Inorg. Chem. **2003**, *42*, 8878–8885

Complexes of Schiff Bases and Intermediates in the Copper-Catalyzed Oxidative Heterocyclization by Atmospheric Oxygen§

Martin E. Bluhm,† Michael Ciesielski,† Helmar Görls,‡ Olaf Walter,† and Manfred Döring*,†

Institute for Technical Chemistry (ITC-CPV), Forschungszentrum Karlsruhe, P.O. Box 3640, 76021 Karlsruhe, Germany, and Department of Inorganic Chemistry, University of Jena, August-Bebel-Strasse 2, 07743 Jena, Germany

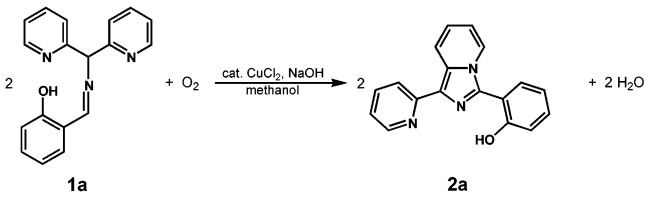
Received July 7, 2003

After complexation with copper(II) ions, Schiff bases **1a**–**d** may undergo an oxidative ring closure using atmospheric oxygen to give a number of imidazo[1,5-*a*]pyridines **2**, an imidazo[1,5-*a*]imidazole **3,** and an imidazo[5,1-*a*]isochinoline **4**. This ligand oxidation can be performed with catalytic amounts of copper ions in the reaction. A catalytic cycle for the copper-catalyzed oxidative heterocyclization will be presented together with isolated copper complexes of Schiff bases **1a**,**b** and intermediates **5** and **8** that were found by X-ray structure analyses which confirm this reaction scheme.

Introduction

Previously, an ecologically compatible synthesis of new heterobicyclic compounds was described, which can be applied as pharmaceuticals or ligands for the development of new homogeneous catalysts.[1a,b] Imidazo[1,5-*a*]pyridines **2**, an imidazo[1,5-*a*]imidazole **3**, and an imidazo[5,1-*a*]isochinoline **4** were prepared from Schiff bases **1a**,[1c] **1b**, and **1c**−**d**[1a] with an oxidative ring closure reaction by atmospheric oxygen and catalytic amounts of copper(II) and a base (Chart 1). This method easily and rapidly yields new nitrogen-fused heterocycles which cannot be prepared in the traditional synthetic way of dehydrating amides under severe conditions.[2−4] Even sensitive functional groups such as hydroxy or amine groups at aromatic positions of the Schiff bases **1a**−**c** do not disturb the catalysis. The Schiff bases **1a**,**b**,**e**[5] were used as reactants in reactions examined later.

Scheme 1. Reaction Equation of the Copper-Catalyzed Oxidative Formation of **2a**



1a **2a**

The reaction equation of the copper-catalyzed formation of the heterobicycle **2a** with **1a** and atmospheric oxygen shows the transfer of altogether four electrons from two imines **1a** toward molecular oxygen (Scheme 1).

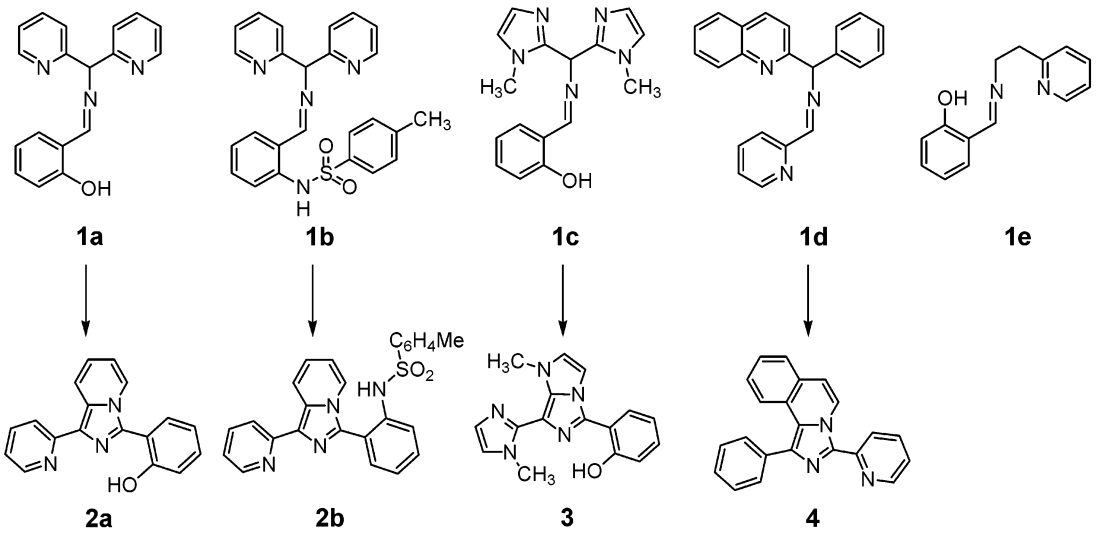
The catalytic reaction pathway can be described as follows: First, the Schiff base **1** coordinates to copper(II) (Scheme 2, **5a**). After deprotonation of the coordinated ligand, both copper(II) ions are reduced to copper(I) in a two-electron process. A C−N bond is established between the carbon of the imino group and a nitrogen atom of a 2-pyridyl, 2-imidazolyl, or isochinolyl group in **1** (Scheme 2, step I). This leads to the closure of nitrogen-fused heterocycles, whereby the derivatives **2**−**4** are formed. As result of the oxidation process, the number of coordinating

* To whom correspondence should be addressed. E-mail: manfred.doering@itc-cpv.fzk.de.
† Forschungszentrum Karlsruhe.
‡ University of Jena. E-mail: goerls@xa.nlwl.uni-jena.de.
§ Dedicated to Professor Eckhard Dinjus on the occasion of his 60th birthday.

