ently of the carrier, a slower nonselective diffusion transport also takes place. Surprisingly, at a much higher substrate concentration (2.5 mM) in the feed, D-phenylalanine is transported faster. This unexpected result can be explained by the fact that at this concentration the D enantiomer successfully competes for the binding site of PAL and occupies it for a much longer period of time, so that little free enzyme remains available for transporting the L enantiomer. The selectivity coefficient in this case also decreases after 30 min and approaches equilibrium asymptotically.

The immobilized HAL mutant E414A behaved differently. HAL is known to be strictly enantioselective for L-histidine.[8] Indeed, its mutant facilitated the transport of the L enantiomer at all three concentrations applied (Figure 3b). However, the selectivity coefficient in this case also reached the highest value (13.3) at the lowest concentration (0.1 mM). After 70 min the selectivity decreased, clearly for the same reason discussed for the PAL experiment. At high concentrations in the feed side, the maximum was much lower (2–3) and was reached faster (30 min.). As a control, the same membrane system without encapsulated enzyme has been also examined for its capacity to transport phenylalanine enantiospecifically. Analysis on a chiral column (see Experimental Section) showed that both enantiomers diffused through the membrane at the same rate.

Our results show that enzymes can be converted into enantioselective receptors by site-directed mutagenesis and used in an immobilized form to facilitate enantioselective transport across a membrane. The technique described herein differs from previously published methods in which enantioselective membranes that contain nonselective proteins, for example, serum albumin or other chiral materials.[9–11] Such membranes as well as chiral chromatography columns work by binding and retarding the transport of one enantiomer, while the other enantiomer can passively diffuse or can be eluted without retardation. In our method, the transport of one enantiomer is accelerated while the other diffuses through the membrane, but much more slowly. Continuous removal of the enriched enantiomer from the permeate (strip) side could lead to resolution on a preparative scale. Whether the present method may become competitive with other established racemate separations or not, is the subject of future research.

It is the first time that not only the concentration dependence but also the time course of the enantioselectivity of the transport through an enzyme-loaded membrane are reported. A further aspect of our results is that as a consequence of the broad substrate specificity of PAL, the present membranes have the potential to resolve the racemates of a large number of aryl alanines.[12]

Experimental Section

Membrane coating: The membrane was first equilibrated for 5 min with the vapor of dichlorodimethylsilane, and water was then applied to one side of the membrane for an additional 5 min. The coated membranes were washed for 1 min with water and dried at room temperature.

Analytical methods: the HPLC separations were run on a Hewlett Packard Series 1050 HPLC with the following columns and under the following conditions: D,L-phenylalanine: Grom Symbasic 125 × 4.6 mm equipped with a 10 × 2.5-mm guard column, 5 μm, isocratic elution with doubly distilled water with TFA (0.1 vol%); D,L-histidine: Grom Sil ODS-O AB, 250 × 4.0 mm, 5 μm, isocratic elution with CH_3CN (20%) and potassium phosphate buffer (pH 8.0, 10 mM, 80%); Astec Chirobiotic T, 250 × 2.5 mm with a 10 × 2.5-mm guard column for chiral analysis.

Conditions according to the Chirobiotic handbook (Advanced Separation Technologies, Inc.).

All chromatograms were monitored at 210 nm.

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[1] B. B. Lakshmi, C. R. Martin, *Nature* **1997**, *388*, 758 – 760.
[2] T. F. Schwede, J. Rétey, G. E. Schulz, *Biochemistry* **1999**, *38*, 5355 – 5361.
[3] D. Röther, D. Merkel, J. Rétey, *Angew. Chem.* **2000**, *112*, 2592 – 2594; *Angew. Chem. Int. Ed.* **2000**, *39*, 2462 – 2464.
[4] D. Röther, L. Poppe, S. Viergutz, B. Langer, J. Rétey, *Eur. J. Biochem.* **2001**, *268*, 6011 – 6019.
[5] B. Langer, D. Röther, J. Rétey, *Biochemistry* **1997**, *36*, 10867 – 10871.
[6] D. Röther, L. Poppe, G. Morlock, S. Viergutz, J. Rétey, *Eur. J. Biochem.* **2002**, *269*, 3065-3075.
[7] All electron-microscope images were recorded at the "Lehrstuhl für Elektronenmikroskopie (LEM)" at the University of Karlsruhe (Germany).
[8] P. C. Wu, T. A. Kroening, P. J. White, K. E. Kendrick, *J. Bacteriol.* **1992**, *174*, 1647 – 1655.
[9] M. Nakamura, S. Kiyohara, K. Saito, K. Sugita, T. Sugo, *Anal. Chem.* **1999**, *71*, 1323 – 1325.
[10] P. C. Wang, J. Gao, C. S. Lee, *J. Chromatography A* **2002**, *942*, 115 – 122.
[11] J. T. F. Keurentjes, F. J. M. Voermans, in *Chirality in Industry* II (Eds.: A. N. Collins, G. N. Sheldrake, J. Crosby), Wiley, New York, **1997**, pp. 157 – 180.

