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Syntheses of Hemoprotein Models that can be Covalently Attached onto Electrode Surfaces by Click Chemistry

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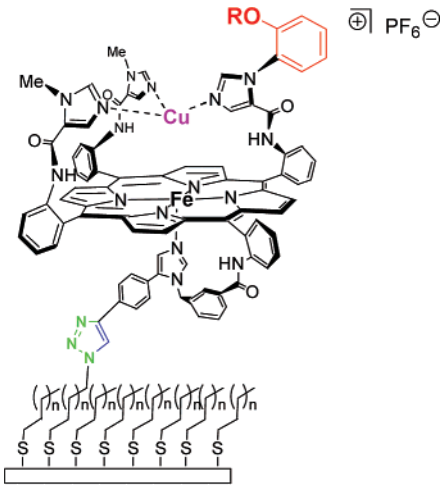

Five alkyne-containing hemoprotein models have been synthesized in a convergent manner. Sonogashira coupling was used to introduce the alkyne functional group on the proximal imidazole before or after being attached on the porphyrin. One model was immobilized onto a gold electrode surface via copper-(I)-catalyzed azide−alkyne cycloaddition (Sharpless click chemistry).

Introduction

Cytochrome *c* oxidase (CcO) is the heme/copper oxidase in the respiratory chains of mitochondria and aerobic bacteria that performs the 4e$^-$ reduction of dioxygen to water.[1] On the basis of crystal structures,[2a,b] our group has designed several models that structurally mimic the active site of the enzyme.[3a,d] Past electrocatalytic studies of O_2 reduction with these models have been conducted on an edge-plane-graphite electrode. Though convenient, this method relies on poorly defined physisorbed catalyst films that are in direct contact with the electrode allowing rapid electron delivery.[4a,c] To allow a slow and controlled rate of electron transfer as in the enzyme, we proposed to tailor the length and conjugation of azide-terminated alkyl chains that form self-assembled monolayers (SAM) coating the electrode. Such attachment has been achieved by the use of copper(I)-catalyzed azide−alkyne cycloaddition, a form of

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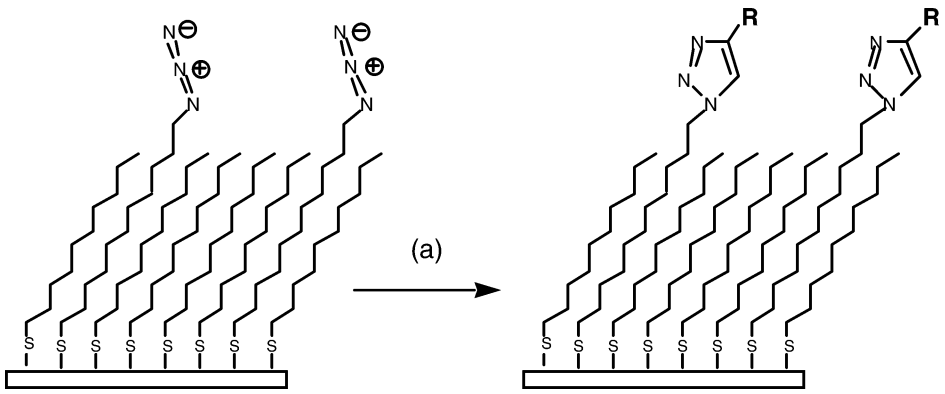


FIGURE 1. Click Chemistry on Surfaces. Reagents and conditions: (a) sodium ascorbate, Cu(I), R−CCH, where R = ferrocene, DNA, a hemoprotein model such as **1**−**5** (example with **5b** in Scheme 7).

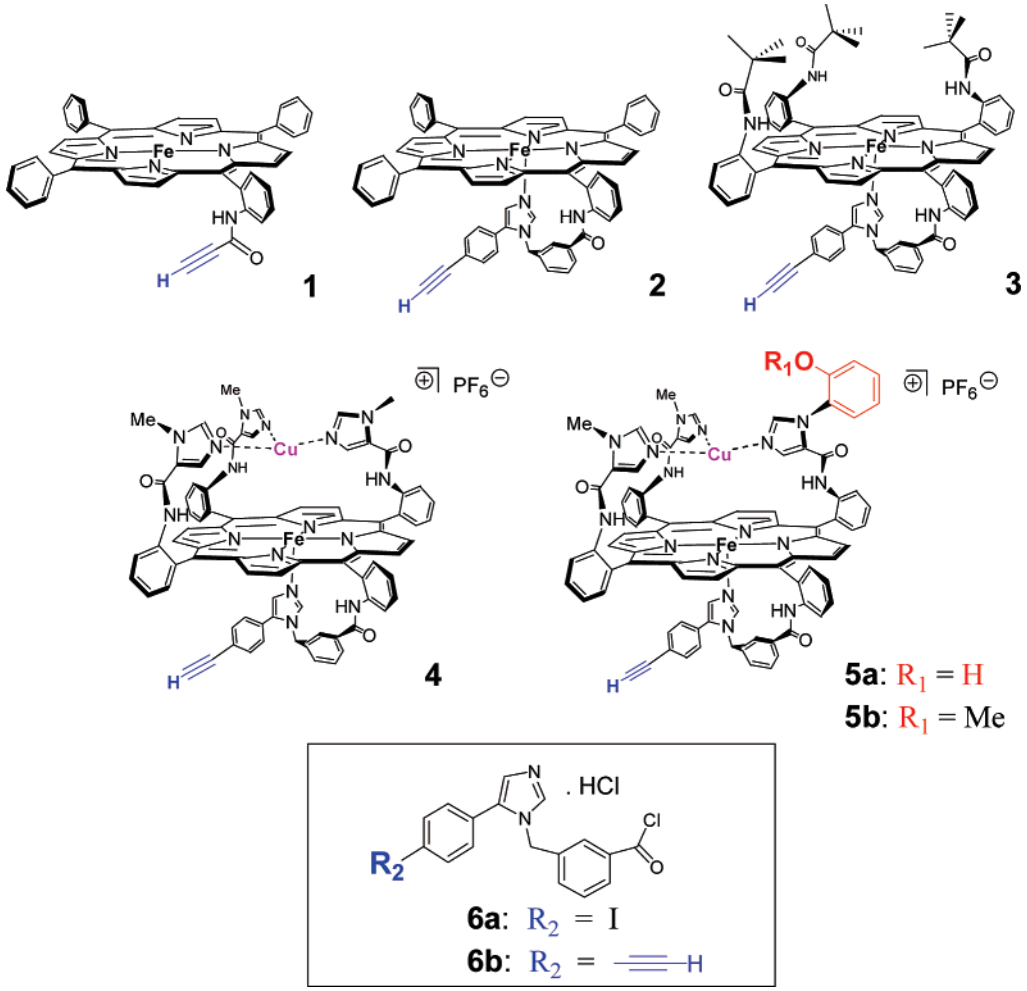
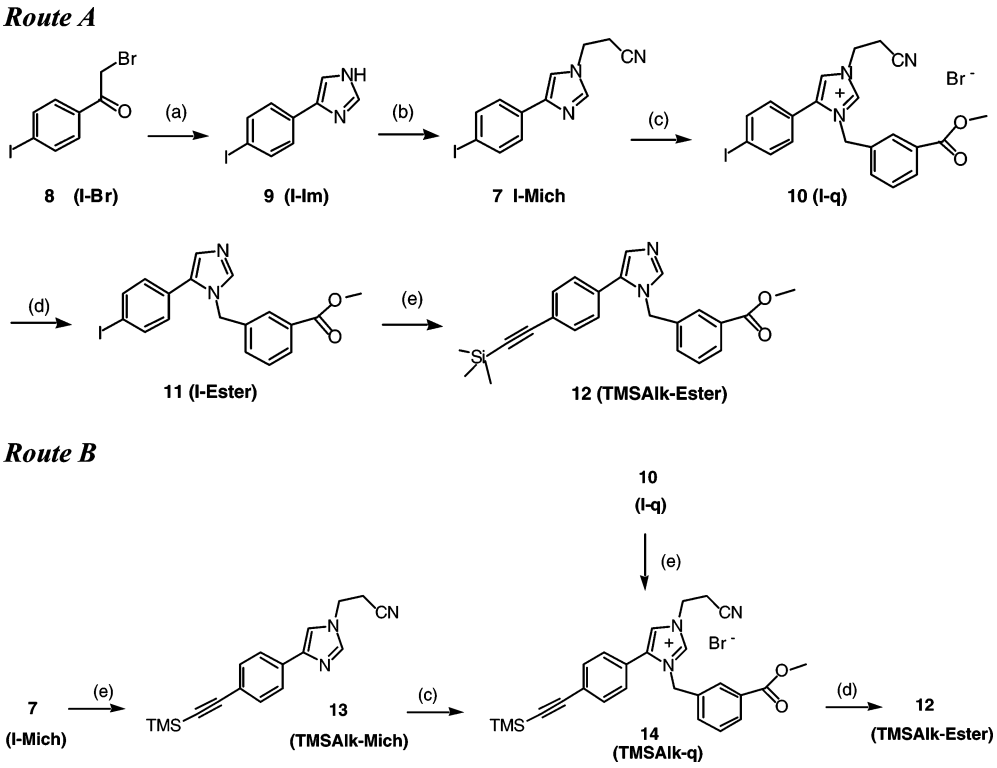


FIGURE 2. Alkyne-containing iron porphyrins **1**−**5** with increasing structural complexity for covalent attachment onto Au surfaces and the corresponding key alkyne-containing imidazole synthons (**6a**,**b**) that models **2**−**5** have in common.

