; van der Donk, W. A. *Chem. Rev.* **1998**, *98*, 705–762.
- Goldberg, D. P.; Koulougliotis, D.; Brudvig, G. W.; Lippard, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 3134–3144.
- Chang, C. J.; Chng, L. L.; Nocera, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 1866–1876.
- Liu, S.-Y.; Nocera, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 5278–5279.
- Balland, V.; Banse, F.; Anxolabéhère-Mallart, E.; Ghiladi, M.; Mattioli, T. A.; Philouze, C.; Blondin, G.; Girerd, J.-J. *Inorg. Chem.* **2003**, *42*, 2470–2477.
- Hureau, C.; Sabater, L.; Anxolabéhère-Mallart, E.; Nierlich, M.; Charlot, M.-F.; Gonnet, F.; Rivière, E.; Blondin, G. *Chem. Eur. J.* **2004**, *10*, 1998–2010.
- Lachaud, F.; Quaranta, A.; Pellegrin, Y.; Dorlet, P.; Charlot, M.-F.; Un, S.; Leibl, W.; Aukauloo, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1536–1540.
- Sabater, L.; Guillot, R.; Aukauloo, A. *Tetrahedron Lett.* **2005**, *46*, 2923–2926.
- Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
- Ooi, T.; Maruoka, K.; Yamamoto, H. *Org. Synth.* **1995**, *72*, 95–103.
- Lahti, P. M.; Liao, Y.; Julier, M.; Palacio, F. *Synth. Met.* **2001**, *122*, 485–493.
- Satoh, Y.; Shi, C. *Synthesis* **1994**, 1146–1148.
- Felix, A. M. *J. Org. Chem.* **1974**, *39*, 1427–1429.
- Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444–4446.
- Mayer, J. M.; Rhile, I. J. *Biochim. Biophys. Acta* **2004**, *1655*, 51–58.