Copper-Catalyzed Oxidative Heterocyclization by Atmospheric Oxygen

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Although molecular oxygen is the most low-priced of all known oxidants, it is applied only rarely in synthetic chemistry. This is because the O_2 molecule has a low reactivity at moderate temperatures due to kinetic barriers, and because of its commonly poor selectivity in the oxidation of organic substrates. However, O_2 can be activated in living organisms by catalytically active metalloenzymes, showing that many selective oxidations are feasible even under very mild conditions. Therefore, metal complexes possessing similarities

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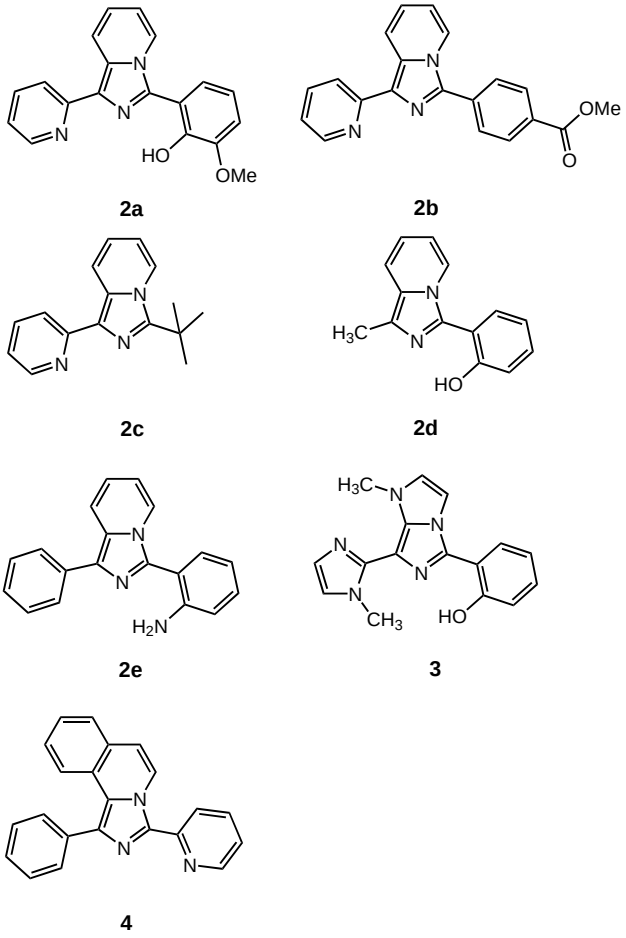
with the active site of copper-containing oxygenases and oxidases, for example bilirubin and sulochrin oxidase, have attracted increasing interest.[1] To date, the transfer of the chemical reactivity of a biooxidase into a simple synthetic complex has been successful in a few cases only. Examples include amino and phenoxy ligands as mimics for the copper-containing enzyme galactose oxidase,[2] as well as mononuclear and binuclear copper(I) complexes as models of the biological oxygenases.[3] In addition, the oxidation of a bis(pyridine)imine ligand in vanadium(V) complexes has been described;[4] however, this oxidation has not yet been performed in a closed catalytic cycle. Recently an oxidative heterocyclization of thiosemicarbazones to 1,3,4-oxadiazole derivatives was described,[5] in which the reactand had to be coordinated to copper(II) ions with $KBrO_3$ as oxidant. Likewise, this reaction was not carried out catalytically.