Sharpless "click" chemistry[5] that we and others have adapted for the functionalization of surfaces (Figure 1).[6a−e] The conditions required for such reactions are mild and chemoselective, allowing for compatibility with a large number of functional groups.[5,6a−e] Moreover, this method is a practical alternative to previous immobilization methods on gold surfaces[6f,g] because it affords quantitative yields and no side products.[5,6a−e]

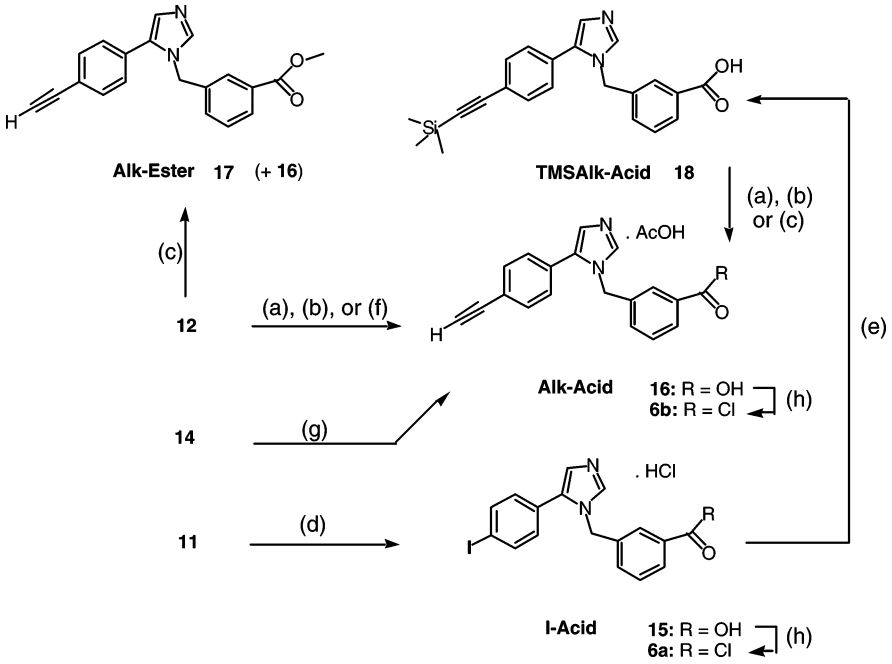
This present study is aimed at designing and synthesizing alkyne-containing CcO models and at clicking these models on azide-functionalized electrodes. The structural complexity is gradually increased from model **1** to model **5** (Figure 2) to revisit, under the regime of slow electron transfer, the role played by each key component of the CcO active site in the reduction of dioxygen. From a simple iron porphyrin (model **1**, that we previously clicked on a SAM),[6e] we have constructed a built-in proximal base mimicking His376 (model **2**). Then, a series of distal superstructures were added to a $\alpha_3\beta$-porphyrin atropisomer. Three simple picket fences in model **3** are designed to

SCHEME 1. Synthesis of TMSAlk-Ester (12)[a]



[a] Reagents and conditions: (a) formamide, 155 °C, 4 h, 34%; (b) acrylonitrile, vacuum, 190 °C, 2 h, 74%; (c) 3-bromomethylphenyl-3-methylcarboxylate, MeCN, 4.5 h, 100 °C, 48% (**10**), 80% (**14**); (d) CH_3ONa/CH_3OH, rt, 45 min, 48%; (e) trimethylsilylacetylene, $Pd(PPh_3)_4$, CuI, Et_3N, THF, rt, 75% (**12**), 88% (**13**), 70% (**14**).

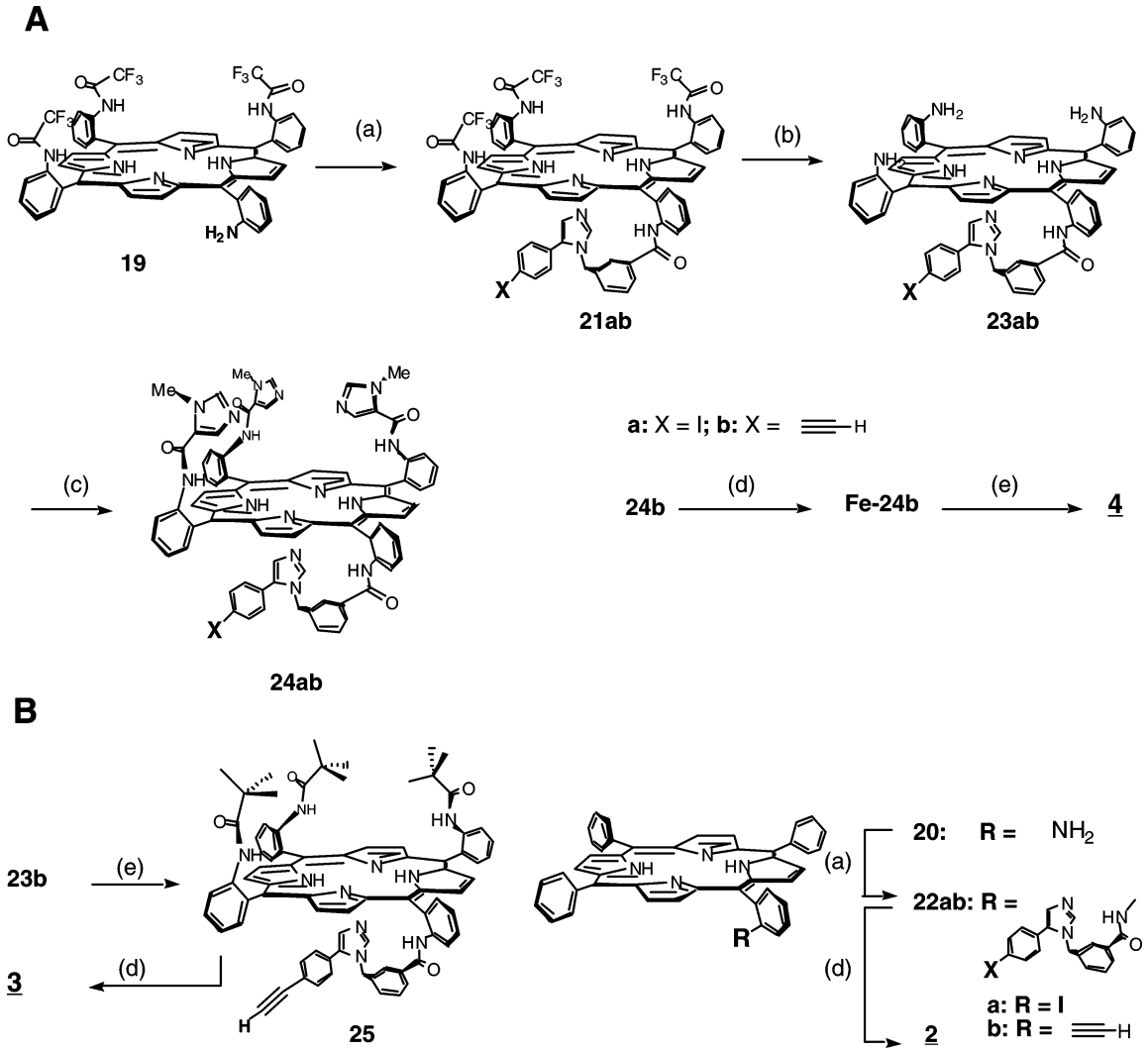
SCHEME 2. Deprotection of Ester and Alkyne Functions in 12: Synthesis of Alk-Acid 16[a]