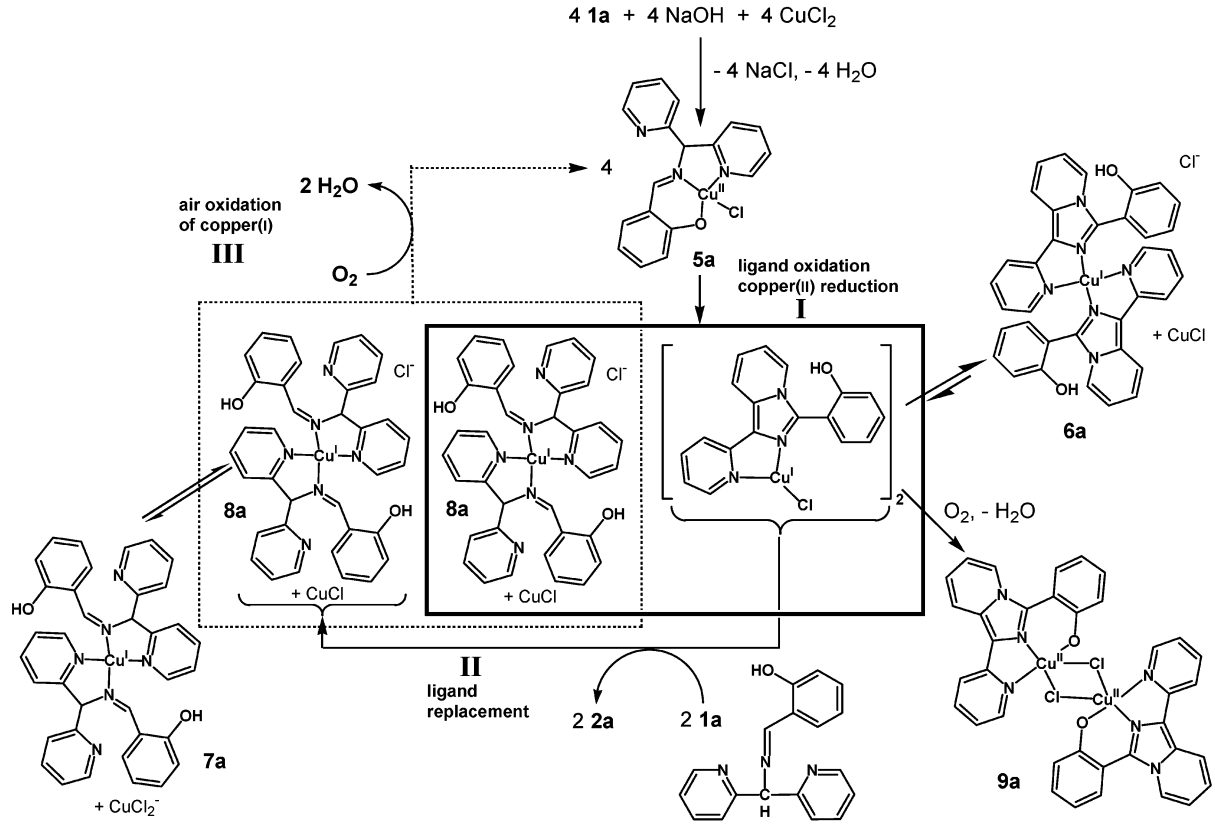
(1) (a) Bluhm, M. E.; Ciesielski, M.; Görls, H.; Döring, M. *Angew. Chem., Int. Ed.* **2002**, *41* (16), 2962; *Angew. Chem.* **2002**, *114* (16), 3104. (b) Bluhm, M.; Ciesielski, M.; Görls, H.; Döring, M. *Chem.-Ing.-Tech.* **2002**, *74* (5), 556. (c) Ligtenbarg, A. G. J.; Spek, A. L.; Hage, R.; Feringa, B. L. *J. Chem. Soc., Dalton Trans.* **1999**, *3*, 659.
(2) (a) Bower, J. D.; Ramage, G. R. *J. Chem. Soc.* **1955**, 2834. (b) Winterfeld, K.; Franzke, H. *Angew. Chem.* **1963**, *22*, 1101. (c) Abushanab, E. *Tetrahedron Lett.* **1971**, *18*, 1441. (d) Edgar, M. T.; Pettit, G. R.; Krupa, T. S. *J. Org. Chem.* **1979**, *44*, 396. (e) Tachikawa, R.; Tanaka, S.; Terada, A. *Heterocycles* **1981**, *15* (1), 369. (f) Katritzky, A. P.; Rees, C. W. *Compr. Heterocycl. Chem.* **1984**, *5*, 634. (g) Krapcho, A. P.; Powell, J. R. *Tetrahedron Lett.* **1986**, *27* (32), 3713. (h) Renz, M.; Hemmert, C.; Donnadieu, B.; Meunier, B. *Chem. Commun.* **1998**, 1635.
(3) (a) Aryuzina, V. M.; Shchukina, M. N. *Khim. Geterotsikl. Soedin.* **1968**, *3*, 506. (b) Kochergin, M. P.; Lifanov, V. A. *Khim. Geterotsikl. Soedin.* **1994**, *4*, 490.
(4) Reimlinger, H.; Vandewalle, J. J. M.; Lingier, W. R. F.; de Ruiter, E. *Chem. Ber.* **1975**, *108*, 3771.
(5) Mousser, A.; Le Marouille, J.-Y. *J. Organomet. Chem.* **1986**, *312*, 263.

10.1021/ic034773a CCC: $25.00
Published on Web 11/22/2003

Chart 1. Examples of Prepared Schiff Bases **1a**−**e** and Heterocycles **2a,b**, **3**, and **4**



Scheme 2. Catalytic Cycle for the Synthesis of **2a** with Cu(II) as Catalyst and O_2 as Oxidant



atoms in the formed heterocycle is reduced. The heterocycle is then substituted by another Schiff base **1** (Scheme 2, step II). Atmospheric oxygen regenerates the copper(II) ions (Scheme 2, step III).

To elucidate the different steps of the copper-catalyzed oxidative heterocyclization, X-ray diffraction studies of copper(I) and copper(II) coordination compounds will be presented.