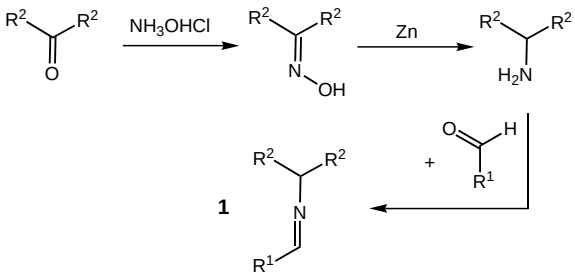
Most interesting is the ecologically compatible synthesis of new heterocyclic compounds that are not easily accessible and that can be applied as pharmaceuticals or as ligands for the development of new catalysts. A series of imidazo[1,5-*a*]pyridines (**2a–e**), the imidazo[1,5-*a*]imidazole **3**, and the imidazo[5,1-*a*]isoquinoline **4** were prepared by copper-catalyzed oxidation with atmospheric oxygen.[6] Here, we describe the synthesis of the seven heterobicycles **2a–e, 3,** and **4** by catalytic ring closure starting from the Schiff bases **1a–g** (Scheme 1). The Schiff bases **1a–g** were prepared readily from the appropriate aldehydes and primary amines. The required amines are accessible by the reduction of the oximes with zinc.[7] The isolation of the imine **1** is not necessary; that is the copper-catalyzed reaction of **1** was performed in situ, as shown, for example, by the synthesis of **2b**.

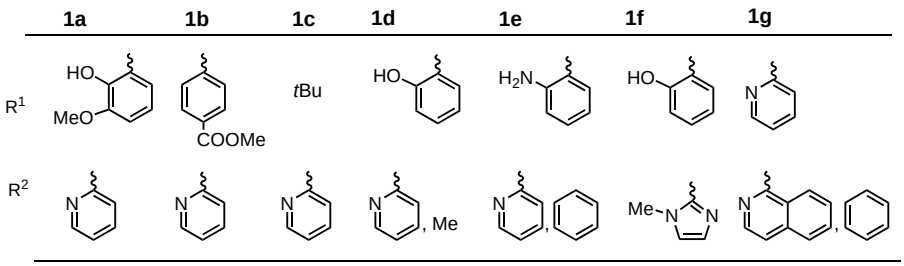
A methanolic solution of **1** and catalytic amounts of $CuCl_2$ and base (sodium hydroxide, triethylamine) were heated in the presence of air (Scheme 2). The Schiff base **1** undergoes an oxidative dehydrogenation after coordination to a copper(II) ion. Then, a C–N bond was generated between the imino-carbon atom and the nitrogen atom of the 2-pyridyl, 2-imidazolyl, or isoquinolyl group in **1**, leading to the formation of the five-membred heterobicycles.[8] The copper(II) ions are regenerated after the oxidative cyclization when atmospheric O_2 is present. The oxidized, monodentate ligands **2–4** coordinate more weakly to the Cu^{II} center than the bidentate imine starting material **1** and can therefore be substituted by ligand exchange; in this way the catalysis cycle begins anew.

Neither hydroxy or amine groups at R^1 (**1a**, **d–f**) nor other substituents (**1b**, **c**, **g**) hamper the reaction. The selective oxidation of **1** by molecular oxygen is only feasible in this reaction with copper ions as catalyst. Nevertheless, for the catalytic reaction the Schiff base **1** must contain three donor atoms, whereas two donor atoms are sufficient for the stoichiometric copper-mediated reaction.[6] The copper-catalyzed reaction affords heterobicycles (yields between 35 and 60%), which are either not accessible with the stoichiometric variant or can only be obtained in very low yields.



The X-ray structure analyses of **2a** (Figure 1) and **3** (Figure 2) show the planar arrangement of the imidazo[1,5-*a*]-





Scheme 1. Synthesis of the aldimines **1**.