[a] Reagents and conditions: (a) 1.5 N KOH, $THF/CH_3OH/H_2O$ 1:1:2 vol, 1 h; (b) AcOH, excess H_2O, 10 min, 85% (from **12**), 48% (from **14**); (c) KF or K_2CO_3, CH_3OH, rt, 4 h, quantitative; (d) HCl, reflux, quantitative; (e) trimethylsilylacetylene, $Pd(PPh_3)_4$, CuI, NEt_3, THF, rt, 88%; (f) LiI, acetone, rt, 24 h, 50%; (g) $CH_3ONa/CH_3OH/H_2O$, rt 1.5 h, 60%; (h) $(COCl)_2$, MeCN, DMF (cat.), rt, 2-4 h, 80% quantitative.

stabilize the oxygen complex with respect to **2** because of the hydrophobic environment provided by the *t*-Bu groups and the stabilizing hydrogen bond between dioxygen and a proton of an amide. Then, Cu^I in a trisimidazole environment is added (model **4**, mimicking Cu_B, His240, His290, and His291) at a biomimetic distance from the Fe center (ca. 5 Å). The final

SCHEME 3. (A) Synthesis of Trisimidazole-alkyne-Tailed Model 4 and (B) Synthesis of Picket-Fence-Tailed Model 3 and "Flat"-Tailed Model 2[a]



[a] Reagents and conditions: (a) **6a** or **6b**, MeCN/THF 2:1 vol, rt, 30 min, 70−80%; (b) NH_3-saturated MeOH/CH_2Cl_2 3:7 vol, 65%; (c) *N*-methyl imidazole acyl chloride,[3c] MeCN−THF, 70%; (d) (i) $FeBr_2$, THF/MeOH, reflux, 1 h (**24b, 25**) or 10 h (**22**), (ii) EDTA, H_2O (for **Fe-24b** only), ca. 80%; (e) $CuPF_6(MeCN)_4$, MeCN, THF, rt, 10 min, quantitative; (f) pivaloyl chloride, THF, $Et_2NC_6H_5$, rt, 1 h, 88%.

model and closest structural analogue of the cytochrome *c* oxidase active site (model **5a**) was designed to have one imidazole cross-linked to a phenol mimicking Tyr244.

The site chosen for introducing the alkyne function is the para position of the phenyl ring that is grafted on carbon 5 of the proximal imidazole tail. This strategy depends on an imidazole synthon **6** that is crucial for models **2**−**5** to undergo click chemistry. During the convergent synthesis of models **2**−**5**, the coupling of the acetylene to the imidazole ring can be carried out either before (**6b**) or after (**6a**) being attached to the porphyrin. With such a location for the alkyne, the electrons tunneling from the electrode through the alkyl chain are expected to reach the iron center of the immobilized bimetallic catalyst first.

Results and Discussion

The first stage in the synthesis of **12**, the ester precursor of the proximal imidazole tail **6a**,**b**, involved the preparation of the Michael acceptor I-Mich **7** (Scheme 1, route A). This was prepared by acid-catalyzed bromination of 4-iodoacetophenone with Br_2 leading to bromoacetophenone I-Br **8**, which subsequently was treated with formamide to give imidazole I-Im **9** in 45% yield. The Horvath protection strategy[7] conducted on **9** led to I-Mich **7** in a regiospecific manner. Two equally efficient

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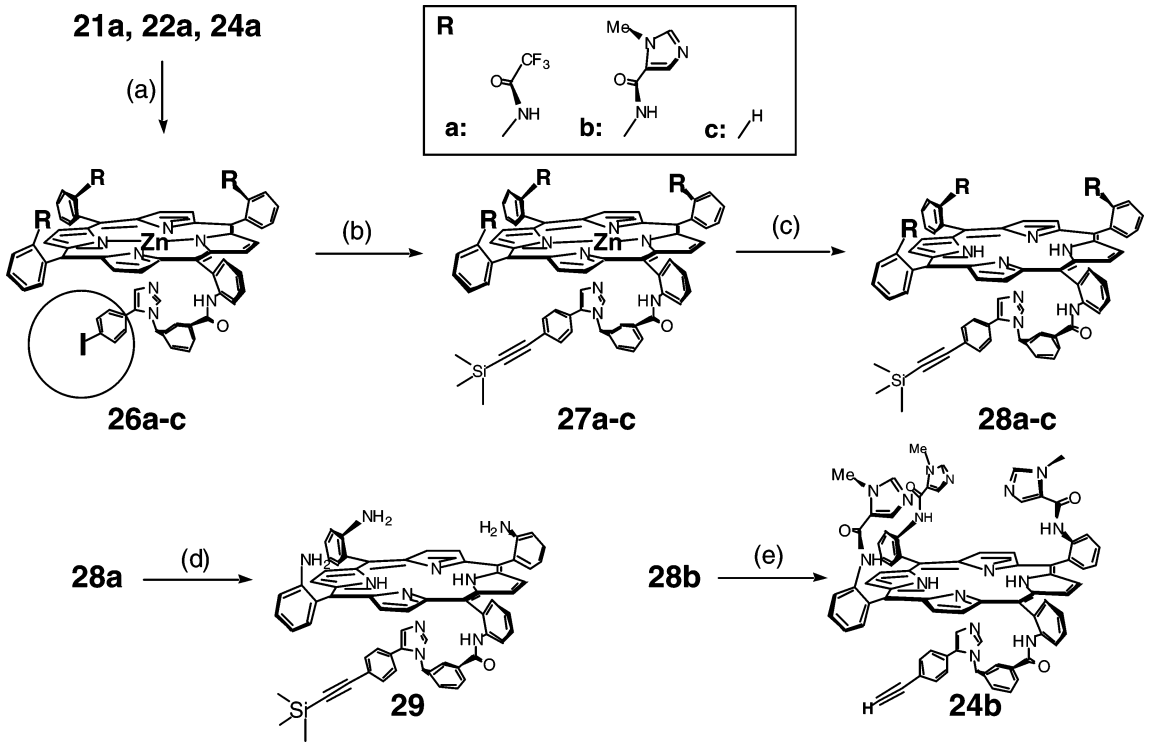
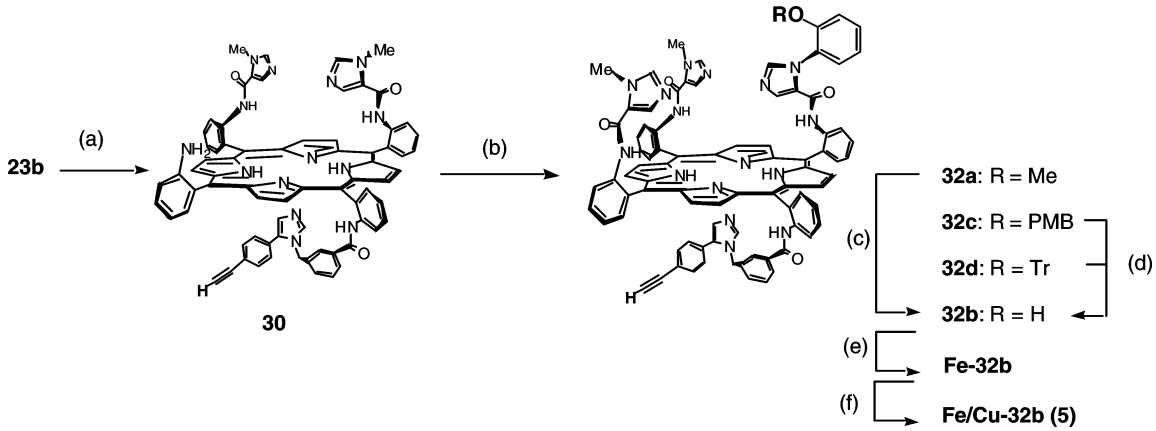
(9) (a) Free acid-sensitive alkyne could no longer sustain harsh HCl refluxing conditions previously used for the imidazole ester hydrolysis.[3c] Instead, LiI or saponification was more appropriate. (b) This delicate step requires starting from a pure ester precursor, free of Pd contaminants, and also prohibits long reaction times or a high concentration of NaOH solution. (c) No reaction of acyl chloride with alkyne was noticed unlike in ref 9d,e. (d) Brownstein, S.; Morrison, A.; Tan, L. K. *J. Org. Chem.* **1985**, *50*, 2796. (e) Martens, H.; Janssens, F.; Hoornaert, G. *Tetrahedron* **1975**, *31*, 177. (f) Cu can be removed by acidic treatment but not Pd. (g) Porphyrin **30-mono** could also be recycled and used for the synthesis of **30-bis** following a method reminiscent of the synthesis of 2 + 1 species **32a**,**c**,**d** (not shown).[3d] (h) For simplification, only the cis regioisomer of bisimidazolyl-porphyrin synthon **30** is depicted in Scheme 5. The reaction of porphyrin **23b** with *N*-methyl imidazole acyl chloride also leads to the trans regioisomer and to mono- and trisimidazolyl porphyrins (**30-mono** and **30-tris**). (i) No side product was noticed from the metalation of alkyne-containing species with iron(II) and especially Cu(I) salts. (j) The position of the alkyne function allowed a click reaction to proceed.