Results and Discussion

To investigate the course of this reaction, **1a** was used as model ligand. The OH substituents in **1a** facilitate the isolation of copper(I) and copper(II) complexes **5a**−**8a**. Those complexes of the salicylaldimines of bis(2-pyridyl)-methylamine (**1a)** and the heterobicycle **2a** are characterized either as intermediates or as stable compounds which exist in equilibrium with a more reactive species. A one-pot reaction starting with **5a** directly leads to the isolated copper complexes **7a** and **8a**. In this reaction the intermediate **8a** is converted again to **5a**, which is used as starting material. All isolated intermediates except for **9a** may be converted into each other. Complexes of **9** are formed only if no more imine **1** is present for further reacting with copper. Hence, these complexes are no intermediates of the catalysis. The

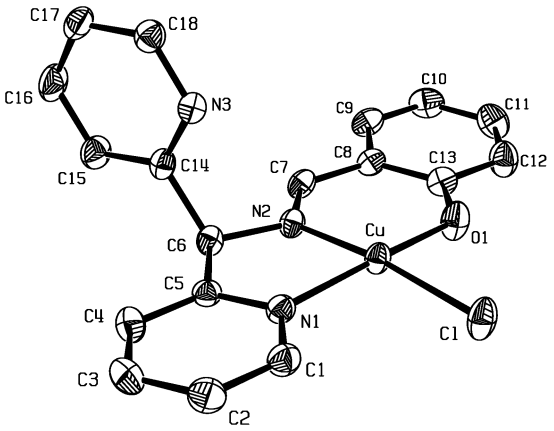
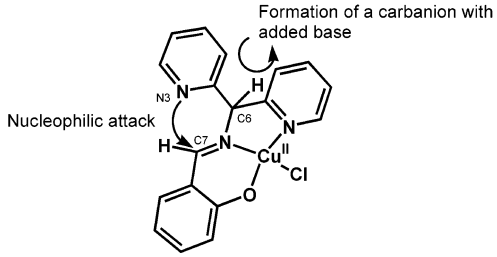


Figure 1. ORTEP[14] drawings of the copper(II) complex **5a**.

Table 1. Interatomic Distances (Å) and Angles (deg) Selected for **5a**

Cu−N1	2.023(2)	Cu−Cl	2.272(1)
Cu−N2	1.973(2)	C7−N2	1.296(3)
Cu−O1	1.9159(15)		
N1−Cu−N2	81.7(1)	O1−Cu−Cl	89.9(1)
N2−Cu−O1	92.5(1)	N1−Cu−Cl	95.3(1)

Scheme 3. Formation of the Heterobicycle **2a** in the Copper(II) Complex **5a**



discussion of the catalytic cycle (Scheme 2) starts with the isolated copper(II) imine complex **5a**.

For the formation of **5a** a reaction with equimolar amounts of **1a**, $CuCl_2$, and sodium hydroxide was carried out in methanol at −60 °C. The mixture was warmed to −30 °C and for a short period of time to −5 °C. **5a** crystallized as dark green crystals suitable for X-ray structure analysis (Figure 1). The mononuclear complex has an essentially undistorted square planar geometry around the copper(II) ion. The Cu−N1 bond of 2.02 Å (Table 1) has the normal distance found for Cu−N(pyridine) bonds in tetracoordinated copper(II) complexes.[6] The Cu−N2 (1.97 Å), Cu−O1 (1.92 Å), and Cu−Cl (2.27 Å) bond distances are in the range expected for this coordination geometry with copper(II).

5a is the first intermediate in the copper-catalytic reaction to the imidazo[1,5-*a*]pyridine **2a**. It has a high thermal stability and does not convert in the crystal state and only slowly in solution, while heated for several hours. However, when a base like sodium hydroxide or triethylamine is added to a solution of methanol with **5a**, the redox process starts immediately. This suggests the increased release of the acidic C6 hydrogen atom with a base as first step of the reaction cascade (Scheme 3).

(6) Orpen, A. G.; Brammer, L.; Allen, F. H.; Kennard, O.; Watson, D. G. *J. Chem. Soc., Dalton Trans.* **1989**, S1−S83.

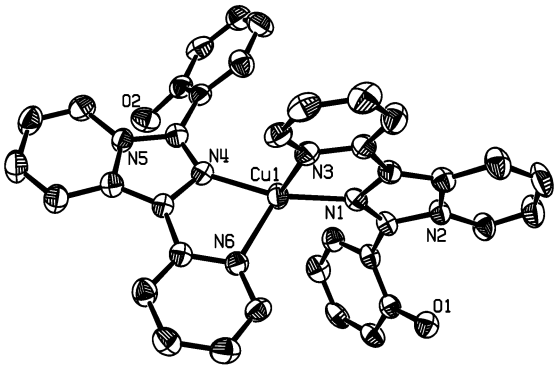
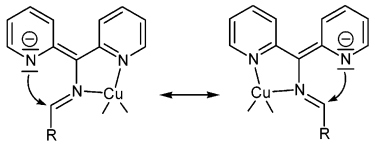


Figure 2. ORTEP[14] drawing of the copper(I) complex **6a** with two coordinated heterobicycles **2a**. One chloride counterion is not reported in this figure.

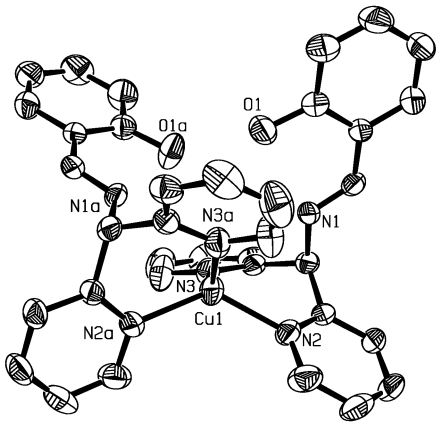
Scheme 4. Nucleophilic Attack by the Negatively Charged Pyridine-*N* Atom N3 at the Imino Carbon C7



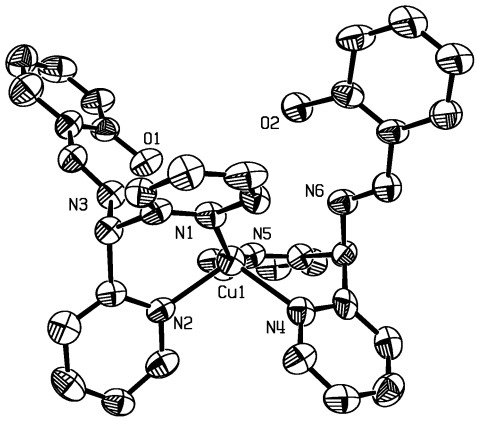
It is known that the acidity of a C−H bond in the α-position to an imino group is markedly increased if the imino nitrogen atom is coordinated to a copper(II) center.[3] The addition of a base is not necessary in every case of the used imine **1**. Basic acceptors, such as pyridines, have the ability to deprotonate the imino carbon-bound hydrogen atom. Electron-withdrawing substituents also facilitate the release of this hydrogen atom. In the case of **5a**, the conversion is possible without an additional base, but it proceeds very slowly.