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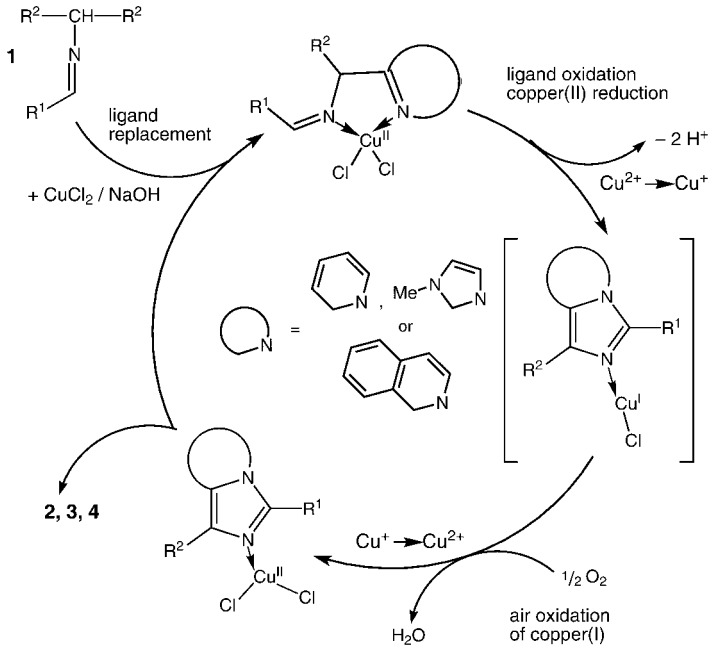

Scheme 2. Catalytic cycle with Cu^{II} catalyst and O_2 as oxidant (for R^1, R^2 see Scheme 1).

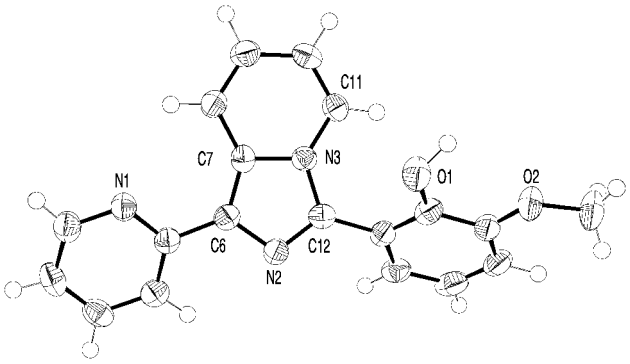

Figure 1. Molecular structure of **2a**. Selected C–N distances [Å] and C-N-C angles [°]: C12-N2 1.330, C6-N2 1.377, C12-N3 1.382, C11-N3 1.386, C7-N3 1.401; C12-N2-C6 107.0, C12-N3-C7 107.3, C11-N3-C7 121.8.

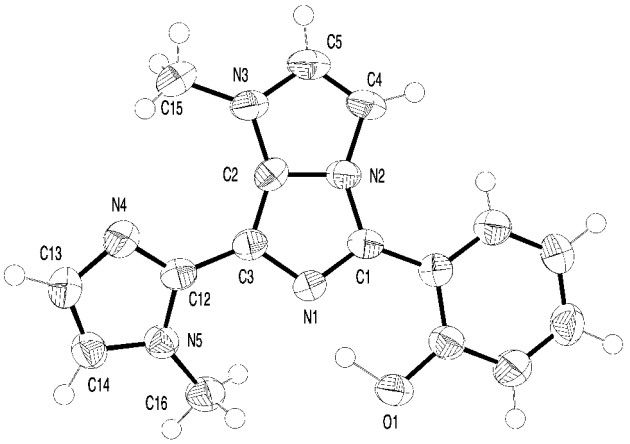

Figure 2. Molecular structure of **3**. Selected C–N distances [Å] and C-N-C angles [°]: C1-N1 1.342, C3-N1 1.386, C1-N2 1.389, C2-N2 1.388, C2-N3 1.373, C5-N3 1.390, C15-N3 1.463, C12-N5 1.378, C16-N5 1.458, C12-N4 1.333, C13-N4 1.384, C14-N5 1.385; C1-N1-C3 109.4, C1-N2-C2 107.9, C2-N3-C5 106.9, C2-N2-C4 108.4, C12-N4-C3 104.8, C12-N5-C14 106.3.

pyridine (**2a**) and the imidazo[1,5-*a*]imidazole (**3**) heterobicycles. The 1-methylimidazol-2-yl unit in **3** is flipped by 20° from the imidazo[1,5-a]imidazole backbone. The H atom at O1 in **3** forms a hydrogen bond with the N1 atom (1.53 Å). In contrast, in **2a** the analogous *ortho*-hydroxy group forms a hydrogen bond with the pyridyl-N1 atom of a second molecule (1.95 Å).