SCHEME 4. Sonogashira Coupling onto Iodo-porphyrin[a]



[a] Reagents and conditions: (a) $Zn(OAc)_2$, $CHCl_3$/MeOH, 2:1 vol, rt, 2 h, 92−95%; (b) trimethylsilylacetylene, CuI, $Pd(PPPh_3)_4$, Et_3N, THF, rt, 18 h, quantitative; (c) HCl, CH_2Cl_2, rt, 15 min, 92% quantitative; (d) NH_3-saturated CH_3OH/CH_2Cl_2, 1:3 vol, rt, 3 days, 65%; (e) CH_2Cl_2, CH_3OH, K_2CO_3, rt, 16 h, quantitative.

SCHEME 5. Synthesis of the CcO Model Having a Tyr244 Mimic Following a 2 + 1 Approach[a]



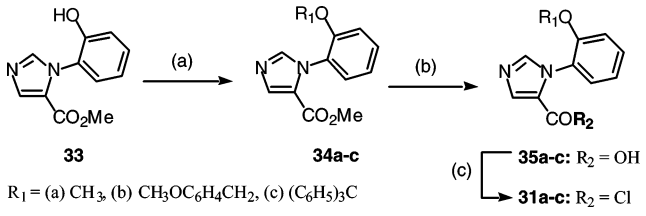
[a] Reagents and conditions: (a) 2 equiv of *N*-methyl imidazole acyl chloride,[3c] MeCN−THF, rt, 20 min, 70%; (b) (i) HCl gas; (ii) **31ac**, MeCN/THF, rt, 70%; (c) (i) 20 equiv of BBr_3, CH_2Cl_2, −78 °C, 30 min, then 0 °C, 1 h, (ii) MeOH, H_2O, −78 °C, 30 min, then 0 °C, 1 h; (d) HCl, CH_2Cl_2, rt, 1 h, 80%; (e) (i) $FeBr_2$, THF/MeOH, reflux, 1 h, (ii) EDTA, H_2O, rt, 15 min, 80%; (f) $Cu(MeCN)_4PF_6$, MeCN/THF, rt, 10 min, quantitative.

routes were followed to obtain TMSAlk-Ester **12** from I-Mich **7**. Route A involved the quaternization of **7** (leading to I-q **10**), cyanoethyl deprotection (leading to I-Ester **11**), and Sonogashira alkyne coupling[8] leading to TMSAlk-Ester **12**.

In route B, Sonogashira coupling is conducted first on I-Mich **7** leading to the alkyne-containing imidazole TMSAlk-Mich **13** in 75% yield which is then quaternized and deprotected leading to TMSAlk-q **14** and TMSAlk-Ester **12**, respectively. Sonogashira coupling was also carried out on imidazole salt I-q **10** despite its low solubility and led to **14**.

Ester deprotection (Scheme 2) in the robust imidazoles I-ester **11** was carried out in refluxing acid and led quantitatively to I-acid **15**. The acid-sensitive alkyne-ester **12**[9a] was deprotected by saponification in 1.5 N NaOH (or K_2CO_3/MeOH) at room temperature followed by neutralization with acetic acid and led to the alkyne-deprotected species Alk-Acid **16**.[9b] The use of milder reagents such as LiI under refluxing conditions also effected both deprotection reactions, whereas K_2CO_3 or KF led to **17** resulting from a selective deprotection of the alkyne. An alternative was to run the alkyne coupling on the poorly soluble iodo-imidazole I-acid **15**, leading to TMSAlk-Acid **18**, followed by treatment with a nucleophile giving **16**. The most efficient method to synthesize **16** was achieved by the simultaneous removal of TMS, ester, and cyanoethyl protective groups in **14**.

SCHEME 6. Synthesis of the Imidazole Picket Having a Tyr244 Mimic[a]



[a] Reagents and conditions: (a) 4-methoxybenzyl bromide (for **34b**), trityl bromide (for **34c**), K_2CO_3, THF, rt, 24 h, 70% (**34bc**); (b) (i) 1.5 N NaOH, MeCN/THF/H_2O, (ii) AcOH, H_2O, 70%; (c) $(COCl)_2$, MeCN, DMF (cat.), rt, 3 h, 80%.

This triple deprotection reaction was carried out in a CH_3ONa/CH_3OH/H_2O (1:1:0.1 mol) mixture in 60% yield. Finally, imidazole acyl chlorides **6a**,**b** were prepared by reaction of oxalyl chloride with their carboxylic acid precursors **15** and **16**.[3c,9c−e]

The synthesis of models **3**−**5** represents significant modifications to the general synthetic scheme reported earlier for the synthesis of CcO models[3a−d] because of the presence of the alkyne function. The iodo- or alkyne-tail acyl chlorides **6a** and **6b** reacted with porphyrin $\alpha_3F\beta A$ **19**[3b] (Scheme 3A) or trisphenyl *o*-aminophenyl porphyrin **20**[10a] (Scheme 3B) leading to porphyrins $\alpha_3F\beta XT$ **21a**,**b** (X = I, CCH) and **22** (tailed "flat" porphyrin), respectively. The three distal amines were deprotected to give the α_3-amino synthon $\alpha_3A\beta XT$ **23a**,**b** (X = I, CCH). This was used as a platform for reaction with *N*-methylimidazole acyl chloride[3c] or pivaloyl chloride[10a,b] leading to trisimidazole-tailed porphyrin **24a**,**b** and picket-fence-tailed porphyrin **25**, respectively.

The introduction of the alkyne function was also carried out on the iodo-imidazole-tailed porphyrins **21a** or **24a** (Scheme 4). Prior protection of the porphyrin with zinc was mandatory to prevent metalation of the porphyrin by Cu or Pd from occurring during the coupling. After reaction of zinc porphyrins **26a**,**b** with trimethylsilylacetylene in the presence of Cu^I and Pd^0 catalysts, zinc was removed by bubbling HCl through the solution of porphyrins **27a**,**b**.[9f] The TMS protective group was removed in **28b** by treatment of the porphyrin with a solution of K_2CO_3 leading to **24b**. None of the four steps involved in the Sonogashira coupling on tetrakisimidazolyl porphyrins **24a** could be monitored by TLC because the polarities of the reactant **24a** and the product **24b** are the same. This is unlike the coupling reaction carried out on less-polar zinc tristrifluoroacetamidoporphyrin **26a**. Interestingly, once the protected alkyne group had been coupled to the porphyrin $\alpha_3F\beta IT$ **21a**, the TMS protective group remained stable during all subsequent steps of the synthetic scheme (Scheme 4), such as the deprotection of the distal amines in **28a** leading to **29**. This offered substantial advantages for the purification of porphyrin intermediates (solubilty and separation of regioisomers).