The carbanion formed at C6 increases the nucleophility at the heterocyclic nitrogen atom N3, which facilitates a nucleophilic attack at the imino carbon C7 (Scheme 4). In the course of the reaction, the ligand is oxidized and the phenolate anion is reprotonated. In this oxidation two involved copper(II) ions are reduced to copper(I) (Scheme 2, step I).

To investigate step I of the catalytic cycle, molecular oxygen has to be excluded. If **1a** reacts with equimolar amounts of $CuCl_2$ and sodium hydroxide in boiling methanol under argon, a brown reaction mixture is obtained from which **6a** crystallizes because of its low solubility. **8a** is also formed in step I, but it is dissolved in the reaction mixture. Using orange crystals of **6a**, an X-ray crystallography study was performed (Figure 2). In the ionic **6a** two imidazo[1,5-*a*]pyridines chelate with four nitrogen atoms around one copper(I) ion. Both phenoxy groups are protonated and not used as chelating units with the copper ion. The coordination sphere around the copper(I) ion is a distorted tetrahedron with N−Cu−N angles ranging between 81 and 154° (Table 2). The Cu−N1 and Cu−N6 bond distances are 1.96 and 2.09 Å, respectively, which is in the normal range for those bonds.[6] Both distances between the copper ion and the coordinated pyridine nitrogen atoms are unusually large (2.09 and 2.15 Å). A similar C−N(pyridine) bond length was found in one of the [*N*-alkyl-2-pyridylmethanimine]copper(I) com-



7a



8a

Figure 3. ORTEP[14] drawing of the copper(I) complexes **7a** and **8a** with two coordinated imines **1a**. Half of **7a** was generated by a crystallographic 2-fold axis. The $CuCl_2^-$ counterion of **7a** and the Cl^- counterion of **8a** are not reported in this figure.

Table 2. Interatomic Distances (Å) and Angles (deg) Selected for **6a**

Cu−N1	1.958(3)	Cu−N4	1.993(3)
Cu−N3	2.145(3)	Cu−N6	2.088(3)
N1−Cu−N3	81.2(1)	N3−Cu−N4	109.3(1)
N4−Cu−N6	81.9(1)	N1−Cu−N4	154.4(1)
N1−Cu−N6	120.1(1)	N3−Cu−N6	100.0(1)

Table 3. Interatomic Distances (Å) and Angles (deg) Selected for **7a**

Cu1−N2	2.042(3)	Cu1−N3	2.015(3)
N3−Cu1−N3a	134.91(15)	N3−Cu1−N2a	105.5(1)
N3−Cu1−N2	93.8(1)	N3a−Cu1−N2a	93.8(1)
N3a−Cu1−N2	105.5(1)	N2−Cu1−N2a	128.46(15)

Table 4. Interatomic Distances (Å) and Angles (deg) Selected for **8a**

Cu1−N1	2.023(7)	Cu1−N4	2.107(8)
Cu1−N2	2.074(8)	Cu1−N5	1.985(8)
N1−Cu1−N5	144.9(3)	N4−Cu1−N5	91.2(3)
N2−Cu1−N5	109.1(3)	N1−Cu1−N4	109.6(3)
N1−Cu1−N2	91.7(3)	N2−Cu1−N4	107.5(3)

plexes described by Haddleton et al.[7] **6a** is quite stable against molecular oxygen and, hence, does not represent any catalytic intermediate. **6a** only slowly converts into **9a** in refluxing methanol and in the presence of air. This reveals the existence of a more labile but also more soluble heterobicyclic copper(I) complex as catalytic intermediate which could not be isolated yet. As proposed in Scheme 1, **6a** is in equilibrium with this more reactive copper(I) species.

After the heterobicycle has been released from the metal ion of the intermediate which is in equilibrium with **6a**, a heterocyclic imine coordinates to the copper(I) ion (Scheme 2, step II). The tridentate imine **1a** coordinates better to the copper(I) center than the formed heterobicycle **2a**, which is bidentate. The intermediate **8a** is also formed in this reaction step. **8a** is in equilibrium with a thermodynamically more stable species **7a**. To isolate the relevant copper(I)−imine complexes **7a** and **8a**, **5a** was reacted with **1a** in the presence of small amounts of NaOH under argon. The conversion of **5a** into **6a** and, thus, into **7a** and **8a** already happens at room temperature (steps I and II, Scheme 2). This gives a brown and very air sensitive solution. During removal of some solvent and cooling of the solution, crystals were obtained of **7a** and **8a** with additional small amounts of **6a**. **7a** is also formed directly with **1a** and CuCl. **7a** and **8a** were isolated and structurally characterized (Figure 3). Both complexes are very similar to each other but show a different behavior in their reactivity toward molecular oxygen and in their solubility properties. While the copper(I) complex **7a** obtains $CuCl_2^-$ as coordinating anion, it is Cl^- and the formation of neutral CuCl in **8a**. Both compounds **7a** and **8a** contain a copper(I) atom coordinated to two imines **1a** each. The angle around the copper(I) ion is distorted tetrahedrally, while the angle N1−Cu1−N5 is larger (144.9 deg) in **8a** compared to the angle N3−Cu1−N3a (134.9 deg) in **7a** (Tables 3 and 4). The Cu1−N4 bond in **8a** is expanded (2.107 Å), while the Cu1−N5 bond is shorter (1.958 Å) compared with the Cu1−N bonds (2.015−2.042 Å) in **7a**. The expansion and the lower shielding of the copper ion in **8a** explain the much higher reactivity toward molecular oxygen and a better solubility in organic solvents. Like **6a**, both phenoxy groups are protonated in **7a** and **8a** and not used as chelating units with the copper ion (Scheme 2). **7a** and **8a** prove the coordination of imines to copper(I) in the catalysis. The ^{1}H spectrum of **8a** shows a broader set of imine signals compared to the noncoordinated ligand **1a**, which suggests a kinetically labile coordination of the imine to the copper(I) ion.

