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Aromatic oxidative decompositions of copper Schiff base complexes

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ABSTRACT

Copper Schiff base complexes used in enantioselective aziridination reactions were shown to possess a proclivity for aromatic oxidative coupling reactions.

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The aziridine functionality is present in a number of naturally occurring molecules and the biological properties of aziridine-containing compounds such as mitomycins, azinomycins, FR-900482, maduropeptin, and azicemicins are of significant medicinal interest. In addition, aziridines are useful synthetic entities since they can give rapid access to a variety of functional groups.[1] Extensive studies were conducted to develop aziridination catalysts giving high enantioselectivities and turnover numbers (TONs).[2] However, aziridinations of challenging substrates still often require extended reaction times and high catalyst loading which is incompatible for manufacturing scale syntheses. The understanding of the catalysts decomposition pathways becomes crucial for designing a catalyst with longer lifetime and higher turnover numbers.

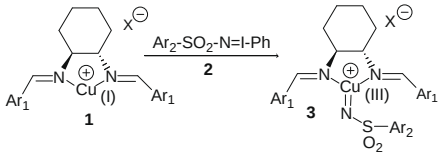
Ongoing research in our laboratory has provided us with an opportunity to affect a Jacobsen-type aziridination of an olefinic substrate.[3] Experimental and theoretical studies of this reaction suggest that the catalytically active species emerging from the interaction of a Cu(I)-bis-imine complex, **1** (derived from nonracemic 1,2-cyclohexane diamine) with imidoiodinane, **2**,[4] is a Cu(III) complex of structure **3** (Scheme 1).[5]

The exact oxidation state of copper during the reaction has been the subject of intensive investigations.[6] On the basis that complex **1** gave the same enantioselectivity for the aziridination of styrene using imidoiodinane **2** or the corresponding photogenerated tosylnitrene obtained from tosylazide, Jacobsen has concluded that the reaction involved the same Cu(III)-nitrene species.[3b] More recently, high-level quantum chemical calculations confirmed this result and suggested a Cu(III)-nitrene species to be the reactive intermediate in a Cu(I)/Cu(III) catalytic cycle.[3a] In these studies, the phenyl moiety of PhI in PhI=NSO_2Ar_2 was shown to have no influence on the reactivity and selectivity. Therefore, a redox pathway where PhI is fully dissociated from the complex to form a discreet Cu(III)-nitrene species prevails as the accepted mechanism.

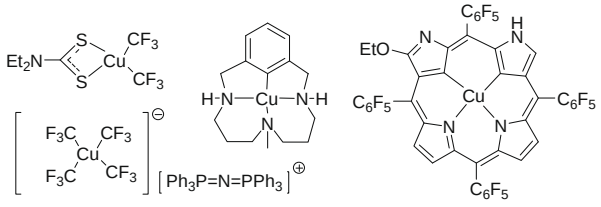
The organochemistry of copper with oxidation state greater than (+I) is not well known and only a few tetradentate copper(III) species were characterized (Scheme 2).[7] The literature records no direct observation of species **3**, and of course, a number of mechanistic issues pertaining to the aziridination reaction as well as to the decomposition of **3** remain to be clarified. Herein, we report the first characterization of complexes **3** by mass spectrometry (MS-ESI$^+$). We also bring an explanation based on the decomposition products formed through the interaction of complexes **4** with imidoiodinane **2** as to why certain catalysts give high selectivity and TON and others fail in those regards.

Complexes **4** were prepared in acetonitrile solution by the customary method (Scheme 3). Copper(I) being d^{10} and diamagnetic, standard NMR experiments can be performed.

The best diimine catalysts described for the aziridination reaction, **4c** and **4h**, possess *ortho* chloro substituents on Ar_1. Addition



Scheme 1. Presumed copper(III) complex **3** formed during the interaction of **1** with imidoiodinane **2**.