The preparation of model **5** having a Tyr244 mimic followed the 2 + 1 strategy previously reported for the CF_3 counterpart (Scheme 5).[3d] Reaction of the freshly prepared *N*-methylimidazole acyl chloride picket[3c] with **23b** led to the bisimidazolyl porphyrin **30**.[9g,h] Efficient separation of the regioisomers of this alkyne-containing synthon was achieved on rotating chromatography plates (chromatotron) without decomposition of the porphyrins. However, **30** appeared unstable on preparative TLC plates, unlike CcO models bearing the other imidazole tails reported previously.[3d] After mandatory reprotection of the imidazole pickets of cis regioisomer **30** by acidification,[3b,d] reaction with a methyl-protected tyrosine imidazole picket acyl chloride[3d] yielded the protected 2 + 1 species **32a**. Phenol deprotection of **32a** with BBr_3 led to a mixture of **32b** and a compound that corresponds to a bromoalkene derivative, as shown by mass spectrometry with an additional peak at m/z = 1444. Integration of the signal corresponding to the benzylic methylene on the NMR spectrum shows that the contaminant is present in 10−25%. Separation by chromatography could not be achieved because they have similar polarities. Click chemistry on the SAM-coated electrode using a metalated version of this mixture appeared to be the only way to remove the bromoalkene-containing porphyrin: the model containing an alkyne was clicked on the electrode, whereas the bromoalkene side product did not react and remained in solution. To overcome these problems, the syntheses of phenol-protected imidazole synthons **31b**,**c** bearing various protective groups (Scheme 6) and the corresponding 2 + 1 porphyrin intermediates **32c**,**d** (Scheme 5) were undertaken. Trityl (Tr) and *p*-methoxybenzyl (PMB) were chosen as protective groups because they offer a good compromise between robustness and lability under various acidic conditions.[11a−c] They were chosen because they could possibly be sufficiently acid-resistant during the steps where acid is necessary or generated in small amounts. These steps are the neutralization with 1 equiv of acetic acid after saponification of the imidazole ester leading to **35b**,**c**, the acyl chloride synthesis leading to **31b**,**c**, and the condensation reaction of **31b**,**c** with the bisimidazolyl porphyrin **30** in preacidified media leading to **32c**,**d**. However, the PMB and Tr protective groups display enough acid sensitivity to be removed under mild conditions to prevent side reactions on the proximal alkyne.

Reaction of phenol-imidazole ester **33**[12] with *p*-methoxybenzyl bromide or trityl bromide, in the presence of potassium carbonate, led to imidazole **34b**,**c**, respectively. After saponification and careful neutralization, imidazole acids **35b**,**c** were converted into acyl chlorides **31b**,**c** under anhydrous conditions. Reaction of **31b**,**c** with the bisimidazolyl porphyrin **30** proceeded as with OMe-protected phenol **31a** (Scheme 6). Both protective groups turned out to be too labile to resist the acidic conditions in the 2 + 1 condensation between **31b**,**c** and the bisimidazolyl porphyrin **30** (although they were sufficiently robust to achieve purification of the imidazole ester precursors **34b**,**c** by long chromatography). Surprisingly, when this reaction was carried out with a large excess of **31b**,**c**, the phenol deprotected species **32b** was isolated in 50% yield. Such a yield was still acceptable considering that two side reactions may occur: an intramolecular reaction in the phenol-deprotected version of **36b**,**c** leading to a δ-lactone and an intermolecular esterification reaction between phenol-porphyrin **32b** and acyl chloride **31b**,**c** (and subsequent

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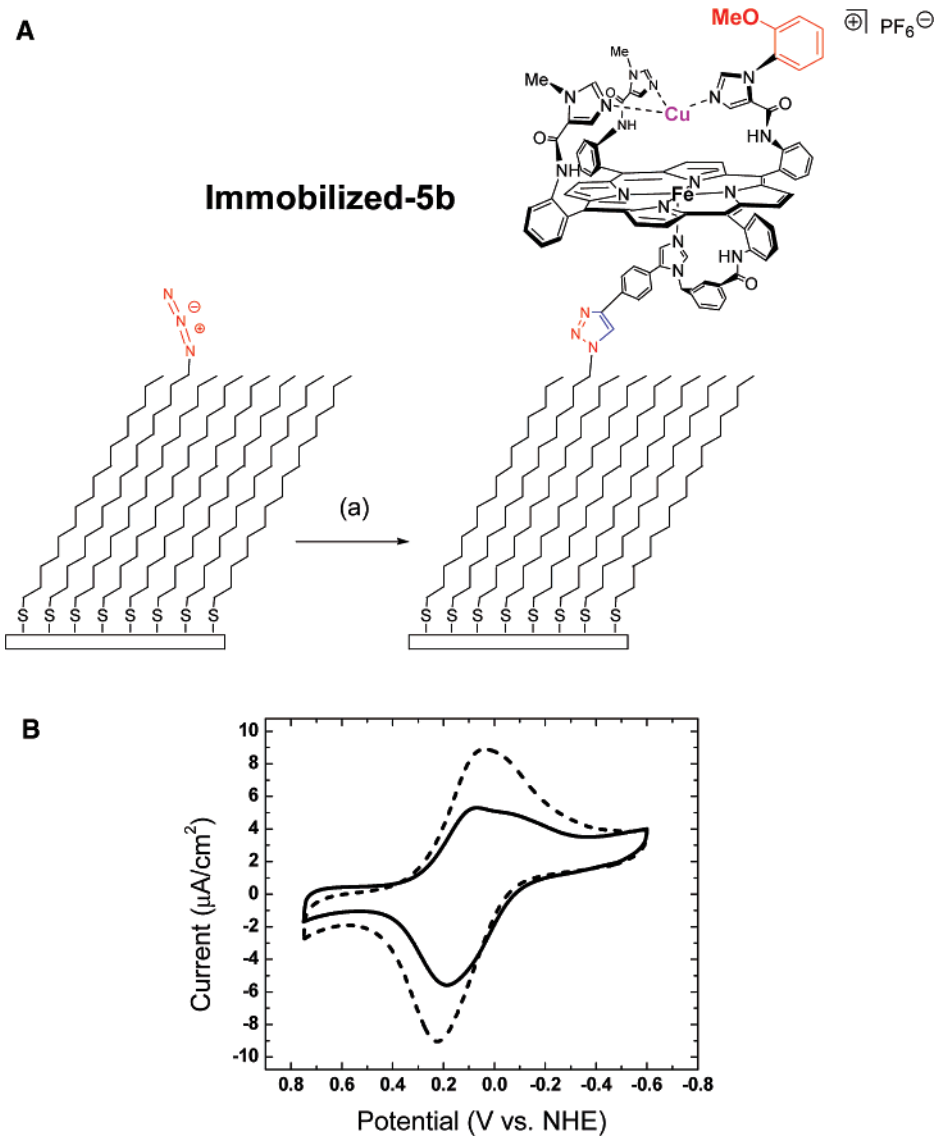
SCHEME 7. (A) Clicking Model 4 onto an Electrode Surface and (B) Characterization of Immobilized Catalyst 4 by Cyclic Voltammetry[a]



[a] Reagents and conditions. (A): (a) (i) DMSO/H_2O, **5b**, $CuSO_4$−TBTA, sodium ascorbate, 30 min, (ii) rinse with DMSO and buffer. Mixed monolayer was formed from $N_3(CH_2)_{16}SH$ and $CH_3(CH_2)_{15}SH$. (B): Cyclic voltammogram of immobilized CcO model **5b** (surface coverage: 4.4×10^{-11} mol cm^{-2}).[14b] Scan rate: 300 mV/sec. Plain, **Fe-32a**; dashed, **Fe/Cu-32a** (model **5b**).

oligomerization reactions with other phenol-deprotected versions of **31b**,**c**) that may not be favored sterically. The small amount of the porphyrins **32c**,**d** that could be isolated by chromatography was easily and quantitatively deprotected by acidic treatment leading to **32b**.