In step III molecular oxygen oxidizes copper(I) to copper(II), while both phenoxy substituents in the ligand are deprotonated. A total of 2 equiv of **8a** react with oxygen under release of two molecules of water to the intermediate **5a**. A yellow-brown methanolic solution of **8a** immediately turns green with atmospheric oxygen, and crystals of **5a** are formed while cooling the closed flask. **7a** reacts much more slowly with molecular oxygen to **5a**. Like **5a**, **8a** may well be considered as important intermediate of the catalysis. The catalytic cycle starts from the beginning with the formation of **5a**.

The formation of **9a** is possible only when all imine molecules of **1a** have reacted to the heterobicycle **2a**. Then, **2a** coordinates to copper(II) ions which have been oxidized

(7) Haddleton, D. M.; Duncalf, D. J.; Kukulj, D.; Crossman, M. C.; Jackson, S. G.; Bon, S. A. F.; Clark, A. J.; Shooter, A. J. *Eur. J. Inorg. Chem.* **1998**, 1799.

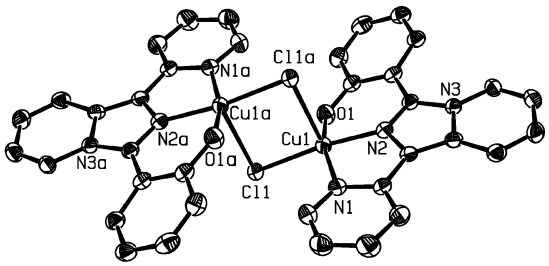


Figure 4. ORTEP[14] drawing of the binuclear copper(II) complex **9a**. Half of **9a** was generated by a crystallographic inversion center.

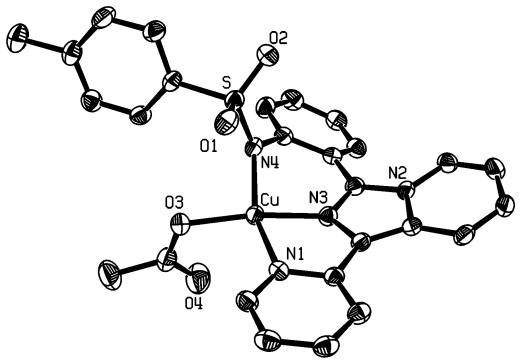


Figure 5. ORTEP[14] drawing of the copper(II) complex **9b**.

Table 5. Interatomic Distances (Å) and Angles (deg) Selected for **9a**

Cu1−N1	2.056(2)	Cu1−Cl1	2.276(1)
Cu1−N2	1.924(2)	Cu1a−Cl1	2.723(1)
Cu1−O1	1.929(2)	Cu1a−Cu1	3.480(2)
N1−Cu1−N2	80.3(1)	O1−Cu1−Cl1a	98.8(1)
N1−Cu1−Cl1	97.1(1)	N2−Cu1−Cl1	172.6(1)
N1−Cu1−Cl1a	93.0(1)	N2−Cu1−Cl1a	94.8(1)
N1−Cu1−O1	164.4(1)	Cu1−Cl1−Cu1a	87.7
N2−Cu1−O1	88.6(1)	Cl1−Cu1−Cl1a	92.3
O1−Cu1−Cl1	92.6(1)		

by molecular oxygen to give the characterized complex **9a**. If **5a** is heated in methanol in the presence of air for several hours, the product **9a** is formed. Crystals suitable for X-ray crystallography are obtained while cooling the reaction mixture of refluxing **1a**, $CuCl_2$, and NaOH in the presence of air (Figure 4). In the bimetallic complex **9a** both copper(II) ions have a distorted square pyramidal geometry. Two chlorides act as bridging ligands. Whereas the Cu−N(pyridine) length (2.06 Å; Table 5) is the distance commonly found for those bonds, the Cu−N(imidazo) distance (1.92 Å) is relatively short. The Cu−O1, Cu−O1a (1.93 Å) and Cu−Cl1, Cu−Cl1a (2.28 Å) bond distances are in the range expected for this coordination geometry with copper(II).[6]

The imine **1b** that bears a toluenesulfonyl amino group instead of the *o*-hydroxy group reacts in a way similar to **1a**. In the presence of O_2 and sodium hydroxide, **1b** reacts with copper(II) acetate to the copper(II) complex **9b**, which contains the imidazo[1,5-*a*]pyridine **2b** as chelating ligand (Figure 5). The X-ray structure was determined using crystals of **9b**, which have been obtained by recrystallization from methanol. In contrast to **9a**, a mononuclear complex **9b** is formed and the coordination number of the copper is 4 only. The imidazo[1,5-*a*]pyridine **2b** acts as a tridentate chelating ligand and an acetate oxygen atom is attached to the copper(II) ion. The molecular geometry around the copper ion is distorted square planar. Like in **9a**, the complex **9b** has a similarly short Cu−N(imidazo) bond length (1.93 Å; Table 6). **9b** also is a product of the reaction of **1b** with copper(II) ions. If all imines **1b** have been reacted in the catalysis, no ligand replacement in step II (Scheme 2) can occur.