Scheme 2. Examples of tetradentate copper(III) complexes.

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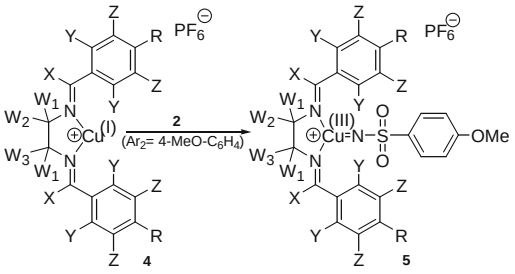
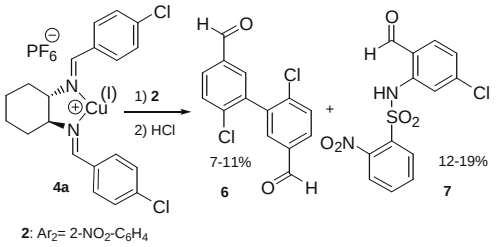


a R = Cl; W_1 = *c*-C_4H_8; W_2 = *β*-H; W_3 = *α*–H; X = Y = Z = H
b R = Cl; W_1 = *c*-C_4H_8; W_2 = *β*-H; W_3 = *α*–H; X = H; Y = Z = D
c R = X = Z = H; W_1 = *c*-C_4H_8; W_2 = *β*-H; W_3 = *α*–H; Y = Cl
d R = Cl; W_1 = W_2 = W_3 = X = Y = Z = H
e R = Cl; W_1 = W_2 = W_3 = Y = Z = H; X = D
f R = Cl; W_1 = W_2 = W_3 = D; Y = Z = X = H
g R = Cl; W_1 = W_2 = W_3 = X = H; Y = Z = D
h R = X = Z = W_1 = W_2 = W_3 = H; Y = Cl

Scheme 3. Copper(I) and copper(III) complexes **4** and **5**.

of **2**, Ar_2 = 4-MeO–C_6H_4, to an acetonitrile solution of complex **4h**, Ar_1 = 2,6-dichlorophenyl, caused a color change from yellow to blue-green. An electrospray mass spectrum of this blue–green solution displayed an isotopic cluster corresponding to the molecular mass of the intact cationic portion of complexes **5h** (Fig. 1).[8] The simultaneous presence of 4 chlorines and 1 copper atom generated an isotopic pattern for **5h** (*m/z* = 620, 622, 624, 626, 628, and 630), whose intensity ratios were in accord with predictions. The complex emerging from the interaction of **4h** with **2,** Ar_2 = 4-MeO–C_6H_4, was also soluble and stable in different solvents (MeOH, DCM).[9]

In order to determine the factors that influence the reactivity and selectivity of the catalysts, specifically the *ortho* substitution of the aromatic Ar_1, known complex **4a** and its deuterated non-cyclic equivalent **4g** was synthesized. Jacobsen showed that complexes **4** lacking *ortho* substituents on Ar_1 (e.g., **4a**) gave low enantiomeric excess and low TON for both aziridination and cyclopropanation reactions. Addition of 1 equiv of imidoiodinane **2**, Ar_2 = 4-MeO–C_6H_4, to a solution of **4a** in acetonitrile resulted in an immediate color change from yellow to green and formation of a catalytically active species, presumed to possess structure **5a**. Addition of excess styrene (1.9 equiv) to this solution caused formation of the expected aziridine in 1 h (yield = 82%).

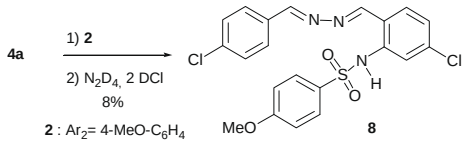


Scheme 4. Decomposition products **6** and **7** from reaction of **4a** with **2**.