Before metalation and immobilization of the catalysts, the free-base models were characterized and purified according to the standards of porphyrinoid and porphyrin chemistry previously established.[3a,b,10a,b,13] The metalation of porphyrins **22**, **24b**, **25**, and **32a**,**b** with $FeBr_2$ was adapted from previous methods (Schemes 2, 3, and 5)[3c] and was carried out in refluxing THF/methanol mixtures followed by washing with EDTA to remove the distal Fe atom coordinated to the imidazoles (Schemes 3A and 5). No side reactions were observed during metalation with free-base porphyrins, neither on the alkyne (models **1**−**5**) nor on the phenol (model **5**).[9i] Copper insertion in **Fe-24b**, **Fe-32a**, and **Fe-32b** was achieved by reaction with 1 equiv of $CuPF_6(CH_3CN)_4$ leading to models **4**, **5a**, and **5b**, respectively (Schemes 3A and 5). NMR characterization of models **2**−**5** and porphyrin intermediates **Fe-24b**, **Fe-32a**, and **Fe-32b** was made possible by reacting the complexes with CO leading to diamagnetic low-spin Fe−CO adducts.[3c]

Immobilization of models **1**−**5** by click chemistry with alkyl−azide-functionalized electrodes was conducted in a water−DMSO mixture in the presence of a Cu^I catalyst for 30 min (Scheme 7A). The surfaces were cleaned by two washes with DMSO. Immobilization of the models by covalent linkage to the alkyl chain through a robust triazole ring has been demonstrated by means of cyclic voltammetry and IR spectroscopy (Scheme 7B), as was previously shown with ferrocene.[6a,e] Cyclic voltammetry of immobilized species **Fe-32a** and **Fe/Cu-32a** (model **5b**) clearly shows a broad reversible couple assigned to iron and copper centers in these models.[14] Immobilization

(13) Collman, J. P.; Decréau, R. A. *Org. Lett.* **2005**, *7*, 975.

of **5b** monitored by grazing-angle infrared spectrometry shows no evidence of the azide stretch at 2100 cm^{-1} (data not shown). The surface coverage was electrochemically determined to be approximately 4.4×10^{-11} mol/cm^2.[14]

Conclusions

A general method has been developed to prepare hemoprotein models bearing an alkyne functionality to allow their immobilization by click chemistry. The efficiency of this reaction, particularly for electrode surface functionalization, has been demonstrated with complex molecules such as cytochrome *c* oxidase models. Models **1**−**5** that bear an alkyne function on the proximal side should lead to a better understanding of the contribution of each redox-active component in the CcO active site during the $4e^-$ reduction of dioxygen under a slow regime of electron delivery. Electrocatalytic studies with models **1**−**5** will be reported elsewhere.[14]

Experimental Section

General Sonogashira Coupling Procedure. Imidazole (6 mmol, **I-Mich**, **7**, 1.9 g; **I-Ester**, **11**, 2.5 g; **I-q**, **10**, 3.3 g), CuI (22 mol %), $Pd(PPh_3)_4$ (10 mol %), and 3.0 equiv of Et_3N (2.5 mL) were mixed in THF (100 mL). The resulting suspension was degassed (five pump−thaw cycles), and 7 equiv of trimethylsilylacetylene was added (6 mL). The mixture was stirred for 16 h. The progress of the reaction was monitored by TLC and was indicated by the formation of a large amount of white precipitate (triethylammonium iodide). The solvent was removed under reduced pressure and the residue was subjected to chromatography (SiO_2, eluent CH_2Cl_2/CH_3OH 195:5 vol). The reaction conducted on iodo-porphyrins (70 μmol scale) used a 1:0.5:1:3 ratio of zinc-protected iodoporphyrin (**26a**,**26b**)/$Pd(PPh_3)_4$/CuI/Et_3N and a 100 mg/20 mL concentration in porphyrin. Chromatography (SiO_2)/eluents CH_2Cl_2 (**27a**), gradient elution of CH_2Cl_2/MeOH (100:2−100:6 vol) (**27b**). Yield: **TMSAlk-Ester**, **12**, 1.7 g, 75%; **TMSAlk-Mich**, **13**, 1.5 g, 88%; **TMSAlk-q**, **14**, 1.94 g, 73%; porphyrin **27a**, 0.097 g, 99%; porphyrin **27b**, 0.096 g, 98%.

3-{5-[4-(Trimethyl-silanylethynyl)-phenyl]-imidazol-1-ylmethyl}-benzoic Acid Methyl Ester (TMSAlk-Ester, 12): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.92 (d, 1H, J = 7.00 Hz), 7.67 (s, 1H), 7.58 (brs, 1H), 7.34 (t, 1H, J = 8.0 Hz), 7.30 (AA′BB′, 4H, J = 8.5 Hz), 7.14 (brs, 1H), 7.09 (d, 1H, J = 6.0 Hz), 5.16 (s, 2H), 3.87 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 139.0, 137.1, 132.5, 131.2, 131.1, 129.5, 129.4, 128.7, 128.1, 122.9, 104.3, 95.8, 52.6, 48.8, 0.2; MS (ESI^+) m/z = 389.7 $[M]^+$ (calcd for $C_{23}H_{24}N_2O_2Si$ 388.5); TLC (silica, CH_2Cl_2/CH_2Cl_2 95:5 vol); R_f = 0.25; Mp = 136−138 °C.

α_3-(*o*-4-(3-Methylimidazolyl)-amidophenyl)-β-(*o*-3-(1-(5-*p*-trimethylsilyl acetylenyl phenyl)imidazolylmethyl)benzamidophenyl) Zinc Porphyrin. ([Zn(α_3(*N*-MeIm)βTMSAlk-T)], 27b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (d, 1H, J = 8.0 Hz), 8.85 (m, 6H), 8.74 (d, 2H, J = 4.5 Hz), 8.57 (d, 2H, J = 8.5 Hz), 8.43 (d, 1H, J = 7.5 Hz), 8.07 (m, 5H), 7.81 (m, 7H), 7.62 (s, 2H), 7.52 (m, 3H), 7.42 (t, 1H, J = 7.5 Hz), 7.08 (t, 1H, J = 7.5 Hz), 6.94 (d, 2H, J = 8.5 Hz), 6.84 (s, 2H), 6.74 (s, 1H), 6.44 (d, 1H, J = 7.5 Hz), 5.86 (d, 2H, J = 8.5 Hz), 5.15 (s, 2H), 5.06 (s, 1H), 4.66 (s, 1H), 3.78 (s, 2H), 3.42 (s, 6H), 3.36 (s, 3H), 2.69 (s, 1H), 0.11 (s, 9H); MS (ESI^-) m/z = 1416.5 $[M]^{\bullet-}$ (calcd for $C_{81}H_{64}N_{16}O_4SiZn$ 1416.4); UV/vis (CH_2Cl_2) λ_{max} (10^{-3} ϵ, M^{-1} cm^{-1}) 412 (48), 434 (466), 564 (21); TLC (SiO_2, NH_3-saturated CH_2Cl_2); R_f = 0.15.

General Phenol Protection. A solution of phenol-imidazole ester **33** (0.430 g, 1.8 mmol) in THF (60 mL) was cooled at 0 °C for 30 min, then ca. 3 equiv of NaH (0.133 g) was added portionwise. The resulting mixture was stirred at 0 °C for 2 h, then 2.2 equiv of 4-methoxybenzyliodide (ca 1.0 g) or trityl bromide was added at once. The resulting mixture was stirred for 24 h. Two-thirds of the solvent was removed under reduced pressure. Then the vessel was cooled again, and an excess of triethylamine and cool water (20 mL) was added. After extraction with CH_2Cl_2 (3 × 200 mL) and drying ($MgSO_4$), the solvents were distilled and the residue was subjected to chromatography [SiO_2, 3 × 15 cm, gradient elution, hexane/CH_2Cl_2 (1:2 vol), CH_2Cl_2 100%, and CH_2Cl_2/CH_3OH (95:5 vol)]. **34b** (0.240 g, 38%) (yellow oil); **34c** (0.367 g, 43%).

3-(2-Trityloxy-phenyl)-3*H*-imidazole-4-carboxylic Acid Ethyl Ester (Tr-O-Im-Ester, 34c): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.87 (d, 1H, J = 1.0 Hz), 7.33 (d, 1H, J = 1.0 Hz), 7.22−7.28 (m, 15H), 7.18 (d, 1H, J = 7.5 Hz, J = 2 Hz), 7.00 (t, 1H, J = 7.0 Hz, J = 1.0 Hz), 6.92 (t, 1H, J = 7.5 Hz, J = 1.0 Hz), 6.63 (d, 1H, J = 8.5 Hz, J = 1.5 Hz), 4.28 (q, 2H, J = 7.0 Hz), 1.25 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 160.0, 151.4, 143.6, 142.3, 136.9, 129.1, 128.74, 128.65, 128.0, 127.64, 127.58, 125.6, 121.4, 120.8, 91.4, 60.7, 14.4; MS (ESI^+) m/z = 474.9 $[M]^+$, MS (ESI^-) m/z = 473.1 $[M - H]^{\bullet-}$ (calcd for $C_{31}H_{26}N_2O_3$ 474.5); HPLC-MS (200 μL/min, mobile phase H_2O/CH_3CN, gradient 2−95%, 35 min); R_t = 29.1 min; TLC (SiO_2, hexane/ethyl acetate 6:4 vol); R_f 0.5.