To investigate the selective influence of the copper catalyst on the reaction, we attempted to oxidize different Schiff bases in the absence of copper ions. No selective oxidation was observed for reactions with other oxidants, such as iron(III) salts, manganese(IV) and lead(IV) acetate, and air oxygen under basic conditions, and no heterobicyles were isolated.

This copper-catalyzed reaction provides a facile route to heterobicycles which previously had only been accessible in low yields by dehydration of amides under severe conditions (imidazo[1,5-*a*]pyridines,[9] imidazo[1,5-*a*]imidazoles,[10] and imidazo[5,1-*a*]isoquinolines[11]). Analogous copper-catalyzed reactions of other Schiff base compounds, as well as the isolated copper(I) and copper(II) intermediates will be reported in due course.

Experimental Section

2a: The Schiff base **1a** (1920 mg, 6 mmol), NaOH (25 mg, 0.6 mmol), and $CuCl_2$ (80 mg, 0.6 mmol) were heated in methanol (50 mL) under reflux for 7 h, while dry air was bubbled through the solution. After the mixture had been allowed to cool to room temperature, a solution containing NH_4CH_3COO (10 g) and NaCl (10 g) in distilled water (50 mL) was added, and the mixture was heated up to 60 °C for 10 min. After the mixture had cooled down to room temperature, the crystallisate was dissolved in $CHCl_3$. The solution was extracted three times with $CHCl_3$, and the combined organic layers were dried with Na_2SO_4. The $CHCl_3$ was then removed in vacuo. Column chromatography of the brown oil on silica in acetone afforded **2a** as a major yellow band. After removal of the solvent, **2a** was recrystallized from ethanol. The crystallization was completed by cooling the mother liquor to −20 °C. Yield of **2a**: 670 mg (2.1 mmol, 45 %); m.p. 185 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 11.58$ (s, br., OH), 8.70 (m, 1H), 8.58 (m, 1H), 8.37 (m, 1H), 8.05 (m, 1H), 7.68 (m, 1H), 7.33 (m, 1H), 7.07 (m, 1H), 6.91 (m, 3H), 6.67 (m, 1H), 3.94 ppm (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 154.0$, 149.2, 149.0, 146.2, 136.3, 135.5, 129.5, 128.6, 122.6, 122.1, 121.5, 120.7, 119.6, 119.0, 117.5, 114.5, 112.3, 56.2 ppm; EI$^+$-MS: *m*/*z* (%): 317 (100) [M^+]; C,H,N analysis (%) calcd for **2a**: C 71.91, H 4.76, N 13.24; C 71.71, H 4.89, N 12.89.

2b: Method A: The Schiff base **1b** (1160 mg, 3.5 mmol), NaOH (20 mg, 0.5 mmol) and $CuCl_2$ (90 mg, 0.5 mmol) were first heated in methanol (40 mL) under reflux for 1 h, while bubbling dry air through the solution. After the reaction mixture was cooled down to room temperature, the precipitated solid was filtered and recrystallized in ethanol/water (2/1). Compound **2b** (720 mg, 2 mmol; 63 %) was obtained as yellow crystals. Method B: A solution of bis(2-pyridyl)methylamine (2 g, 11 mmol) in ethanol (10 mL) was added dropwise to a solution of 4-formylmethoxybenzoic ester (1.8 g, 11 mmol) in absolute ethanol (10 mL). The mixture was refluxed for 1 h under argon. Then $CuCl_2$ (90 mg, 0.5 mmol) and NaOH (20 mg, 0.5 mmol) were added. The mixture was refluxed for another 1.5 h, while bubbling dry air through the solution. The precipitated yellow solid was filtered and washed with ethanol. After drying in vacuo, **2b** (1.25 g, 3.8 mmol; 35 % relative to the used amine) was obtained as a yellow solid. M.p. 204 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.70$ (m, 1H), 8.60 (m, 1H), 8.16–8.31 (m, 4H), 7.93 (m, 2H), 7.71 (m, 1H), 7.09 (m, 1H), 6.95 (m, 1H), 6.68 (m, 1H), 3.94 ppm (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta =$ 166.6, 154.8, 149.0, 136.8, 136.2, 134.4, 131.4, 130.8, 130.2, 129.9, 127.8, 122.1, 121.5, 121.4, 120.6, 120.0, 114.5, 52.2 ppm; EI$^+$-MS: *m*/*z* (%): 329 (100) [M^+]; elemental analysis calcd (%) for **2b**: C 72.94, H 4.59, N 12.76; found: C 72.93, H 4.63, N 12.61.