Alternatively, conducting the reaction with complex **4a** and imidoiodinane **2**, Ar_2 = 2-NO_2–C_6H_4 for 1 h without addition of styrene followed by hydrolysis with hydrochloric acid provided the decomposition products **6** (7–11% yield) and **7** (12–19% yield) (Scheme 4).[10] The remaining of the hydrolyzed complex was recovered as *p*-chlorobenzaldehyde and *o*-nitrosulfonamide. An X-ray structure of compound **6** was obtained and confirmed the *ortho* relationship of the two aromatics relative to the chlorine atoms.[11] Compound **7** was unambiguously assigned by NMR analysis as the isomer with the sulfonamide *ortho* to the aldehyde.[12]

Next, we explored on a synthetic scale the effect of quenching the reaction with deuterated hydrazine. Hydrazine could act either as a competing amine for the formation of **7** or as a reducing agent for copper salts.[13] Complex **4a**, dissolved in acetonitrile-d_3, was reacted for 1 h with a stoichiometric amount of imidoiodinane **2**, Ar_2 = 4-OMe–C_6H_4, and then quenched with anhydrous hydrazine-d_4, dideuterochloride. After chromatography, diimine-hydrazine **8** was isolated as the only oxidized product (Scheme 5).[14]

The formation of compounds **7** and **8** involves the formal oxidative insertion of a nitrogen into a C–H aromatic bond. This process can entail aromatic hydrogen abstraction followed by trapping the



Scheme 5. Decomposition product **8** from reaction of **4a** with **2** and quenching with N_2D_4, 2DCl.

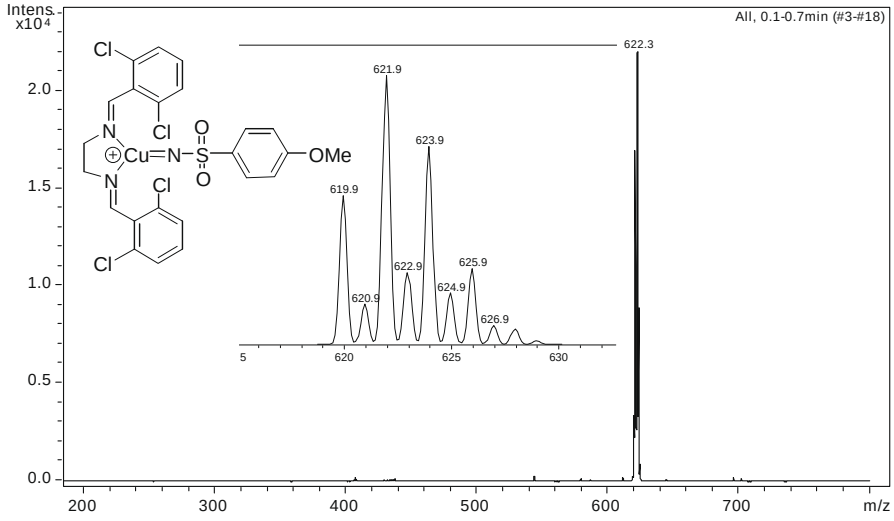


Figure 1. Positive-ion electrospray mass spectrum of the cationic portion of complex **5h**.

resulting electrophilic radical with a nucleophilic nitrogen.[15] Alternatively, an aryl-copper complex intermediate can form and trigger a copper-mediated amination.[16] The formation of product **6** is more difficult to explain and might involve a Nazarov-type cyclization with a highly specific geometry round the metal center to promote the coupling. In another experiment, complex **4a** was dissolved in acetonitrile-d_3 and reacted for 1 h with stoichiometric amount of imidoiodinane **2**, Ar_2 = 4-OMe–C_6H_4, followed by addition of different electrophiles (methyl iodide, allyl bromide, or methyl acrylate, 10 equiv). No product corresponding to the addition of iodide, bromide, methyl, allyl, or methyl acrylate or to the formation of deuterated 4-chlorobenzaldehyde was detected by MS-ESI$^+$ and ^{1}H NMR of the crude material.[17] However, the reaction still provided compounds **6** and **7** (8% and 14% yields, respectively) after hydrolysis with HCl. Therefore, a free radical process is unlikely to occur. The aromatic oxidative couplings found in compounds **6**, **7,** and **8** are most likely the result of the formation of an aryl–copper complex as an intermediate. The following experiments provide more evidences for this hypothesis.