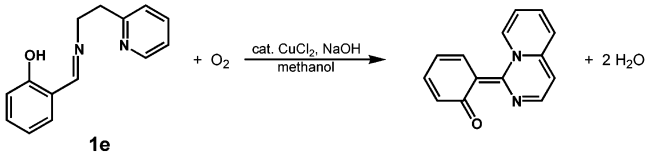
Table 6. Interatomic Distances (Å) and Angles (deg) Selected for **9b**

Cu−N1	2.057(2)	S−N4	1.596(3)
Cu−N3	1.932(2)	S−O1	1.457(2)
Cu−N4	2.005(2)	S−O2	1.450(2)
Cu−O3	1.943(2)		
N1−Cu−N3	80.1(1)	N3−Cu−O3	172.1(1)
N3−Cu−N4	86.7(1)	N4−Cu−O3	100.2(1)
N1−Cu−N4	156.0(1)	O1−S−N4	105.5(1)
N1−Cu−O3	94.7(1)	O2−S−N4	112.7(1)

Table 7. Interatomic Distances (Å) and Angles (deg) Selected for **5e**

Cu1−N1	2.108(3)	Cu1−O1	2.049(2)
Cu1−N2	2.205(3)	Cu2−O6	1.853(2)
Cu2−N3	1.968(3)	Cu1−Na	3.376(1)
Cu2−N4	1.789(2)	Cu2−Na	2.842(1)
N1−Cu1−N2	86.6(1)	O6−Cu2−N4	84.1(1)
N3−Cu2−N4	101.2(1)	O6−Cu2−N3	174.6(1)
O1−Cu1−N2	102.2(1)	Cu1−Na−Cu2	112.9
O1−Cu1−N1	170.7(1)		

Scheme 5. Heterobicycle Which Cannot Be Formed with Imine **1e**



1e

In contrast to **1a**, **1e** does not react to a heterobicycle. In **5e** the imine ligand **1e** has two methylene groups between the pyridine substituent and the imino group (Table 7). The formation of a carbanion under basic conditions in **5e** is less favorable compared to **5a** because of a lower CH acidity and loss of resonance stabilization through the pyridine ring. No C−N bond can be established between the carbon of the imino group and a nitrogen atom of the 2-pyridyl ring. A four-electron process would be necessary for the oxidation of **1e**, which was not observed in the oxidative heterocyclization described. Scheme 5 shows the not achieved formation of the heterocycle.

The attempts to oxidatively heterocyclize **1e** lead to the formation of two copper complexes with **1e**, which were structurally characterized. The imine **1e** forms a copper(II) complex **5e** in methanol, whereby two complex spheres each are bridged by one sodium ion (Figure 6). Three acetate molecules with their oxygen atoms form the bridge between sodium and copper ions, and one methanol molecule forms the bond to the central sodium ion. Both copper ions are coordinated in a slightly distorted square planar coordination sphere. Nevertheless, **5e** is not stable in solution and rearranges by ligand exchange to the copper(II) complex **10** and copper(II) acetate. In **10** the imine **1e** is coordinated with two molecules to one copper(II) center (Table 8). Consequently, another molecule of the ligand **1e** is used to complete the coordination sphere around the copper ion (Figure 6). The Cu−N bond lengths (2.00 Å) and the Cu−O distances

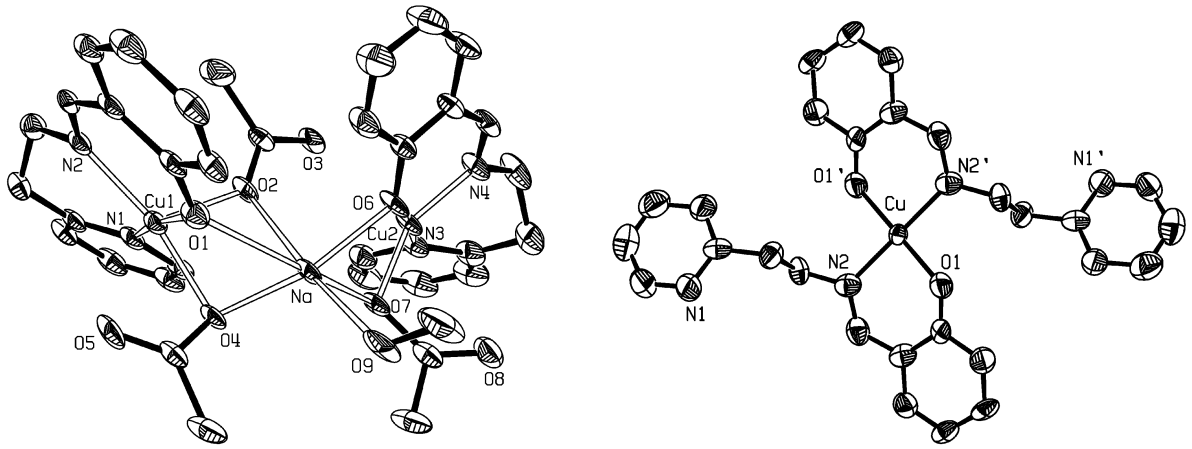


Figure 6. ORTEP[14] drawings of the copper(II) complexes **5e** (two imine units, acetate, and methanol molecules shown with filled bonds) and **10**.

Table 8. Interatomic Distances (Å) and Angles (deg) Selected for **10**

Cu−N2	2.00(1)	Cu−O1	1.88(1)
N2−Cu−O1	92.3(5)	N2−Cu−O1	87.7(5)

(1.88 Å) are in the normal range for this square planar coordination geometry in **10**.