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2c: The Schiff base **1c** (1000 mg, 4 mmol), NaOH (16 mg, 0.4 mmol), and $CuCl_2$ (54 mg, 0.4 mmol) were first heated in methanol (60 mL) under reflux for 7 h, while bubbling dry air through the solution. After the mixture had been stirred at room temperature for a further 12 h, the solvent was removed in vacuo. Column chromatography of the residue on silica with hexane/ethyl acetate (1/3) afforded **2c** as a major yellow band (400 mg, 1.6 mmol; 40%). M.p. 92°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta =$ 8.65 (m, 1H), 8.61 (m, 1H), 8.06–8.21 (m, 2H), 7.69 (m, 1H), 7.05 (m, 1H), 6.83 (m, 1H), 6.55 (m, 1H), 1.59 ppm (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 155.0, 148.5, 145.3, 136.6, 130.6, 127.4, 123.2, 121.8, 120.0, 119.9,$ 112.6, 33.5, 28.2 ppm. EI$^+$-MS: m/z (%): 251 (90) [M^+], 236 (100) [M^+-CH_3]; elemental analysis (%) calcd for **2c**: C 76.46, H 6.82, N 16.72; found: C 76.13, H 6.47, N 16.54.

2d: The Schiff base **1d** (2500 mg, 11 mmol), NaOH (57 mg, 1.4 mmol), and $CuCl_2$ (194 mg, 1.4 mmol) were first heated in methanol (100 mL) under reflux for 3 h, while bubbling dry air through the solution. The solvent was then removed in vacuo. Column chromatography of the residue on silica with hexane/CH_2Cl_2/ethyl acetate (6/6/1) afforded **2d** as a major green fluorescent band. Recrystallization of the collected fraction with toluene yielded pale yellow crystals of **2d** (1250 mg, 5.6 mmol; 50%). M.p. 150°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.92$ (d, 1H), 7.46 (m, 1H), 7.35 (m, 1H), 7.08 (m, 2H), 6.81 (m, 2H), 6.63 (m, 1H), 2.57 ppm (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 156.2, 134.0, 129.8, 127.2, 126.4, 124.6, 122.2, 119.0,$ 118.6, 118.2, 117.7, 114.0, 113.8, 12.0 ppm; EI$^+$-MS: m/z (%): 224 (100) [M^+]; elemental analysis (%) calcd for **2d**: C 74.98, H 5.39, N 12.49; found: C 74.85, H 5.27, N 12.41.

2e: The Schiff base **1e** (2300 mg, 8 mmol), NaOH (40 mg, 1 mmol), and $CuCl_2$ (130 mg, 1 mmol) were heated in methanol (40 mL) under reflux for 30 min while bubbling dry air through the solution. The color of the reaction mixture changed to brown. After the addition of distilled water (150 mL), EDTA (500 mg), ammonium acetate (500 mg) and NaCl (20 g) to the hot reaction mixture a brown solid precipitated. This precipitate was dissolved in ethyl acetate and the aqueous methanolic solution was extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate. The ethyl acetate was removed in vacuo. Column chromatography of the residue on neutral Al_2O_3 with hexane/ethyl acetate (1/1) and removal of the solvents afforded a yellow oil which crystallized in the cold. For the removal of a few impurities the solid was dissolved again in acetic acid (20 mL) and distilled water (50 mL). After addition of NaCl (15 g) and ice (50 g) to the colorless solution a brown precipitate appeared, which was filtered from the dissolved product. $NaHCO_3$ was added to the filtrate and a yellow solid precipitated which was filtered from the solution. Recrystallization of the solid with ethanol/water (1/1) yielded yellow crystals of **2e** (800 mg, 2.8 mmol; 35%). M.p. 146°C; ^{1}H NMR (400 MHz, C_6D_6): $\delta = 8.02$ (d, 2H), 7.55 (m, 1H), 7.36 (m, 1H), 7.29 (m, 2H), 7.12 (m, 1H), 7.00 (m, 1H), 6.59 (m, 1H), 6.40 (m, 1H), 6.12 (m, 1H), 5.72 (m, 1H), 4.77 ppm (s, 2H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 147.1, 136.8, 136.0, 131.6,$ 129.9, 128.9, 128.4, 127.1, 126.6, 122.5, 119.5, 119.0, 117.1, 116.8, 114.2, 112.5 ppm; EI$^+$-MS: m/z (%): 286 (30) [M^+]; elemental analysis (%) calcd for **2e**: C 79.98, H 5.30, N 14.73; found: C 79.53, H 5.13, N 14.34.