Results obtained from mass spectroscopy analyses confirmed that the aromatic portion Ar_1 of the ligand was oxidized during the interaction of complexes **4a, 4b,** and **4d–g** with imidoiodinane **2**.[18] For the first part of this study, non-chiral ligands **4d–g** were used for commodity of deuterium labeling.[19] A mass spectrum of a solution of **4d** (electrospray ionization, ESI$^+$) exhibited an isotopic cluster arising from its intact cationic portion. Specifically, M^+ signals appeared at *m/z* = 367, 369, 371, and 373 in a ratio of 36.1:45.3:16.3:2.3, in complete accord with predictions. No signals arising from doubly charged ions were observed, indicating that passage of the analyte through the ionizing sector of the mass spectrometer does not promote oxidation of Cu(I) to Cu(II). The ESI spectrum of an acetonitrile solution containing equimolar amounts of **4d** and the imidoiodinane **2**, Ar_2 = 4-MeO–C_6H_4, was quite simple, displaying an isotopic cluster at *m/z* = 551, 553, 555, and 557. The intensity ratios of these four signals were in accord with the presence of 1 Cu and 2 Cl atoms. These masses correspond to the cationic portion of **5d** (nominal masses 552, 554, 556, and 558) *minus one hydrogen* (Fig. 2). Signals were also observed at *m/z* = 429 and 431 corresponding to a fragment of the original complex **5d** in which one of the imine group was cleaved. No signals belonging to the cationic portion of **4d** or to the intact cationic portion of **5d** were apparent. Additionally, MS/MS experiment of the peaks centered at *m/z* = 551 provided a cluster of peaks at *m/z* = 382. This fragment was assigned as $[Cu(L)N]^+$ based on the excellent matching of the observed and simulated isotope distributions. This fragment corresponds to the cleavage of the N–Ts bond and loss of a sulfinic radical (−171). The facile formation of a nitrido–copper complex $[Cu(L)N]^+$ in the gas phase for **5d** is very interesting. This suggests that this nitrido-copper complex possesses a great thermal stability and the cleavage of the N–Ts bound in **5d** is much easier than that in **5h**.

In order to determine which hydrogen was lost from the presumed **5d**, we examined the behavior of deuterated complexes **4d–g**. The ESI$^+$-MS of a solution containing equimolar amounts of **4e** and **2**, Ar_2 = 4-MeO–C_6H_4, or of **4f** and the same imidoiodinane, again exhibited an isotopic cluster at $[M-1]^+$ relative to **5e** and **5f**. Thus, the species arising from **4e** produced signals at *m/z* = 555, 557, 559, and 561, and that obtained from **4f** at *m/z* = 553, 555, 557, and 559. A high-resolution MS measurement of the ion of *m/z* = 553 confirmed its composition to be $C_{23}H_{18}D_2N_3O_3S_{35}Cl_2{}^{63}Cu$. However, reaction of complex **4g** with **2**, Ar_2 = 4-MeO–C_6H_4, yielded a species that displayed ESI$^+$-MS signals two mass units lower than expected for **5g**, signaling loss of deuterium. These $[M-D]^+$ signals appeared at *m/z* = 558, 560, 562, and 564. One must thus conclude that the formation of the $[M-H]^+$ species in all such experiments is due to loss of an aromatic H.