Conclusion

It was possible to investigate in detail the single steps of the copper-catalyzed heterocyclization with the oxidation of **1a** to **2a**. The isolated copper(II) and copper(I) complexes of **5a**, **6a**, **7a**, and **8a** characterized by X-ray structure

Table 9. Crystallographic Data

	5a	**5e**	**6a**	**7a**
empirical formula	$C_{18}H_{14}ClCuN_3O{\cdot}CH_3OH$	$C_{35}H_{39}Cu_2N_4NaO_9$	$C_{36}H_{26}ClCuN_6O_2$	$C_{18}H_{15}ClCuN_3O$
fw	419.35	809.77	673.62	388.32
temp (K)	183	183	200	200
λ (Å)	0.710 73	0.710 73	0.710 73	0.710 73
cryst system	triclinic	monoclinic	monoclinic	monoclinic
space group	$P\bar{1}$	$P2_1/n$	$P2_1/c$	$C2/c$
a (Å)	7.7047(4)	8.2228(2)	11.6733(5)	13.5373(12)
b (Å)	8.5429(4)	21.5194(6)	20.0909(9)	14.9827(13)
c (Å)	14.3676(4)	20.9198(5)	12.9625(6)	18.4163(16)
α (deg)	89.319(3)	90	90	90
β (deg)	77.905(3)	99.002(2)	90.366(1)	111.1590(10)
γ (deg)	80.714(4)	90	90	90
V (Å^3)	912.34(7)	3656.2(2)	3040.0(2)	3483.5(5)
Z	2	4	4	8
ρ_{calcd} (g cm^{-3})	1.527	1.471	1.472	1.481
μ (cm^{-1})	13.62	12.33	8.51	14.16
R [$I > 2\sigma(I)$][a]	R1 = 0.0316	R1 = 0.0388	R1 = 0.0512	R1 = 0.0437
	wR2 = 0.0776	wR2 = 0.111	wR2 = 0.1092	wR2 = 0.1018
R (all data)[a]	R1 = 0.0404	R1 = 0.0416	R1 = 0.1446	R1 = 0.1076
	wR2 = 0.0824	wR2 = 0.117	wR2 = 0.1382	wR2 = 0.1173

	8a	**9a**	**9b**	**10**
empirical formula	$C_{38}H_{36}ClCuN_6O_{4.70}$	$C_{18}H_{12}ClCuN_3O_3$	$C_{28}H_{26}CuN_4O_5S$	$C_{28}H_{28}CuN_4O_2$
fw	750.92	417.31	594.13	516.08
temp (K)	200	183	183	183
λ (Å)	0.710 73	0.710 73	0.710 73	0.710 73
cryst system	monoclinic	orthorhombic	monoclinic	monoclinic
space group	$P2_1/c$	Pccn	$P2_1/c$	$P2_1/c$
a (Å)	14.730(4)	17.5223(6)	14.5787(4)	10.0403(3)
b (Å)	18.355(6)	20.5783(7)	16.3295(4)	25.0150(10)
c (Å)	15.654(5)	9.5807(2)	11.1576(3)	10.6396(4)
α (deg)	90	90	90	90
β (deg)	112.018(5)	90	100.825(1)	118.139(2)
γ (deg)	90	90	90	90
V (Å^3)	3924(2)	3454.60(18)	2608.94(12)	2356.38(15)
Z	4	4	4	4
ρ_{calcd} (g cm^{-3})	1.271	1.605	1.513	1.455
μ (cm^{-1})	6.72	14.42	9.65	9.61
R [$I > 2\sigma(I)$][a]	R1 = 0.1132	R1 = 0.0307	R1 = 0.0378	
	wR2 = 0.2943	wR2 = 0.0826	wR2 = 0.1001	
R (all data)[a]	R1 = 0.3175	R1 = 0.0379	R1 = 0.0547	
	wR2 = 0.3931	wR2 = 0.0983	wR2 = 0.1193	

[a] $R1 = [\Sigma||F_o| - |F_c||]/\Sigma|F_o|$, $wR2 = [[\Sigma w(|F_o^2 - F_c^2|)^2]/[\Sigma w(F_o^2)]]^{1/2}$, $w = 1/[(\sigma F_o)^2 + (aP)^2]$. The value of aP was obtained from structure refinement.

analyses confirm the suggested reaction mechanism in Scheme 2. The isolated complexes **5a** and **8a** were successfully converted into each other according to the catalytic cycle. This proves the significance of this reaction mechanism. The catalysis starts with the copper(II) complex **5a**. **5a** can only react after the coordinated imine **1a** is deprotonated close to the imine group. This explains the reaction-accelerating effect of strong bases such as sodium hydroxide, including the fact that such imines can react only where the deprotonation is structurally favored. The oxidative dehydrogenation takes place after the deprotonation to give copper(I) complexes of the heterobicycle **2a**. Because of its low solubility, **6a** was isolated. A rapid ligand exchange occurs under the reaction conditions existing in the catalysis, forming copper(I) complexes of the imine **1a**. **7a** and **8a** both were isolated and characterized. The high sensitivity of **8a** to molecular oxygen suggests that this step of the catalysis is responsible for the coordination and activation of oxygen. The oxidation of **8a** with air leads to the starting material **5a**. This shows the importance of **8a** as intermediate in the catalytic cycle. The elementary steps of oxygen activation at the copper center and the steps of the oxidative heterocyclization remain unclear. Kinetic investigations with isolated intermediates are in progress and will be reported in due course.

Experimental Section

Preparation of 1b. A solution of 1 g (5.5 mmol) of bis(2-pyridyl)methylamine was added dropwise to a solution of 1.5 g (5.5 mmol) of toluene-4-sulfonic acid (2-formylanilide)[8] in 7 mL of ethanol. Then the mixture was refluxed for 1 h. The dark solution was cooled to −25 °C, as a result of which **1b** precipitated. Yield: 1 g (2.2 mmol, 40%). Mp: 135 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 13.20 (s, 1H), 8.57 (m, 3H), 6.61−8.16 (m, 14H), 5.89 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 165.4, 160.4, 149.4, 143.3, 139.4, 137.1, 136.8, 133.7, 131.9, 129.4, 128.5, 127.0, 126.1, 122.6, 122.5, 122.2, 120.7, 117.7, 81.6, 21.4. EI$^+$-MS [*m*/*z* (%)]: 443 (100), $[M + H]^+$.

Preparation of 5a. Method A. A methanolic solution (30 mL) of equimolar amounts of 1.45 g (5 mmol) of **1a**, 0.67 g (5 mmol) of $CuCl_2$, and 0.20 g (5 mmol) of sodium hydroxide was prepared at −60 °C under formation of a green suspension. The mixture was warmed to −30 °C to give a green solution. After 3 h, **5a** crystallized as a dark green solid. The methanolic suspension of the crude complex was warmed to −5 °C for 20 min and slowly cooled again. This procedure was repeated three times, thus leading to large compact crystals of **5a**.