3: The Schiff base **1f** (970 mg, 3.3 mmol), NaOH (20 mg, 0.4 mmol), and $CuCl_2$ (50 mg, 0.4 mmol) were heated in ethanol (30 mL) under reflux for 1 h, while bubbling dry air through the boiling solution. The color of the reaction mixture changed from green to brown. After cooling the mixture to room temperature, the crude product **3** precipitated. The product was recrystallized in a water/DMSO (1/1) mixture to give crystalline **3** (345 mg, 1.1 mmol; 36%). M.p. 204°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 12.65$ (s, br., OH), 6.84–7.50 (m, 8H), 4.06 (s, 3H), 3.95 ppm (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 155.6, 137.4, 127.7, 127.4, 127.1, 126.6, 122.0, 121.1,$ 118.8, 116.9, 114.6, 104.7, 102.5, 35.1, 34.8 ppm; EI$^+$-MS: m/z (%): 293 (100) [M^+]; elemental analysis calcd for **3**: C 65.52, H 5.15, N 23.88; found: C 65.31, H 5.01, N 23.72.

4: The Schiff base **1g** (890 mg, 2.8 mmol) and $CuCl_2$ (40 mg, 0.28 mmol) were heated in methanol (20 mL) under reflux for 30 min, while bubbling dry air through the solution. The color of the reaction mixture changed to brown. After the addition of distilled water (200 mL), EDTA (250 mg) and ammonium acetate (1000 mg) to the hot reaction mixture a yellow-brown solid precipitated. The residue was filtered from the solution and dissolved in ethyl acetate. Column chromatography of the residue on weak basic Al_2O_3 with hexane/ethyl acetate (1/1) afforded **4** as a major blue fluorescent band. Recrystallization of the collected fraction with hexane/toluene (4/1) (35 mL) yielded pale-yellow crystals of **4** (310 mg, 0.97 mmol; 35%). M.p. 197°C; ^{1}H NMR (200 MHz, C_6D_6): $\delta = 10.07$ (d, 1H), 8.73 (m, 1H), 8.48 (m, 1H), 8.39 (m, 1H), 8.03 (m, 2H), 7.44 (m, 2H), 7.03–7.30 (m, 5H), 6.68 ppm (m, 2H); ^{13}C NMR (50.3 MHz, C_6D_6): $\delta = 152.2, 148.5,$ 138.1, 137.6, 137.2, 137.0, 136.7, 130.8, 129.6, 128.2, 127.4, 127.3, 126.3, 126.2, 125.3, 123.6, 123.5, 122.2, 114.4 ppm; EI$^+$-MS: m/z (%): 321 (100) [M^+]; elemental analysis (%) calcd for **4**: C 82.22, H 4.70, N 13.08; found: C 81.88, H 4.76, N 12.69.

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[1] a) E. I. Solomon, U. M. Sundaram, T. E. Machonkin, *Chem. Rev.* **1996**, *96*, 2563; b) E. I. Solomon, P. Chen, M. Metz, S.-K. Lee, A. E. Palmer, *Angew. Chem.* **2001**, *113*, 4702; *Angew. Chem. Int. Ed.* **2001**, *40*, 4570; c) P. Gamez, P. G. Aubel, W. L. Driessen, J. Reedijk, *Chem. Soc. Rev.* **2001**, *30*, 376.

[2] P. Chaudhuri, M. Hess, U. Flörke, K. Wieghardt, *Angew. Chem.* **1998**, *110*, 2340; *Angew. Chem. Int. Ed.* **1998**, *37*, 2217.