Because the lost of the H atom is part of the strongest C–H bond present in the molecule, it is improbable that such a loss is due to direct fragmentation. In fact, varying the ionization potential and the inlet temperature of the ESI mass spectrometer had virtually no effect on relative signal intensities. Moreover, removal of one electron from any kind of Cu(III) complex, is likely to be more difficult than removal of an electron from Cu(I) complexes **4**. But as detailed earlier, no such evidence of oxidative events appear in the mass spectra of **4**, suggesting that the oxidation does not take place during passage through the mass spectrometer; but that the redox event occurs beforehand. These complexes (**5d–g–H**$^\cdot$) were also soluble and stable in different solvents (DCM, MeOH, and acetonitrile). The formal aryl radical emerging from the removal of a hydrogen is somehow highly stabilized. It is known that a σ_{C-H-Cu} interaction can significantly reduce the pK_a of an aryl C–H group and therefore could explain the lost of the hydrogen atom.[20] A base-assisted C–H_{arom} bond cleavage mechanism that retains the formal oxidation state of the metal atom is likely for this

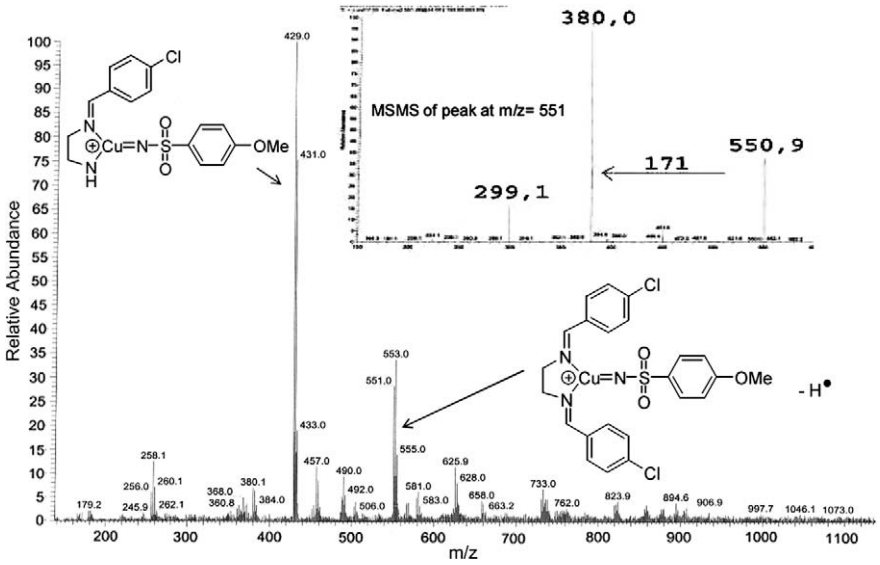
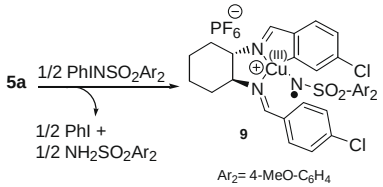


Figure 2. Positive-ion electrospray mass spectrum of the cationic portion of complex **5d**–**H**$^\cdot$ and in the inset MS/MS spectrum of the peak at *m/z* = 551.



Scheme 6. Possible C–H activation product.

process: ($M^{n+} + R - H_{arom} \rightarrow M^{n+} - R + H^+$). No C–H activation of Cu(III) complexes has been described in the literature whereas few reports detail the reaction for Cu(II) complexes. Thus, this would be the first example of this type of C–H activation on a Cu(III) complex. The oxidation of metal amine complexes readily gives metal aminyls or metal amides depending on the metal and ligands.[21] Further oxidation of complex **5a–H**$^{\cdot}$ with excess imidoiodinane **2** or with complex **5a**, or by dismutation is therefore expected to give aminyl radical complex **9** whose cationic portion is observed in mass spectrometry (Scheme 6).