Method B: Oxidation of 8a with Air (Reconversion to 5a). Under argon, 1 g (1.5 mmol) of **8a** was dissolved in 40 mL of methanol. A small amount of a nondissolved solid was removed by filtration. The yellow-brown filtrate was stirred under air for 3 min at ambient temperature whereby the color changed to deep-green. Then the solution was transferred into a closed vessel and stored for 3 days at −25 °C. Green crystals of **5a** suitable for X-ray structure determination were obtained.

Preparation of 5e. A methanolic solution of equimolar amounts of **1e**, copper(II) acetate, and sodium hydroxide was stirred at 0 °C in the presence of air for 2 h. The binuclear copper(II) complex **5e** was formed in the reaction. **5e** crystallized directly from the reaction mixture.

Preparation of 6a. Under argon, a methanolic solution (30 mL) of equimolar amounts of 1.45 g (5 mmol) of **1a**, 0.67 g (5 mmol) of $CuCl_2$, and 0.20 g (5 mmol) of sodium hydroxide was heated under reflux for 3 h. After the solution had been cooled to room temperature, a brown solid precipitated. Yellow crystals of **6a** suitable for X-ray structure determination were obtained by recrystallization of the crude product from methanol under argon.

Preparation of 7a. Under argon, a mixture of equimolar amounts of 1.73 g (6 mmol) of **1a** in 40 mL of methanol and a solution of 0.25 g (6 mmol) of CuCl in acetonitrile and hexane was heated under reflux for 15 min. After the solution had been cooled to room temperature, it was layered with diethyl ether and stored for 1 day. Brown-red crystals of **7a** precipitated, which were suitable for X-ray structure determination.

Preparation of 8a. Under argon, a mixture of 2.2 g (4.5 mmol) of **5a**, 1.30 g (4.5 mmol) of **1a**, and 0.018 g (0.45 mmol, 0. 1 equiv) of NaOH in 30 mL of methanol was stirred for 2 h at ambient temperature. The obtained brown solution was stored at −20 °C for 15 h. Then a small amount of **6a** was removed by filtration under argon. The filtrate was concentrated to approximately 20 mL in vacuo. The solution was cooled slowly, whereby yellow crystals of **8a** were obtained which were suitable for X-ray structure analysis. After decanting from the solid, the mother liquor was concentrated to 10 mL. While the solution was cooling to −25 °C overnight, pure **8a** crystallized. ^{1}H NMR (200 MHz, MeOH-d_4): δ = 8.83 (s, br., 1H), 8.31 (s, br., 2H), 7.95 (m, 2H), 7.82 (m, 2H), 7.43 (m, 1H), 7.29 (m, 3H), 6.81 (m, 2H), 6.22 (s, 1H). ^{13}C NMR (50.3 MHz, MeOH-d_4): δ = 170.0, 161.6, 159.1, 150.8, 139.8, 134.5, 133.3, 125.6, 125.3, 120.5, 120.3, 117.7, 77.9.

Preparation of 9a. Method A. A methanolic solution of equimolar amounts of **1a**, $CuCl_2$, and sodium hydroxide was heated in the presence of air for 1 h. The binuclear copper(II) complex **9a** was formed in the reaction. **9a** crystallized directly from the reaction mixture under cooling.

Method B. The copper(I) complex **6a** was heated in methanol in the presence of air for 8 h. Cooling of the methanolic solution yielded crystals of **9a**.

Preparation of 9b. A methanolic solution of equimolar amounts of **1b**, copper(II) acetate, and sodium hydroxide was heated in the presence of air for 2 h. The binuclear copper(II) complex **9b** was formed in the reaction. **9b** crystallized directly from the reaction mixture under cooling.

Preparation of 10. Under argon, a methanolic solution of equimolar amounts of **1e**, $CuCl_2$, and sodium hydroxide was heated under reflux for 3 h. After the solution had been cooled to room temperature, a brown solid precipitated. Brown crystals of **10** suitable for X-ray structure determination were obtained by recrystallization of the crude product from methanol under argon.

Crystal Structure Determination. The intensity data for the compounds were collected by a Nonius KappaCCD and a Siemens Smart 1000 CCD diffractometer (compounds **6a**, **7a**, and **8a**) using graphite-monochromated Mo Kα radiation. Data were corrected for Lorentz and polarization effects but not for absorption.[9,10]

(8) Chernova, N. I.; Ryabokobylko, Y. S.; Brudz, Y. G.; Bolotin, B. M. *Zh. Neorg. Khim* **1971**, 1680.
(9) *COLLECT, Data Collection Software*; Nonius BV: Delft, The Netherlands, 1998.
(10) Otwinowski, Z.; Minor, W. Processing of X-ray Diffraction Data Collected in Oscillation Mode. In *Methods in Enzymology, Vol. 276, Macromolecular Crystallography*; Carter, C. W., Sweet, R. M., Eds.; Academic Press: San Diego, CA, 1997; Part A, pp 307−326.

The structures were resolved by direct methods (SHELXS[11]) and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-97[12]) (Table 9). For the compounds **5a**,**e** (not for the methyl groups), **6a**, **7a** (only for the O1−H), and **8a**, the hydrogen atoms were localized by difference Fourier synthesis and refined isotropically. The hydrogen atoms of the other structures were included at the calculated positions with fixed thermal parameters. The quality of the data for compound **10** is too bad. We will only publish the conformation of the molecule and the crystallographic data. The data shall not be deposited in the Cambridge Crystallographic Data Centre.

All non-hydrogen atoms were refined anisotropically.[12] XP (Siemens Analytical X-ray Instruments, Inc.) was used for structure representations.

IC034773A

(11) Sheldrick, G. M. *Acta Crystallogr. Sect. A* **1990**, *46*, 467−473.
(12) Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Göttingen, Germany, 1993.
(13) CCDC 197824, 197825, 197827, and 197828 (**5a**, **5e**, **9a**, **9b**), CCDC 221808 (**6a**), CCDC 199953 (**7a**), and CCDC 212673 (**8a**) 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, U.K.; fax (+44) 1223−336−033 or e-mail deposit@ccdc.cam.ac.uk).
(14) Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.