Ester Hydrolysis Procedures for Acid-Sensitive Imidazoles. A solution of imidazole ester (1.4 mmol;**TMSAlk-Ester**, **12**, 0.543 g; **PMBO-Ester**, **34b**, 0.492 g; **TrO-Ester**, **34c**, 0.665 g) in THF/CH_3OH (2:1 vol, 10 mL) was mixed with 1.5 N NaOH solution, and the resulting mixture was stirred at room temperature for 1 h. Then, only 1.0 equiv of acetic acid (with respect to NaOH, ca. 200 μL) was slowly added to the mixture containing the acid-sensitive PMBO- or TrO-imidazole pickets to neutralize the mixture, followed by an excess of water (200 mL) causing the imidazole to precipitate. It was isolated by filtration and dried under a vacuum. Yield: **Alk-Acid**, **16**, 0.360 g, 85%; **PMBO-Acid**, **35b**, 0.431 g, 85%; **TrO-Acid**, **35c**, 0.500 g, 80%.

3-[5-(4-Ethynyl-phenyl)imidazol-1-ylmethyl]-benzoic Acid (Alk-Acid, 16): ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 7.85 (d, 1H, J = 1.0 Hz), 7.82 (t, 1H, J = 7.5 Hz, J = 1.5 Hz), 7.69 (s, 1H), 7.38 (AA'BB', 4H), 7.26 (t, 1H, J = 7.5 Hz), 7.10 (d, 1H, J = 1.0 Hz), 6.98 (d, 1H, J = 8.0 Hz, J = 1.0 Hz), 5.33 (s, 2H), 3.53 (s, 1H); MS (ESI^+) m/z = 303.7 $[M + H]^+$; HR−MS (m/z) = 303.1136 $[M+H]^+$; MS (ESI^-) m/z = 301.1 $[M - H]^{\bullet-}$ (calcd for $C_{19}H_{14}N_2O_2$ 302.3267); HPLC-MS (Vydac, 200 mL/min, mobile phase H_2O/CH_3CN, gradient 20−95% in CH_3CN (20 min); R_t 14.6 min; TLC (silica, CH_3OH 100%); R_f 0.65; mp = 262−265 °C; FT−IR (KBr) 1665 cm^{-1}.

General Procedure for the Attachment of a Proximal Imidazole Tail. To a suspension of imidazole tail acyl chloride hydrochloride[3c] (1.164 mmol; IT−Cl **6a**, 0.472 g; AlkT-Cl **6b**, 0.416 g) in dry MeCN (10 mL) (*sonicated* to brake the aggregates) was slowly added a solution of aminophenylporphyrin α_3FβA **19**[3b] (up to 1 equiv, 1.12 g) or TPMAPP **20**[10a] (0.73 g) in MeCN (up to 10 mL). The resulting mixture that progressively turned green was stirred for 20 min. Dichloromethane was added (100 mL), and the mixture was washed with sodium bicarbonate and water (the color went back to purple). The solvent was evaporated, and the residue was subjected to chromatography: SiO_2 gel built with CH_2Cl_2, eluent (1) CH_2Cl_2, (2) gradient of CH_2Cl_2/CH_3OH (up to 97:3 vol). Average yield obtained for **α_3FβI-T**, **21a** (1.4 g, 90%); **α_3FβAlk-T**, **21b** (1.3 g, 89%); **TPI-T**, **22b** (0.946 g, 80%); **TPAlk-T**, **22a** (0.851 g, 80%).

α_3-(*o*-Trifluoroacetamidophenyl)-β-(*o*-3-(1-(5-*p*-acetylenylphenyl)imidazolyl methyl) benzamidophenyl)-porphyrin, α_3FβAlk-T (21b): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.91 (d, 2H, J = 4.4 Hz), 8.78 (m, 6H), 8.62 (m, 4H), 8.05 (d, 1H, J = Hz), 7.96 (d, 2H, J = 7.2 Hz), 7.90 (m, 5H), 7.61 (m, 4H), 7.50 (s, 2H), 7.44 (s, 2H), 6.92 (d, 2H, J = 8.5 Hz), 6.81 (s, 1H), 6.61 (s, 1H), 6.48 (d, 2H, J = 8.5 Hz), 6.46 (s, 1H), 6.30 (m, 2H), 6.10 (d, 1H, J = 6.5

(14) Collman, J. P.; Devaraj, N. K.; Decréau, R. A.; Yang, Y.; Yan, Y.; Ebina, W.; Eberspacher, T. A.; Chidsey, C. E. D. *Science* **2007**, *315*, 1565.

Hz), 4.16 (s, 2H), 3.00 (s, 1H), −2.68 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −77.22 (s, 6F), −77.74 (s, 3F); MS (ESI^+) m/z = 1248.2 $[M + H]^+$, (ESI^-) m/z = 1246.2 $[M - H]^{\bullet -}$ (calcd for $C_{69}H_{43}F_9N_{10}O_4$ 1247.13); UV−vis. (CH_2Cl_2) λ ($10^{-3} \times \epsilon$/ mol^{-1} L cm^{-1}) 290 (15.2), 352 (10.3), 374 (13.0), 402 (sh, 37.0), 420 (141.7), 484 (65.7), 514 (8.0), 548 (2.3), 588 (2.6), 648 (0.8); TLC (silica, CH_2Cl_2/CH_3OH 96:4 vol); R_f 0.35; mp (CH_3CN) 200 °C (decomp.).

General Procedure for the Hydrolysis of Distal Amides. To a solution of **α_3FβXTail** porphyrins (0.34 mmol; **α_3FβIT**, **21a**, 0.450 g; **α_3FβAlkT**, **21b**, 0.423 g; **α_3FβTMSAlkT**, **28a**, 0.449 g) in CH_2Cl_2 (24 mL) cooled at 0 °C and protected from light was slowly introduced a cold NH_3-saturated CH_3OH solution (13 mL). The resulting mixture was stirred for 2 to 3 days. After addition of CH_2Cl_2 (100 mL), washings with water (2 × 100 mL), and drying over $MgSO_4$, the solvents were then distilled. The residue was subjected to chromatography: SiO_2 gel, built with CH_2Cl_2, 20 × 5 cm; loading of porphyrin in solution in CH_2Cl_2; gradient elution of CH_2Cl_2/CH_3OH 200:0−200:2.0 vol. The target porphyrin moves at 200:2.0 vol. Yields in **α_3AβXT 23a,b** vary according to the initial concentration in NH_3 and the reaction time (50−80%). Average yield found for **α_3AβI-T**, **23a**, 0.202 g, 56%; **α_3AβAlkT**, **23b**, 0.192 g, 59%; **α_3AβTMSAlkT**, **29**, 0.196 g, 56%.

α_3-(*o*-Aminophenyl)-β-(*o*-3-(1-(5-*p*-acetylenylphenyl)imidazolylmethyl)benzamido-phenyl)-porphyrin, α_3AβAlk-T (23b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (m, 9H), 8.08 (d, 1H, J = 7.5 Hz), 7.87 (t, 1H, J = 8.0 Hz), 7.74 (d, 3H, J = 7.5 Hz), 7.57 (m, 4H), 7.52 (s, 1H), 7.12 (m, 6H), 6.89 (d, 2H, J = 8.0 Hz), 6.84 (s, 1H), 6.79 (s, 1H), 6.48 (d, 2H, J = 8.0 Hz), 6.29 (t, 1H, J = 8.0 Hz), 6.21 (m, 2H), 6.16 (d, 1H, J = 8.0 Hz), 3.93 (s, 2H), 3.54 (s, 2H), 3.50 (s, 4H), 2.99 (s, 1H), −2.66 (s, 2H); MS (ESI^+) m/z = 959.6 $[M + H]^+$ (calcd for $C_{63}H_{46}N_{10}O$ 959.4); UV/vis(CH_2Cl_2) λ_{max} ($10^{-3}\epsilon$, M^{-1} cm^{-1}) 420 (241), 516 (16); HPLC-MS (Vydac, 200 mL/min, mobile phase H_2O/CH_3CN, gradient 20−95% in CH_3CN (20 min)); R_t = 27 min; TLC (SiO_2, NH_3-saturated CH_2Cl_2); R_f = 0.67.