[3] a) K. D. Karlin, J. C. Hayes, Y. Gultneh, R. W. Cruse, J. W. McKown, J. P. Hutchinson, J. Zubieta, *J. Am. Chem. Soc.* **1984**, *106*, 2121; b) I. E. Markó, P. R. Giles, M. Tsukazaki, S. M. Brown, C. J. Urch, *Science* **1996**, *274*, 2044.

[4] A. G. J. Ligtenbarg, A. L. Spek, R. Hage, B. L. Feringa, *J. Chem. Soc. Dalton Trans.* **1999**, 659.

[5] P. Gómez-Saiz, J. Garciá-Tojal, M. A. Maestro, F. J. Arnaiz, T. Rojo, *Inorg. Chem.* **2002**, *41*, 1345.

[6] a) M. Döring, M. Ciesielski, H. Görls, *J. Inorg. Biochem.* **1999**, *74*, 117; b) M. Ciesielski, O. Walter, M. Döring, *J. Inorg. Biochem.* **2001**, *86*, 475.

[7] E. Niemers, R. Hiltmann, *Synthesis* **1976**, 593.

[8] No additional base is necessary if R^1 in **1g** is a heterocyclic fragment.

[9] a) J. D. Bower, G. R. Ramage, *J. Chem. Soc.* **1955**, 2834; b) K. Winterfeld, H. Franzke, *Angew. Chem.* **1963**, *22*, 1101; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 736; c) E. Abushanab, *Tetrahedron Lett.* **1971**, *18*, 1441; d) M. T. Edgar, G. R. Pettit, T. S. Krupa, *J. Org. Chem.* **1979**, *44*, 396; e) R. Tachikawa, S. Tanaka, A. Terada, *Heterocycles* **1981**, *15*(1), 369; f) A. P. Katritzky, C. W. Rees in *Comprehensive Heterocyclic Chemistry, Vol. 5* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Elsevier Science, Oxford, **1984**, S. 634; g) A. P. Krapcho, J. R. Powell, *Tetrahedron Lett.* **1986**, *27*, 3713; h) M. Renz, C. Hemmert, B. Donnadieu, B. Meunier, *Chem. Commun.* **1998**, 1635.

[10] a) V. M. Aryuzina, M. N. Shchukina, *Khim. Geterotsikl. Soedin.* **1968**, *3*, 506; b) M. P. Kochergin, V. A. Lifanov, *Khim. Geterotsikl. Soedin.* **1994**, *4*, 490.

[11] H. Reimlinger, J. J. M. Vandewalle, W. R. F. Lingier, E. de Ruiter, *Chem. Ber.* **1975**, *108*, 3771.

[12] Crystal structure analyses: Data were collected on a Nonius Kappa CCD diffractometer ($Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, φ and ω scans), at 183 K, up to $\theta_{max} = 27.44°$. The structure was solved by direct methods, and refined by least-squares against F^2 (SHELXTL V5.10); non-hydrogen atoms anisotropic, hydrogen atoms located and refined isotropically. **2a**: $C_{19}H_{15}N_3O_2$, $M_r = 317.34$, monoclinic, space group $P2(1)/n$, $a = 10.183(1)$, $b = 9.179(2)$, $c = 16.393(3)$ Å, $\beta = 104.50(2)°$, $V = 1483.4(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.421$ Mg m^{-3}; 3117 measured reflections, 3011 independent reflections ($R_{int} = 0.0382$), 2370 parameters, $R1 = 0.0416$ (for reflections with $I > 2\sigma(I)$), $wR2 = 0.1085$ (for all reflections), residual electron density 0.213/−0.214 e Å^{-3}. **3**: $C_{16}H_{15}N_5O$, $M_r = 293.33$, monoclinic, space group $P2(1)/n$, $a =$ 9.7170(9), $b = 7.1997(7)$, $c = 20.147(1)$ Å, $\beta = 98.953(5)°$, $V =$ 1392.3(2) Å^3, $Z = 4$, $\rho_{calcd} = 1.399$ Mg m^{-3}; 5001 measured reflections, 2805 independent reflections ($R_{int} = 0.0715$), 2805 parameters, $R1 =$ 0.0715 (for reflections with $I > 2\sigma(I)$), $wR2 = 0.1580$ (for all reflections), residual electron density 0.195/−0.303 e Å^{-3}. CCDC-172796 (**2a**) and CCDC-172797 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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