In conclusion, we have demonstrated by mass spectrometry that the aryl moiety Ar_1 of complexes **4** was oxidized with an imidoiodinane if no *ortho* substituents are present. The reactivity of such a species differs greatly from the non-oxidized one and opens the door to decomposition pathways (formation of compounds **6** and **7**) that significantly shorten the lifetime of the complex. Indeed, Jacobsen observed that Cu(I) complexes of the type **1**, wherein the aryl segments Ar_1 carried only 1 *ortho*-substituent, afforded both low TONs ($\leqslant$3.6) and moderate ees.[22] In contrast, changing Ar_1 to 2,6-dichlorophenyl **4c** resulted in a particularly active aziridination catalyst, in terms of both TON ($\approx$16) and enantioselectivity (ee >98%). A similar trend was also observed by P. Scott for the enantioselective aziridination using copper complexes of biaryl Schiff bases.[23] Details of the mechanism of formation of compound **6** and synthetic applications of this C–H activation are currently being investigated in our laboratory and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedures and analytical data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.100.

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8. *General procedure for mass spectrometry analysis of complex* **5**: tetrakis(acetonitrile)copper hexafluorophosphate (93 mg, 0.25 mmol) was added to a solution of the Schiff base (0.25 mmol) in 2 mL of acetonitrile or DCM. After the solution was stirred for 15 min, a homogeneous yellow solution formed. Imidoiodinane **2** (0.25 mmol) was then added at room temperature. The color of the solution changed from yellow to green. The reaction mixture was stirred for 10 min and 50 μL of the solution was withdrawn and diluted with 2 mL of methanol. Mass spectrometry analyses were obtained on this sample.
9. Performing the run in acetonitrile, MeOH, or DCM did not change the result of the MS experiment.
10. Longer reaction times (12 h) do not change the yield of **6** and **7**.
11. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC 705130.
12. *6,6′-Dichloro-biphenyl-3,3′-dicarbaldehyde* (**6**) *and N-(5-chloro-2-formyl-phenyl)-2-nitro-benzenesulfonamide* (**7**): To complex **4a** (142 mg, 0.25 mmol) in acetonitrile (2 mL) was added iminoiodine **2** (Ar_2 = 2-NO_2–C_6H_4), (101 mg, 0.25 mmol) at 0 °C whereupon the color of the solution changed from yellow to green. The reaction was stirred for 1 h at room temperature then cooled down again to 0 °C and quenched with concentrated aqueous HCl or DCl (2 mL). The reaction was stirred for 20 minutes at room temperature followed by addition of EtOAc (15 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give 165 mg of a white solid containing mainly *p*-chlorobenzaldehyde, *o*-nitrobenzensulfonamide, and iodobenzene. Careful TLC chromatography using EtOAc/hexanes (1/9) allowed the separation and the isolation of the biphenyl compound **6** as transparent crystals (7.6 mg, 11% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.03 (2H, s), 7.91 (2H, dd, J = 8.1, 1.9), 7.81 (2H, d, J = 1.9), 7.69 (2H, d, J = 8.1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.4, 140.1, 138.1, 134.9, 132.1, 130.6, 130.5 ppm. IR (KBr): 1687, 1199 cm^{-1}. Mp: 43–45 °C. MS (EI): m/z = 278 (M^+), 249 (–CO). From the crude material obtained in the previous experiment, compound **7** was isolated as an oil (16.5 mg, 19% yield) by TLC chromatography using a gradient of solvent starting with EtOAc/hexanes (2/8) and finishing with EtOAc/hexanes (4/6). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.50 (1H, br), 8.23 (1H, dd, J = 9.1, 3.6), 7.87 (2H, m), 7.76 (2H, m), 7.59 (1H, d, J = 8.2), 7.19 (1H, dd, J = 8.2, 1.8) ppm. MS (ESI$^+$): m/z = 363.0 (M+Na$^+$). HRMS (ESI$^+$): calcd for $C_{13}H_9ClN_2O_5SN$ 362.9818; found 362.9816.
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