General Procedure for the Attachment of Distal Imidazole Pickets. To a suspension of imidazole acyl chloride (105 mg, 0.58 mmol) in acetonitrile (20−35 mL) was slowly added a solution of porphyrin (**29**, 100 mg, 0.097 mmol; **23a**, 212 mg, 0.20 mmol) and diethylaniline (51 μL, 0.32 mmol; for **24a**, 95 μL, 0.60 mmol) in CH_3CN/THF (1:1 vol; for the synthesis of **28b**, 5 mL; for **24a**, 10 mL). After the addition, the reaction mixture was stirred for 1−2 h. The solution was diluted with CH_2Cl_2 (∼150−200 mL) and washed with 50% saturated aqueous $NaHCO_3$ and water. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The solid residue was subjected to chromatography (SiO_2, 20 × 3 cm). For **28b**: gradient elution of CH_2Cl_2/MeOH (100:2−100:6 vol). The target compound moves at 100:5 vol. Yield: 0.098 g, 75%. For **24a**: gradient elution of CH_2Cl_2/MeOH (100:2−100:10 vol). The target compound moves at 100:10 vol. Yield: 0.165 g, 60%.

α_3-(*o*-4-(3-Methylimidazolyl)-amidophenyl)-β-(*o*-3-(1-(5-*p*-iodophenyl)imidazolylmethyl)benzamidophenyl)-porphyrin (α_3-(*N*-MeIm)βI−T, 24a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (m, 9H), 8.53 (d, 2H, J = 8.0 Hz), 8.40 (d, 1H, J = 8.0 Hz), 8.07 (m, 3H), 7.99 (d, 1H, J = 8.0 Hz), 7.84 (m, 4H), 7.78 (s, 2H), 7.60 (t, 1H, J = 7.5 Hz), 7.55 (m, 4H), 7.41 (s, 1H), 6.99 (d, 2H, J = 8.5 Hz), 6.92 (m, 4H), 6.82 (s, 1H), 6.68 (s, 1H), 6.31 (t, 1H, J = 8.0 Hz), 6.20 (m, 3H), 6.15 (d, 1H, J = 8.5 Hz), 5.40 (s, 2H), 5.35 (s, 1H), 3.96 (s, 2H), 3.58 (s, 3H), 3.56 (s, 6H), −2.54 (s, 2H); MS (ESI^+) m/z = 1385.6 (calcd for $C_{76}H_{57}IN_{16}O_4$ 1385.4); UV/vis (CH_2Cl_2) λ_{max} ($10^{-3}\epsilon$, M^{-1} cm^{-1}) 424 (274), 518 (9). HPLC-MS (200 μL/min, mobile phase H_2O/CH_3CN, gradient 2−95%, 35 min); R_t = 21.9 min; TLC (SiO_2, NH_3-saturated CH_2Cl_2); R_f = 0.15; mp (CH_3CN) 240−250 °C (decomp.).

General Procedure for the Metalation of Porphyrins with Iron. A mixture of free base porphyrin (7.3−7.8 μmol, *ca.* 10 mg) and 3 equiv. $FeBr_2$ (6 mg) in MeOH/THF (1:4 vol., 8 mL) was heated for 1h at reflux. The volume was reduced to a 1/third then 0.1 M aqueous Na_2. EDTA (1 mL) was introduced and the resulting mixture was stirred for 10 min. Then the volume was expanded with benzene (30 mL), water was added (20 mL) and stirring was continued for 10 more min. The organic phase was then washed with water (4 × 10 mL), dried by addition of Na_2SO_4 with stirring for 10 min, then filtered through a glass wool plug. Solvents were evaporated under reduced pressure. Yields: 80%-quantitative.

***cis*-α_2-(*o*-4-(3-Methylimidazolyl)-amidophenyl)-α-(*o*-4-(3-(2-methoxyphenyl)imidazole)-5-benzamidophenyl)-β-(*o*-3-(1-(5-*p*-acetylenylphenyl)imidazolylmethyl)benzamidophenyl) Iron(II) Porphyrin, ([Fe(II)α_2(*N*-MeIm)α(*N*-MeOPhIm)βAlk-T)],(Fe-32a):** ^{1}H NMR (500 MHz, $CDCl_3$/1 atm CO) δ 9.03 (d, 1H, J = 8.4 Hz), 8.68 (m, 9H), 8.43 (d, 1H, J = 8.2 Hz), 8.40 (d, 1H, J = 6.4 Hz), 8.21 (m, 3H), 7.94 (d, 1H, J = 7.3 Hz), 7.80 (m, 7H), 7.69 (m, 3H), 7.65 (s, 2H), 7.51 (m, 3H), 7.47 (t, 2H, J = 7.3 Hz), 7.06 (t, 2H, J = 7.70 Hz), 7.00 (d, 1H, J = 7.1 Hz), 6.91 (m, 5H), 6.48 (d, 1H, J = 7.5 Hz), 5.71 (d, 2H, J = 8.2 Hz), 3.96 (s, 1H), 3.72 (m, 2H), 3.62 (s, 3H), 3.58 (s, 3H), 3.38 (s, 3H), 2.93 (s, 1H), 2.34 (s, 1H), 1.93 (s, 1H), 1.41 (s, 1H); MS (ESI^+) m/z = 1430.6 $[M]^+$ (calcd for $C_{84}H_{60}FeN_{16}O_5$ 1430.4); UV/vis (CH_2Cl_2) λ_{max} ($10^{-3}\epsilon$, M^{-1} cm^{-1}) 426 (228), 534 (9).

General Procedure for Distal Metalation with Copper. To a solution of iron trisimidazolyl picket porphyrin (**24b**, **32a**, **32b**) in THF (1 mL) was added 1 equiv of Cu(MeCN)4PF6 (from a stock solution of 12 mg of Cu(I) salt in 120 μL of MeCN). After 10 min (occasionally stirring the solution manually), the solvents were removed.

Copper(I) [*cis*-α_2-(*o*-4-(3-Methylimidazolyl)-amidophenyl)-α-(*o*-4-(3-(2-methoxyphenyl)imidazolyl)-amidophenyl)-β-(*o*-3-(1-(5-*p*-acetylenylphenyl)imidazolylmethyl)benzamidophenyl) Iron Porphyrin] Hexafluorophosphate, {Cu(I)[Fe(II)(α_2(*N*-MeIm))α(*N*-(PhOMe)Im) βAlk-T]}$^+${PF_6}$^-$, Fe/Cu-32a, 5b: ^{1}H NMR (500 MHz, THF-d_8/MeCN-d_3/$CDCl_3$ (9:1:3 vol)/1 atm CO) δ 10.3 (brs, 1H), 9.05 (d, 1H, J = 8.4 Hz), 8.78 (d, 1H, 4.0 Hz), 8.72 (t, 2H, J = 5.0 Hz), 8.69−8.67 (m, 3H), 8.58 (m, 2H), 8.47 (d, 1H, J = 8.5 Hz), 8.38 (t, 2H, J = 8.5 Hz), 8.23 (d, 1H, J = 7.0 Hz), 8.14 (d, 1H, J = 7.5 Hz), 8.05 (s, 1H), 8.03 (d, 1H, J = 7.5 Hz), 7.83−7.66 (m, 8H), 7.55 (t, 1H, J = 7.5 Hz), 7.49−7.45 (m, 3H), 7.27 (t, 1H, J = 8.0 Hz), 7.06 (s, 1H), 7.01 (t, 1H, J = 7.5 Hz), 6.98−6.87 (m, 6H), 6.80 (t, 1H, J = 7.5 Hz), 6.57 (d, 1H, J = 7.5 Hz), 5.86 (d, 2H, J = 8.0 Hz), 5.54 (s, 1H), 5.30 (s, 1H), 5.19 (s, 1H), 4.05 (s, 1H), 3.95 (s, 2H), 3.57 (s, 3H), 3.42 (s, 3H), 3.39 (s, 3H), 2.20 (s, 1H), 2.15 (s, 1H), 1.41 (s, 1H); ^{19}F NMR (376 MHz, THF-d_8/MeCN-d_3/$CDCl_3$ (9:1:3 vol)/1 atm CO) δ −73.6 ppm (d, 6F, J_{FP} = 708 Hz); HR−MS (ESI^+) m/z = 1491.3596 $[M - PF_6]^+$ (calcd for $C_{84}H_{60}CuF_6FeN_{16}O_5 - PF_6$ 1491.3678); UV/vis (CH_2Cl_2) λ_{max} ($10^{-3}\epsilon$, M^{-1} cm^{-1}) 426 (228), 534 (9).

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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